Overview of FDA’s 2005 Risk Management Guidance

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2002 Prescription Drug User Fee Act

• June 2002 -- Congress reauthorized the Prescription Drug User Fee Act (“PDUFA III”).

• “Congress finds that ... the Prescription Drug User Fee Act ... ha[s] been successful in substantially reducing review times for human drug applications and should be ... carried out ... with new commitments to implement more ambitious and comprehensive improvements in [FDA’s] regulatory processes, including ... strengthening and improving the review and monitoring of drug safety.”

• FDA’s PUDFA III goals included: By the end of FY2004, CDER and CBER would jointly develop final guidance documents addressing good risk assessment, risk management, and Pharmacovigilance practices.
Development of Guidance

• March 2003 -- FDA issued three “concept papers” addressing different aspects of risk management.

• April 2003 -- Public workshops held.

• May 2004 -- Draft guidance documents published.

  
  ➢ Premarketing Risk Assessment (“Premarket Guidance”)

  ➢ Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (“Pharmacovigilance Guidance”)

  ➢ Development and Use of Risk Minimization Action Plans (“RiskMAP Guidance”)
March 2005 Guidance Documents

• Premarket and Pharmacovigilance guidances focus on risk assessment.

• RiskMAP guidance focuses on risk minimization.

• Together these constitute risk management.

• “Risk management” is a systematic, iterative, lifecycle process of:
  - Assessing a product’s risk-benefit balance;
  - Developing tools to minimize risks while preserving benefits;
  - Evaluating tools’ effectiveness and reassessing risk-benefit balance; and
  - Making adjustments to risk management tools to further improve risk-benefit balance.
Premarket Guidance

• Risk assessment consists of identifying and characterizing nature, frequency, and severity of risks associated with use of a product.

• Risk assessment occurs throughout a product’s lifecycle – from product concept and development through post-approval period.

• Premarketing risk assessment is the first step in this process.

• The adequacy of risk assessment depends on:
  
  - Quantity (e.g., adequate number of patients studied); and
  
  - Quality of review (e.g., appropriateness of particular assessments performed; the breadth of the patient populations studied; analytical methods used).
Generating Risk Information During Clinical Trials

• Impossible to provide detailed guidance on what constitutes an adequate safety database for all products.

• Nature and extent of safety data needed to provide sufficient risk information based on several factors, including:

  ➢ Size of premarketing safety database

  ➢ Quality and completeness of safety database

  ➢ Ability to detect unanticipated interactions (e.g., drug-drug, product-disease, product-demographics)
Premarketing Safety Database

• There is no fixed standard. Ideal size influenced by:
  ➢ Proposed indication (life-sustaining vs. symptom relief)
  ➢ Availability of alternative therapies and relative safety
  ➢ Intended patient population, disease condition, and duration of use
  ➢ Safety concerns stemming from non-clinical or early clinical findings

• Larger, more comprehensive databases are more likely to detect serious and rare events during clinical development.
  ➢ Smaller databases may be appropriate for life-threatening diseases, particularly when there are no alternative satisfactory treatments.
  ➢ Larger databases are generally necessary for products intended to treat diseases that are neither life-threatening nor associated with major, irreversible morbidity.
Premarketing Safety Database

- For products intended for long-term treatment for non-life threatening conditions (chronic or recurrent intermittent), ICH and FDA generally suggest:
  - 1500 total patients exposed to the investigational product, including
  - 300-600 exposed for 6 months, and
  - 100 exposed for one year.
Premarketing Safety Database

• ICH suggests that database larger than 1500 may be needed when:
  ➢ Concerns are raised about time-related effects on safety (e.g., drug causes late developing adverse events or adverse events increase in severity or frequency over time);
  ➢ There is a need to quantify low-frequency events;
  ➢ There is limited or unknown efficacy; or
  ➢ There are concerns that a product may add to a background rate of morbidity/mortality.

