Enabling Patient Safety Through Risk Management: The Role of Epidemiology

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I am an employee and shareholder of Pfizer, Inc.

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Outline

• Fundamentals of Risk Management
• Epidemiology for Risk Management
  – Risk Assessment
  – Risk Minimization
  – “Big Epidemiology”
• Concluding Comments
Risk Management
Benefit-Risk Balance

• All medicines have benefits and risks, which must be characterized and managed

• Risk Management Planning is essential to ensure that benefits outweigh risks
  – This is a proactive, iterative process
  – It occurs for the entire product life-cycle
  – Routine risk management is built into all products
  – Non-routine assessments and interventions are sometimes needed

• Protection of patient safety is the highest priority at all times
Need Strong Science

- Strong scientifically-based drug regulatory frameworks and capabilities enhance
  - Innovation
  - Patient safety
- Need pragmatic, reliable and flexible approaches
- Partnering to improve methods that inform evidence-based decision-making
  - Consistent and valid observational drug safety research
  - Rapid safety assessment using electronic healthcare data
Risk Management

• RISK MANAGEMENT is defined as the comprehensive and proactive application of scientifically-based methodologies to *identify*, *assess*, *communicate*, *and minimize risk* throughout a drug life cycle to establish and maintain a favorable benefit risk profile in patients.
One size doesn’t necessarily fit all

- EMA
- FDA
- TGA
- PMDA
- Health Canada
- Others
Reference and Local RMPs

**Reference RMP**
- EU RMP required with all new EU Marketing Applications
- Usually the first formal RMP created
- Importance of various risk(s) is discussed
- For the minority of products that require risk minimization, specific goals for reducing risk outcomes are identified
- In many companies, the RMP in effect at EU authorization of the product is considered the global “Reference” RMP

**Local RMP**
- Information, as applicable in the Reference RMP should be presented in an equivalent place in the local RMP, as determined by local regulations, guidelines, and/or templates.
Labeling is the cornerstone of risk management and the foundation for managing the risk of products.

- Investigator Brochure
- Regulator approved prescribing information, e.g., Package Insert, Summary of Product Characteristics
- Risks considered in the context of benefits

Routine assessment and reporting requirements allow contextual evaluation of the evolving data.

- In a small number of products, may need to introduce risk minimization or mitigation tools to minimize or mitigate risks and preserve benefits, i.e., maintain favorable benefit-risk profile
Risk management planning is a global activity

- Disease epidemiology may vary geographically and there may be additional or fewer safety concerns, depending on the target population, indication, burden of disease, or other factors
- Risk minimization activities may need to be tailored to the healthcare delivery system
- Benefits of a medicinal product may also vary between regions
- Thus, the best available and least burdensome tools may not be the same in every jurisdiction
Examples of differences:

- Patient education
  - MedGuides are available in the US
  - Patient Information Leaflets and Patient Safety Cards are used in the EU

- Prescriber education
  - May be provided by MAH with or without metrics
  - May require government certification

- Controlled distribution
  - Free transborder commerce may not permit
Collaboration to Develop and Implement the Risk Management Strategy

Risk Management Program

- Medical & Clinical
- Labeling
- Affiliates
- Regulatory
- Epidemiology
- External Experts
- Safety/PV/Risk Management
- Health Outcomes & Market Access
- Biostatistics
- Legal
Focus of Risk Management Planning

• Target:
  − Important identified risk(s)
  − Important potential risks(s)
  − Important missing information

• “Important” or “Potential”
  − Possible impact on benefit-risk balance
  − May need assessments beyond routine
  − May need interventions beyond routine
Routine vs. Additional Pharmacovigilance and Risk Minimization Activities Comparison

**Pharmacovigilance**
- **Routine pharmacovigilance** to identify and characterize safety concerns:
  - Real-time Review of individual case safety report (ICSR), expedited safety reporting (ESR/SUSAR)
  - Periodic aggregate safety data review, signal detection/data mining
  - Aggregate safety reports (ASR, PSUR, PADER)
- **Enhanced PV:**
  - Supplemental CRFs in clinical trials (CSP for selected event categories)
  - Targeted questionnaires for selected postmarketing spontaneous adverse event reports
- **Additional pharmacovigilance** to further characterize the safety concerns
  - Epidemiology studies to define incidence and/or outcome of AEs
  - Post-marketing non-interventional observational safety studies
  - Drug utilization studies

