New Approaches to Safety and Risk Management

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Agenda

• Introduction
• Drivers for New Approaches
• What are the New Approaches?
• Current Example Processes and Tools
• Challenges and Future
• Introduction: SRM, PV, risks and Signal
• Drivers for New Approaches
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PV Changing Landscape
Evolving Risk Management and Pharmacovigilance

**PAST**

- Mostly post-approval
- Peri-approval
- Reactionary
- Handling Adverse events
- Regulators took the lead
- Rare RMPs

**Future**

- Integrated Life cycle
- Early Phase
- Proactive
- Signal detection and Risk management
- Partnership
- RMS and RMP for each product
Safety & Risk Management

- Application of scientifically-based methodologies to identify, assess, communicate, and minimize risks throughout a drug’s life cycle so as to establish and maintain a favorable benefit/risk profile in patients.
Understanding Medicine Safety as Benefit-Risk Balance

**Medicine Safety**
- Not defined by risks alone
- Benefits Outweigh Risks for intended use
- Benefit-risk balance is part of all Personal Choice

**Appropriate Use**
- Communication Is Critical to informed patient-physician choice
- Risk management goal is to use Variety of Strategies to Ensure Benefits continue to outweigh risks
- Risk Associated with Not Taking or adhering to prescribed therapy
Pharmacovigilance

- *Pharmacon (G): drug* & *Viigilare (L): to keep watch*
- *Science and activities relating to detection, assessment, understanding and prevention of ADRs or any drug-related problems* *
- *Usually refers to post-approval*
- *Signal Detection, prioritization and Evaluation*

* CIOMS VIII
Key Definitions

Signal*
- Information that arises from one or multiple sources which suggests
  - a new potentially causal association or a new aspect of a known association
    - Between an intervention and event (or related events)
    - That is judged to require further verification

Risk*
- The probability of developing an outcome (mostly ADR)
- Identified or potential

* CIOMS VIII
Signals and Risks

- **Signal**
  - Evaluating association
    - Confirmed
    - Refuted association
    - Indeterminate
      - Identified Risk
      - Potential Risk
Safety & Risk Management is Iterative

**Identification of Important risks**

**Evaluation**

**SRM Components**

**Assessment**

Management:
- Communication
- Minimization
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Regulatory Drivers

- Safety
- Risk
- Management

Logos of various regulatory bodies and organizations.
Major changes are already approved

- Proposal to amend published in December 2008
- Legislation was approved in September 2010
- To be applied as of July 2012

What is new?

- Summary of PV System in application for MA
- PV System Master File
- RMP will be required for each new MP, proportionate to risks, PASS requirement, publically available
- PASS
- BRUR
- Reporting obligations centralized
- Medicines safety web portal
• The Final rule:
  – This is the revised regulation for pre-marketing IND safety reporting. Issued on
  – September 29, 2010
  – Effective from September 28, 2011
  – Intended to improve quality of and harmonize safety reporting and allow FDA more Safety monitoring of products (pre-marketing)

• REMS
  – FDA Amendments Act of 2007 (FDAAA):
    • Require sponsors to conduct post-approval clinical trials or studies
    • Require sponsors to implement a REMS to ensure a positive benefit/risk ratio
• General public are more well-informed about diseases, drug safety and benefit risk choice

• Aging population

• Misinformation can be terrifying for patients especially when trust is low
Other Drivers for New Approaches

- Economic
- Political
- Technologies
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What are the New Approaches

• New Focus
  – Benefit risk Assessment Focus
• New Scope
  – End to end Monitoring
  – Massive increase in case volumes
• New System
  – People, Process and Technology
• New Trends in RMPs and REMS
• Risk Communication
• Social Media
New Focus

• Benefit risk Assessment Focus
• Detailed Assessment will be required
• Quantitative & Qualitative
• Changes to PSURs and RMPs
Changes In Scope: End to End Monitoring

Current Pharmacovigilance

Risk Management
Signal Detection
Aggregate Reports
Adverse Events

Future Pharmacovigilance

Risk Management
Signal Detection
Aggregate reports
Adverse events
New System: People, Process and Technology

- Proactive, Early, Across Life Cycle,
- Structured Systematic Approach to SRM and PV
- Improved Data collection and Monitoring
- Safety Teams and Safety Experts
- New Tools
From Reactionary to Proactive
How Early?

