Risk Management: Practical Implications for Pharmaceutical Manufacturers

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The Bar is Being Raised Across the Industry for Formal Risk Management Planning

- While approval times are decreasing, industry has experienced high profile drug withdrawals within the past 5 years
- There are increased public expectations regarding product safety
- Product liability suits are spiraling
- Regulators are directing a significant shift by industry from a passive information oriented role to one of action and accountability toward greater safety assurance
  - FDA Risk Management Framework Document (5/99)
  - EMEA Proposals (5/02), Heads of Agencies (HOA) Summary Report 1/03
  - PDUFA III provides funding to FDA for dedicated Risk Mgt. resources, and stipulates that RM Plans may be a part of NDAs/BLAs submitted post October 1, 2002
  - FDA Public Forum to review Concept Papers (4/03)
  - FDA draft Guidance Documents (5/04)
  - CPMP/ICH/5716/03 – Pharmacovigilance Planning – adopted 12/04, effective 6/05
  - FDA final Guidance Documents (3/05)

- Industry is moving quickly to design and implement Risk Management processes
- Risk Management Programs can enable challenging products to stay on the market (by supporting the appropriate use of products that will maximize benefit and minimize risk)
Pharmaceutical companies have established processes for collection, evaluation and reporting of safety data, both for investigational drugs and marketed drugs.

The new era of Risk Management requires a shift from standard pharmacovigilance to a more active role geared toward proactive Risk Assessment and Risk Minimization.

Companies must acquire the expertise and develop processes to meet these new standards.
Pre-Marketing Risk Assessment:

- Risk Assessment should be planned.
- Consider results of preclinical safety assessments, clinical pharmacology
- Consider characteristics of target population, indication, other drugs in class
- Consider known risks and theoretical risks
- Safety database should be diverse and appropriately sized to detect serious adverse events.
- Clinical trials should address the potential for certain serious adverse events such as drug-related QTc prolongation, liver toxicity, drug-drug interactions, etc.
- Coding of adverse events should be accurate, using one coding convention or dictionary.
To meet these new expectations, Industry must bring additional expertise to the table when planning clinical trials.

- Earlier involvement of Safety group
- Critical role for Epidemiology
- Discussion of known risks and theoretical risks as part of clinical trial design.
- Commitment to dialogue with FDA and other agencies.

In addition, there should be frequent evaluation of safety data and additional assessment (changes to study design, additional studies) of emergent safety issues if necessary.
Risk Assessment
Clinical Development

- Industry must develop processes to ensure that Risk Assessment activities are planned, performed and communicated during clinical development.
  - SOPs
  - Define Roles and Responsibilities
  - Training
  - Documentation/Review
  - Governance bodies

- Risk Assessment Activities should be integrated with other ongoing processes including management of the IB, Development Labeling, etc.
Integration of Risk Management, Labeling with Drug Development Timelines & Decision Points

Drug Development Track

- Develop Track (Phase 0)
- Early Clinical (Phase I/II)
- Pivotal Trials (Phase II/III)
- Registration
- Life Cycle Management

Labeling Policy & Governance

- Negotiate for approved Label
- Produce Launch Materials
- Revisions Tier 3 Labels
- Draft and approve Submission Labeling

Risk Management

- Review of Clinical Trial Safety Data
- Develop Risk Management Plan
- Update Risk Management Plan
- Assessments of Epidem., Comparators, etc.

Begin Competitive Intelligence

- Establish Labeling Goals, Strategy
- Draft DCDS
- Finalize DCDS

Wyeth Research
Risk Minimization Action Plans

- FDA Guidance Document stresses that for most products, routine risk minimization measures are sufficient. (Product label, pharmacovigilance).
- RiskMAPs should be considered for a small number of products – case by case basis.
- RiskMAP tools may include:
  - Targeted Education and Outreach
  - Reminder Systems
  - Performance-Linked Systems
Use of Risk Minimization Action Plans
Implications for Industry

- Design and implementation of RiskMAPs will require collaboration and expertise of various departments across a pharmaceutical company including:
  - Safety – continuing pharmacovigilance, input into development of RiskMAPs
  - Epidemiology – expertise in design and implementation of pharmacoepidemiology studies
  - Medical Affairs – Communication to Health Care Professionals/Patients re: Risks and Benefits, implementation of RiskMAPs, educational materials and activities.
  - Marketing – dissemination of efficacy and safety information.
  - Market research – (evaluation)
    - Usage data/prescription databases
    - Surveys.
  - Public Affairs
  - Global Affiliates
Use of Risk Minimization Action Plans

• Additional challenges –
  ▶ How does Industry implement RiskMAPs on a global basis?
    - Practical considerations – drugs may be marketed in many countries.
    - Legal/Regulatory considerations
  ▶ In order to change prescribing behavior and effectively communicate risk – what additional expertise is necessary?
    - Use of behavioral experts
    - Use of process experts – FMEA, etc
Post-Marketing Risk Minimization Activities

- Industry must develop processes for design, implementation and evaluation of Risk Minimization Plans.
  - Establish “ownership” – group, department, person.
  - Standard processes, training, communication
  - Governance bodies

- Ideal process should be “end to end”. 
Design of an End-to-End Risk Management Process is Critical Toward Optimizing the Safe Use of Products
Pulling it all together….

- New regulations and guidances call for a more strategic approach to risk assessment and minimization.
- Safety and Risk Management planning activities should begin early in development and continue throughout the product lifecycle (end to end).
- Industry is working to develop expertise and processes to meet these new standards.
- Clear roles and responsibilities must be defined and communicated across the business.
Conclusion

- The bar *has been* raised for the formal study of safety and risk, both during clinical trials and after product launch.
- Emerging regulations and guidances reflect the evolution of the field of Pharmacovigilance to the new era of Risk Management:
  - Compliance → Quality of data → Analysis → Proactive signal detection → Strategic Risk Management