**Risk minimization**
- **Routine risk minimization** activities/measures
  - Protocol entry criteria to exclude high risk population, dose modification guideline, concomitant medication guideline, safety monitoring plan, stopping rules, study steering committee review, data monitoring committee review
  - Warning/precaution in reference document-Investigators Brochure and guidance to investigators
  - Informed consent
  - Clear safety information presentation in product label and patient information
  - Package strategy
- **Additional risk minimization** action activities
  - Educational material
  - Training programs for prescribers/pharmacists/patients
  - Restricted access
The Risk Management Lifecycle is an Iterative Process

- Select RM Strategy
- Identify Risks
- Identify & Analyze Options
- Evaluate RM Strategy
- Implement RM Strategy
- Select RM Strategy

Risks identified via PV tools:
- Pre-clinical and clinical safety data
- Epidemiology
- Spontaneous reporting (post-market)
- Non-compliance, overdose
- Abuse Potential
- Potential for Medication Errors

Benefit – Risk Assessment
- Monitor and analyze metrics
- Take corrective action
- Communicate

- Causality assessment
- Comparisons to other products
- Who potentially has the highest risk?
- Are any risks predictable?
- Are any risks preventable?

Which risk minimization tool is the best option?
- Product labeling change
- Education and outreach
- Prescribing/dispensing restrictions
- Reminder/promoting systems

- Select evidence-based risk management strategy
- Obtain stakeholder input

- For first launches, integrate timing with launch activities

- Identify Risks
- Assess Risks for Impact
- Select RM Strategy

- Identify & Analyze Options
- Implement RM Strategy

- Evaluate RM Strategy
### Isotretinoin risk minimization program element

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<td><strong>Warning on label, education, red stickers</strong></td>
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<td><strong>Avoid pregnancy icon, consent form</strong></td>
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<td><strong>Pregnancy test, 2 forms birth control</strong></td>
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<td><strong>2 pregnancy tests, 30-day supply (no refill)</strong></td>
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<td><strong>MedGuide to patient via pharmacist</strong></td>
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<td><strong>Qualification stickers by registered prescribers</strong></td>
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<td><strong>Monthly pregnancy tests</strong></td>
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<td><strong>Registration of patients, prescribers, pharmacists, wholesalers</strong></td>
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<td><strong>Patient qualification questionnaire</strong></td>
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<td><strong>Identify contraceptives each month</strong></td>
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• FDA has a long history of risk management, before today’s vernacular
  – 1932, Food, Drug & Cosmetics Act: Pre-market review of safety
  – 1962, FDA Amendments Act: Approval based on both safety and efficacy
  – 1990, Clozapine “no blood, no drug”
  – 1998, Thalidomide S.T.E.P.S.

• The US Package Insert is the primary Risk Management Plan for the US
Situation In the US (2)

• FDA can require a Risk Evaluation and Mitigation Strategy (REMS)
  – At time of initial marketing application (NDA)
  – With a line extension
  – When “new” safety information is received for an approved product

• FDA must consider specific points specified in legislation before requiring a REMS
  – Very few products meet the criteria for a REMS
  – Summary required for public disclosure
FDA regulates many thousands of products
- “Over-the-counter” REMS not needed
- Prescription products: 70 active REMS
Situation In the EU (1)

- An EU RMP is required for all new marketing applications as of January 2013
  - Most RMPs will specify only routine measures, not a Risk Minimization Plan
  - New format requires integration of benefit and risk
  - Concise summary of all relevant information
  - Prospective, dynamic, risk proportionate
  - Special allowances for generic products
Situation In the EU (2)

- EU RMP is a stand-alone regulatory document
  - Separate summary in lay language
- Clear responsibilities
  - Pharmacovigilance Risk Assessment Committee (PRAC) must approve and periodically assess
  - Authority remains with European Commission
  - EU Qualified Person for Pharmacovigilance (QPPV) must sign-off RMP for company
  - “Proportionate and dissuasive” civil and monetary penalties for non-compliance
Epidemiology
From ‘Nice to Have’ to ‘Must Have’ in Risk Management

- **1990-2004:** Ad hoc, public data, commissioned studies
- **2005-2010:** Registries, Claims, EMRs; Core R&D discipline
- **2012 & beyond:** Large integrated databases, e.g., Sentinel, OMOP, EU-ADR

**Fit for Purpose Lifecycle**
Epidemiology
Part of Pharmacovigilance Regulations Worldwide

**Epidemiology Required**
- Risk Management Plans
- Post-approval safety studies
- Active surveillance
- Evaluation of risk minimization measures
- Observational pediatric safety surveillance