• FDA recommends considering a larger database when:
  ➢ Proposed treatment is for a healthy population; or
  ➢ A safe alternative already exists.
Anticipating Product Safety Issues

• Develop a diverse safety database that considers:

  ➢ Diverse study population (e.g., age, race/ethnicity, concomitant disease); diverse patient population permits development of safety data in a broad population

  ➢ Range of dose effects

  ➢ Drug interactions (including likely concomitant medication, known metabolic pathways, dietary supplements likely to be co-administered)

  ➢ Potential causes of medication errors (e.g., dosage form, packaging and labeling, similar generic or trade name)
Anticipating Product Safety Issues

• Comparative safety data may be useful when:
  
  ➢ Background rate of adverse events is high (analyze similarity or difference as compared to competitor products)
  
  ➢ There exists a well-established treatment with effect on survival or irreversible morbidity
  
  ➢ To support potential superiority claims
Data Analysis and Presentation

• Include careful safety evaluation in all phases of product development.

• When developing and analyzing safety, sponsors should:
  ➢ Adequately describe adverse events to identify safety signals
  ➢ Analyze temporal and other associations
  ➢ Analyze dose effect as a contribution to risk assessment
  ➢ Use data pooling
  ➢ Vigilantly ascertain reasons for patient withdrawals from studies
  ➢ Conduct long-term follow-up
  ➢ Present succinct comprehensive risk assessment information
Pharmacovigilance Guidance

• Not possible to identify all safety concerns during trials.

• Commercial marketing creates new exposures including:
  - Significantly larger patient population
  - Heterogeneous populations (e.g., co-morbid conditions, concomitant medications)

• Postmarketing safety data collection and risk assessment are important for:
  - Evaluating and characterizing a product's risk profile
  - Decisions about risk minimization
Pharmacovigilance Guidance

• Pharmacovigilance means all scientific and data gathering activities related to the detection, assessment, and understanding of adverse events.

• Activities undertaken with the goal of --
  ➢ identifying adverse events; and
  ➢ understanding, if possible, their nature, frequency, and potential risk factors.
Pharmacovigilance Guidance

- Pharmacovigilance principally involves the identification and evaluation of safety signals.

- Safety signal refers to a concern about an excess of AE’s compared with what would be expected from a product’s use.

- Signals can arise from postmarketing data and other sources.

- Signals indicate the need for further investigation, which may or may not lead to causation
Pharmacovigilance Guidance

• **Identifying and Describing Safety Signals** – good pharmacovigilance practice based on acquiring complete data from spontaneous AE reports (case reports).

• **Develop Individual Case Reports** -- establish systems to collect complete, high quality case reports from spontaneous AE reporting systems or other sources.

• **Develop Case Series** -- Review other spontaneous reports for similar cases, and search for additional cases in sponsor's global AE databases, published literature, and FDA’s AERS and VAERS systems.
Pharmacovigilance Guidance

• **Mine Data** -- to identify product-event combinations
  - Use statistical tools to help identify combinations warranting further investigation (e.g., disproportionate number of events).

• **Identify Safety Signals** -- that may warrant further investigation
  - New unlabeled adverse events
  - Apparent increase in severity of adverse event previously unrecognized at-risk population
Pharmacovigilance Guidance

• **Put Signal Into Context**
  - Calculating Reporting Rates vs. Incidence Rates
  - Consider factors such as seriousness of event, population using the product, newness of product to the market, publicity, etc.

• **Choose Methods for Further Investigation** -- may include nonrandomized observational studies or randomized clinical trials. Nonrandomized options include:
  - Pharmacoepidemiologic studies
  - Registries
  - Surveys (patients or health care providers)
Pharmacovigilance Guidance

• In general, FDA believes that routine spontaneous reporting will be sufficient for postmarketing surveillance for a product –
  ➢ Without safety risks identified pre-approval or post-approval and
  ➢ For which at-risk populations are thought to have been adequately studied.

• Conversely, routine pharmacovigilance plans may be needed for any product where --
  ➢ Serious safety risks have been identified pre-approval or post-approval, or
  ➢ At-risk populations have not been adequately studied.
RiskMAP Guidance

- RiskMAP (Risk Minimization Action Plan) -- a “strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits.