Providing Evidence that Benefits Outweigh Risks

Drug Discovery → Phase I Clinical Trials → Phase II Clinical Trials → Phase III Clinical Trials → Approval

Safety Evaluation
Risk Management Team: Membership & Charter

- Multidisciplinary
- Life-cycle dependent
- Flexible and issue-driven

EUQPPV or delegate

Safety (Chair)

Legal

Non-Clinical

Clinical

Medical

Epidemiology

Regulatory

Statistics
Risk Management Team is Integral to Product Teams

- Regulatory & Labelling Teams
- Safety (Risk) Management Team
- Safety Review Team
- Other subteams etc.

Governance Committee

- Benefit-Risk: Final Decisions & Oversight
New Tools

- Signal Detection
- Signal prioritization
- Safety Databases
- Benefit Risk Assessment
- Risk Minimization assessment
Risk Management Plan

A-Safety Specifications
- Important Identified Risks
- Important Potential Risks
- Important Missing Information

B-Pharmacovigilance Plan
- Routine PVP
- Enhanced PVP

C-Risk Minimization Plan
- Routine Minimization measures
- REMS

Characterize risks identified from non-clinical and clinical data
What is New for RMPs?

- Every new product will require a RMP
- RMPs for marketed products
- More focus on enhanced Pharmacovigilance
- More risk minimization actions with more focus on influencing behaviour
- More focus on Measuring effectiveness of minimization measures
- Development RMPs
CIOMS VI recommends for a Development RMP

- Captures the important anticipated or potential risks and the actions taken to assess these risks further and minimize their impact
- Depends on the stage of development but should be evolving
- It may develop into the full RMP
Pre-approval risk mitigation

-risk assessment = Characterizing the risk

-Risk minimization:

✓ Monitoring:
  ✓ In protocol measures
  ✓ Safety Reviews: Internal and DSMBs

✓ Exclusion

✓ Communication
Risk Communication: Transparency and Privacy

To Regulators
- Trial Opening Documents
- License Applications
- Pre-Clinical Study Reports
- Clinical Study Reports
- Regulatory Briefing Documents
- Risk Management Plans
- CIOMS / Medwatch
- Safety Summary Reports ASRs, IND,

To Physicians/Investigators/Patients
- SUSARs
- DIL/DHCP Letters
- Investigator Brochures
- Informed Consent
- Ethics Committees
- Labels, PIL, PPLs
- Reports to External Data Safety Monitoring Boards
- Expert Panels/Scientific Advisory Boards
FDA held an AdCom to discuss social media tools for risk communication

Analysis using Twitter, a social networking and microblogging service, with focus on influence

Twitter is viewed as a useful medium to study influence patterns

Twitter can be used to forecast future outcomes

Action taken by the FDA on the SPRC has included contracting with Nielsen McKinsey Incite to follow social media coverage
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How we do Safety Risk Management

“SAFETY TEAM” e.g. Risk Management Committee

Regulatory and External Guidance

Advisory Bodies/DSMB

Various Sources: Clinical, Non-clinical, Epidemiology

SAFETY PRINCIPLES

RISK MANAGEMENT STRATEGIES, Safety Review Plans

SAFETY REVIEWS

Single case, cumulative, Aggregate

Signal detection Tools

RISK MANAGEMENT PLAN

Identify / Assess

Communicate / Control

Research Development Commercial
“What is there that is not poison? Everything can be poison. What differentiates a poison from a medicine is its dose.”

Paracelsus
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Challenges and Future

• More Investment
• More Collaboration
• More Advanced Tools
• Public Education
• Realistic expectations
• Improved unified Case management
• Harmonized Regulations
• More effective communication
• Better Measurement of effectiveness
• Benefit risk determination
Evolving SRM& PV and Digital Age

No Boundaries for PV
Thank You