**Epidemiology Emerging**
- Risk Management Plans
- Recent guidance on post-approval safety surveillance in China
2012 EU PV Legislation
PASS Definition & Requirements Expanded

**Definition**
- Drug Utilization
- RMM Evaluation
- Systematic Reviews
- Meta-analyses

**Oversight**
- PRAC
- EUQP
- Audit/Inspection

**Disclosure**
- EU PAS Registry
- Protocol/Amendment
- Final Study Report

**Templates**
- Protocol
- Study Report
- AE Reporting

NI PASS Requirements

NI: Non-Interventional
PASS: Post-authorization Safety Study
Epidemiology
Advantages for Drug Safety

• ‘Real World’ or ‘Naturalistic’
  – Permits assessment of outcomes as actually used
• Limited inclusion and exclusion criteria, e.g., approved label
• Heterogeneous patient populations
• Patients enrolled by disease/condition or exposure
  – Describe disease progression and therapy use patterns
  – Contemporaneous comparison groups
  – Evaluate long latency outcomes, e.g., cancer
  – Special or vulnerable populations
    o Elderly using multiple concomitant medications
    o Pregnant women
Epidemiology Contributes to Two Key Risk Management Activities

Safety Profile → Risk Characterization → Risk Assessment

Evolution

Pharmacovigilance

Evaluate Effectiveness and Modify Tool(s) If Indicated

Risk Minimization
Epidemiology
Data Sources for Risk Management

• Study designs use primary or secondary data collection or a combination

• Field of epidemiology has been using ‘Real World Data’ aka automated insurance claims, electronic medical records, registry linkage data, and national population surveys for several decades
  – Collected for administrative/reimbursement purposes by insurance provider, as clinical data by general practitioner, or as part of universal healthcare coverage

• Greater access and diversity of ‘Real World Data’ offer many advantages for pre and post approval safety assessment

• Studies using existing data sources are not always feasible
  – A primary data collection study may be the only option
Evaluate Product Risks

Active Surveillance
Monitor and detect signals in defined patient cohorts using innovative analytic methods

Post Approval Safety Studies
Compare medication risks in the real world, as prescribed and taken during routine clinical practice

Risk Minimization
Evaluate the effectiveness of risk minimization measures (e.g., product label/education)

Characterize Patient Risk Profile

Standing Cohorts

Approval

EMRs
Claims
Registries
Risk Assessment

Case Studies
Lifecycle Risk Management: Use of Epidemiology in the Tofacitinib Rheumatoid Arthritis Program

Ph IIb
- Critical synthesis of RA and DMARD published literature

Ph III
- Standing Cohorts in EU & US
- Conduct analyses to support RCTs
- Describe morbidity & mortality of indicated populations

Ph IV
- Monitor safety profile in patient registries
- Evaluate REMS & RMMs

Approval

Briefing Documents, FDA Advisory Committee, CHMP Oral Explanation
Real World Database Studies
Macugen® (Pegaptanib Sodium Injection)

- A vascular endothelial growth factor (VEGF165) antagonist
- Approved (US in 2004, EU in 2005) for treatment of neovascular age-related macular degeneration (AMD), a primary cause of vision loss in elderly in developed countries
- First approved therapy for neovascular AMD regardless of lesion location, subtype, size or baseline visual acuity
- Administered through intravitreal (IVT) injection every 6 weeks (8-9 times/year)
Real World Database Studies
Macugen® Safety Concern: Endophthalmitis

• In Macugen clinical program, endophthalmitis incidence comparable with other IVT injection clinical studies
• Real-world incidence of endophthalmitis unknown
• Designed one pre-approval and two post-approval epidemiologic safety studies:
  – Both before and after Macugen approval: What is risk of endophthalmitis following IVT injection in AMD patients?
  – What is risk of endophthalmitis among AMD patients after Macugen exposed, under routine care, i.e., in the real world?
Real World Database Studies
Phase I Medicare Study (Pre-Approval Standing Cohort)

**Objective**

- Estimate incidence of IVT injection-related endophthalmitis among AMD patients in the US Medicare population prior to Macugen launch

**Design**

- A cohort study of all Medicare beneficiaries who received an IVT injection for AMD in 2000-2003

**Key Findings**

- The use of IVT injection for AMD treatment increased exponentially, from 210 in 2000 to 14,056 in 2003
- IVT injection performed in earlier years was predictor for endophthalmitis
  - Decreased from 1.9 / 100 injections in 2000/2001 to 0.4 / 100 injections in 2003