- FDA considers product labeling to be “the cornerstone of risk management.”

- For most products, routine risk minimization measures are sufficient to minimize risks and preserve benefits. Only a few products are likely to merit consideration for additional risk minimization efforts. They include:
  - Products posing clinically important and unusual type/level of risk.
  - Schedule II controlled substances.
RiskMAP Guidance

- RiskMAP Guidance addresses:
  - Initiating and designing risk minimization action plans
  - Selecting and developing tools to minimize the identified risks
  - Evaluating RiskMAPs and monitoring tools
  - Communicating with FDA about RiskMAPs
  - Recommended components of a RiskMAP submission to FDA
RiskMAP Goals and Objectives

• A RiskMAP should:

  ➢ Target one or more safety-related “goals” (i.e., ideal health outcomes);

  ➢ Use measurable “objectives” (i.e., intermediate steps toward the goals); and

  ➢ Use selected “tools” (i.e., risk minimization actions) to achieve the goals.
RiskMAP Goals and Objectives

• Example:

  - **Risk**: Drug X is teratogenic
  - **Goal**: Prevent fetal exposure to Drug X
  - **Objectives**: Lower physician prescribing and pharmacist dispensing for women who are or may become pregnant
  - **Tools**: Targeted education and outreach; reminder systems and processes; performance-linked access systems
When To Consider a RiskMAP

• The process of risk identification, assessment, and characterization continues throughout a product’s lifecycle, and can emerge during a premarketing or postmarketing assessment.

• Sponsors are primarily responsible for determining when a RiskMAP is appropriate; however, FDA may recommend a RiskMAP.
RiskMAP Tools

• Processes or systems to minimize known risks
  ➢ Communicate about optimal use
  ➢ Guide practitioners and patients toward appropriate prescribing, dispensing, or use of a product

• RiskMAP tools fall within three general categories (of increasing burden)
  ➢ Targeted education and outreach,
  ➢ Reminder systems, and
  ➢ Performance-linked access systems

• FDA is developing a RiskMAP website that will, among other things, describe currently used RiskMAP tools.
Examples of RiskMap Tools

• Targeted education and outreach
  - Prescriber education
  - Continuing medical education

• Reminder Systems
  - Patient consent forms
  - Physician training programs that document the physicians’ knowledge and understanding
  - Specialized product packaging to enhance safe use

• Performance-Linked Access Systems
  - Systems that link product access to laboratory testing results (e.g., negative pregnancy test) or other documentation
RiskMAP Evaluation

• RiskMAPs should be monitored and periodically evaluated to identify areas for improvement.

  ➢ Try to evaluate effectiveness of tools prior to implementation.

  ➢ Select well-defined, evidence-based, and objective performance measures to determine whether the RiskMAP goals and objectives are being met.

  ➢ Adequately compensate for limitations in evaluation methods.

  ➢ Conduct periodic evaluations of individual RiskMAP tools to ensure each materially contributes to the achievement of the RiskMAP goals and objectives; revise as appropriate.
Elements of a RiskMAP Submission

- A RiskMAP submission to FDA should include:
  - Background
  - Goals and Objectives
  - Strategy & Tools
  - Evaluation Plan

- Sponsors are expected to submit RiskMAP progress reports to FDA containing:
  - Summary of the RiskMAP
  - Methodology
  - Data & Results
  - Discussion & Conclusions
Conclusion

• FDA’s guidance clarifies that many recommendations are not intended to apply generally to all products.

• Current risk assessment and minimization activities for products during development and marketing are often adequate to ensure safe product use (e.g., requirements for professional labeling, AE monitoring and reporting).

• FDA's guidance documents contemplate a rigorous, proactive, systematic framework for product risk management:
  ➢ Acknowledges existence of risk
  ➢ Estimates and evaluates risk
  ➢ Determines acceptable risk levels
  ➢ Acts to control risk at all relevant points
  ➢ Communicates about risk
  ➢ Measures effectiveness of management activities