Jingping Mo, Yinkang Duan, Manju Patel, Ronald Klein, Ingrid U Scott, Kui Huang, Duanping Liao. Risk of Intravitreal Injection-Related Endophthalmitis in Patients with Age-Related Macular Degeneration (AMD) in the US Medicare Population. The 22nd ICPE & Therapeutic Risk Management, Lisbon, Portugal, August 24-27, 2006
### Real World Database Studies
Phase II Medicare Study (Post-approval FDA commitment)

<table>
<thead>
<tr>
<th><strong>Objectives</strong></th>
<th>Estimate incidence of IVT injection-related endophthalmitis among AMD patients after Macugen launch</th>
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<tr>
<td><strong>Design</strong></td>
<td>A cohort study of all Medicare beneficiaries who received an IVT injection for AMD in 2005-2006</td>
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<td>The use of IVT injection for AMD treatment increased significantly, 85,943 patients in 2005 and 160,560 patients in 2006</td>
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<tr>
<td><strong>Key Findings</strong></td>
<td>The incidence of IVT injection-related endophthalmitis decrease over time</td>
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<td>- From 0.16 in 2005 to 0.12 per 100 injections in 2006</td>
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Need For Non-Routine Intervention

- Is routine pharmacovigilance sufficient?
- Are additional interventions needed to minimize an important risk?
  - “Risk minimization” includes interventions that may reduce the occurrence or severity (or both) of a risk or a harm or its outcome
  - What is the goal of each proposed intervention?
  - What interventions can be implemented and will they be effective?
Traditional and Non-Routine Interventions

- **Traditional Risk Interventions**
  - Label changes, Black Box labels
  - Dear HCP letters

- **Non-Routine Interventions**
  - Medication Guides
  - Patient Informed Consent
  - Physician education, authorization or registration
  - Registries or required surveillance
  - Restricted Distribution
Risk Evaluation and Mitigation Strategies (REMS) Effective 25Mar2008

- FDA can require for NDA or approved drug; sponsor can propose voluntarily
- FDA has authority to impose penalty for non-compliance
- Typically 30 or 60 days to submit response to REMS request

- May include:
  - Medication Guides
  - Risk communication plans
  - Elements to ensure safe use (“ETASU”), Restricted access to product

- Required to Assess REMS
  - Typically 18 months, 3 years, and 7 years from REMS approval date
  - May include: patients/physicians’ understanding of risks and safe use; compliance of prescribers to labeling; ultimately reduced event rates
  - Final assessment plans should be submitted to the FDA for approval at least 90 days before the initiation of the assessment
Risk Minimization Measures (RMMs) in the EU

- RMP section covering assessment of risk minimization tools’ effectiveness
- Direct measurement of risk minimization employed whenever feasible
- No pre-specified assessment timelines

An Example of What to Measure

- **Aim**: Objective of Risk minimization tools (education program)
- **Risk Minimization tool**: Education brochure (MD/Pt); patient wallet card
- **Evaluation measure**:
  - **Survey** *(Process Indicator)*
    - Did the educational material arrive (for pts and MD)?
    - Did the MD/pt read it?
    - Did the MD/pt understand it (knowledge assessment)?
    - (Pre/post measurement once intervention has been implemented)
  - **Drug utilization/EMR/EHR study** *(Outcome Indicator)*
    - Has the educational materials/program or intervention impacted the MD/pt behavior
    - Is there evidence of behavior change- i.e. better alignment with treatment protocol and improved health outcomes or a reduction in adverse events)
Measuring the impact of ‘Dear Doctor’ letters on prescribing of contraindicated medications (1)

Figure 1
Number of Cisapride Dispensings per Month

Measuring the impact of ‘Dear Doctor’ letters on prescribing of contraindicated medications (2)

Figure 3
Monthly Codispensing Percentages for Contraindicated Drugs:
Overlapping Supply Days

- Explicit Drugs, Feb/Oct 95
- Example Drugs, Jun 98
- Implied Drugs, Jun 98

The effectiveness of varenicline medication guide for conveying safety information to patients: a REMS assessment survey

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ABSTRACT

Purpose Risk Evaluation and Mitigation Strategies (REMS) include various mechanisms to enhance safe use of medications, including a patient medication guide (MG) that provides key information regarding the potential risks associated with the medication. To evaluate the effectiveness of the varenicline MG as a REMS tool for educating patients, we undertook a survey among patients who were dispensed varenicline.

Methods Varenicline recipients within the Optum Research Database, a large U.S. administrative claims database, were invited to participate in a self-administered survey. Survey questions were general (receipt and reading of the MG) and specific regarding patient’s understanding of the potential varenicline risks outlined in the MG (neuropsychiatric symptoms, skin reactions, and allergic reactions).

Results From 3568 varenicline recipients invited, 640 (18%) responded, with 633 completing at least one of three risk-comprehension questions. The majority (93%) indicated receiving the MG, and 86% read all or part of it. Ninety-one percent, 41%, and 53% correctly answered at least one question on neuropsychiatric symptoms, skin reactions, and allergic reactions, respectively. A higher proportion who read the MG had correct responses to the risk-comprehension questions than those who did not read it.

Conclusions The varenicline MG was widely received and read among survey respondents, and the information conveyed was generally well understood regarding potential risk of neuropsychiatric symptoms. This study provides an assessment of the effectiveness of the varenicline MG in communicating information about potential risks associated with varenicline. This assessment method may apply to the evaluation of the effectiveness of other MGs. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—REMS; medication guide; varenicline; smoking cessation; survey; risk management; risk mitigation evaluation; pharmacoepidemiology
• **Assessment Objectives:** To assess compliance with and effectiveness of SmPC for cabergoline after changes were implemented in July 2008

• **Study Design:** Pre/Post Cohort study (Drug Utilization Study) of patients prescribed cabergoline Jan 2006 - Dec 2011
  - 5 EU databases, ~9.2M individuals
    - The Health Information Network (THIN) – (UK)
    - Integrated Primary Care Information (IPCI) - (NL)
    - PHARMO – (NL)
    - Aarhus healthcare registries – (DK)
    - Health Search Database (HSD) Thales – (IT)
  - **Substudy:** measure incidence/prevalence of CVR pre & post SmPC changes at 3 neurological centers in Italy (results not presented)
Cabergoline RMM Evaluation: Results

- >57 million person-years (PY) of observation
- Annual incidence of cabergoline use for the prolactin reduction indication [♀] declined slightly between 2006 (pre SPC changes) and 2011 (post SPC changes) except in Aarhus (DK)

“Big Epidemiology”
“Big Epidemiology”
Potential Use for Signal Detection and Refinement

How to best utilise the wealth of Real World Data and does its value change depending on purpose?

Product Approval & Launch

Signal Detection
- Any Medical Event
- Designated Medical Events

Signal Refinement

Signal Evaluation

Rapid
Detect the unexpected
Less persuasive

Time Consuming
Test the anticipated
Convincing

"Big Epidemiology"
Use of Natural Language Processing (NLP) in Humedica

IBD Population Identification

Liver Disease (LD) Surveillance Pop Identification

LD Surveillance Pop with LD Indicators

NLP terms Identification for Defining LD Cases

LD Surveillance Pop with LD NLP Terms

Define the Final Set of LD Cases by Applying Case Selection Algorithm

Assess the Contribution of Unstructured Data in Identifying LD Cases

X Zhou, L Weiss, AM Walker, A. Ananthakrishnan, R Shen, RE Sobel, A Bate, RF Reynolds. What does natural language processing add to the structured data available in medical records? Abstract to be presented at 2014 ICPE Taiwan and manuscript being prepared for journal submission.
Concluding Comments (1)

• Labeling is the cornerstone of risk management and the foundation for managing the risks of products
  – A formal Risk Management Plan is required in certain jurisdictions (may be disclosed to public)
  – Risk minimization or mitigation strategies may be needed to ensure that benefits outweigh risks
    o Science evolving rapidly
  – Effectiveness measurements may inform tool application and modification

• Risk management planning is iterative
  – A “Reference” RMP provides a cornerstone for global application that may require local adaptation
Concluding Comments (2)

• Epidemiology’s contributions to risk management
  – A key component of development and post-approval safety assessment
    o Background epidemiology of indication(s) and adverse events
    o Active surveillance
    o Post-approval safety studies
    o Evaluation of risk management/minimization interventions
  – Focus early in candidate development leads to best outcomes
  – Evidence from real world important in benefit-risk decisions

• “Big Epidemiology” changing risk management and role of epidemiology
  – IMEDS (reaganudall.org), IMI PROTECT (imi-protect.eu), EU-ADR (eudar-project.org)
Thank You!