Safety Evaluation in the Post-Marketing Environment: Overview and Analytical Considerations

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Aaron B. Mendelsohn, MPH, PhD
Pierre Engel, PharmD PhD
Your Presenters

Aaron B. Mendelsohn
*Director of Epidemiology, Quintiles Outcome*

Aaron Mendelsohn is Director of Epidemiology at Outcome, in Cambridge, Massachusetts and St. Prex, Switzerland. Dr. Mendelsohn possesses considerable expertise in epidemiologic methods, infectious disease epidemiology, and pharmacoepidemiology. Prior to joining the Outcome team, Dr. Mendelsohn headed the drug safety epidemiology and product risk management functions for two biotechnology companies. He is an alumnus of the Center for Disease Control and Prevention’s Epidemic Intelligence Service (EIS) where he was assigned to the U.S. Food and Drug Administration with the primary responsibility of conducting active surveillance for adverse drug events. In addition to his experience in government and corporate settings, Dr. Mendelsohn has strong ties to academia, having served on the Research Faculty at the University of Pittsburgh, and presently holding Adjunct appointments with George Washington University, Walden University and the University of Liverpool. He has authored/co-authored approximately 100 peer-reviewed publications and scientific presentations at international and domestic meetings. Dr. Mendelsohn is an active member in several professional societies and currently serves as Section Councilor for the Epidemiology Section of the American Public Health Association.

Pierre Engel
*Epidemiologist, Quintiles Outcome*

Pierre Engel is an Epidemiologist for Quintiles Outcome. Dr. Engel has strong expertise in designing prospective and retrospective studies to address real world evidence gaps. Pierre holds a doctorate of Pharmacy, a Master of Public Health and a PhD in Epidemiology. He is member of the HTA Working Group at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance and published in various peer-reviewed journals in epidemiology. He has been involved for six years on international observational studies in various therapeutic areas Pierre previously worked at the French National Institute of Health in charge of developing epidemiological studies on existing data in women’s health. He joined Quintiles-Outcome after having held the position of Epidemiologist in a medium-size CRO responsible for scientific oversight of observational studies.
1. Need for assessing safety following market approval
2. Initiatives for assessing benefit-risk balance
3. Approaches for evaluating safety in post-marketing
4. Challenges in analyzing and interpreting data from safety studies and ways to address these challenges
Today’s Webinar Audience

- Academia
- Biostatistician
- Clinical Operations
- Epidemiology
- Health Economics/Health Outcomes
- Medical Affairs
- Market Access
- Regulatory Affairs
- Risk Management
- Other
Introduction

Aaron B. Mendelsohn
Why do we need to evaluate safety in the post-marketing setting?
Small numbers of patients

For medicines intended for chronic use, the number of patients studied before marketing is insufficient to evaluate safety...

Ref: PLOS Medicine, March 2013, Volume 10(3):e1001407.
Small numbers of patients (cont.):

- Rare adverse events may not be seen with sample sizes under investigation

- Typically, 500-3000 patients are exposed to a drug during Phase III investigations

- “Rule of 3”:
  > If we study 3,000 patients, 95% confidence of detecting at least one of an AE occurring at a true frequency of 1 in 1,000 persons

New or not well-understood risk

A safety discontinuation rate of 3.5% of the products approved in the study period

Off-label use

Off-label Prescribing Among Office-Based Physicians

David C. Radley, MPH; Stan N. Finkelstein, MD; Randall S. Stafford, MD, PhD

**Background:** Unlike medicines prescribed for Food and Drug Administration-approved indications, off-label uses may lack rigorous scientific scrutiny. Despite concerns about patient safety and costs to the health care system, little is known about the frequency of off-label drug use or the degree of scientific evidence supporting this practice.

**Over 20% of use of Rx products found to be off-label.**

**Results:** In 2001, there were an estimated 150 million (95% confidence interval, 127-173 million) off-label mentions (21% of overall use) among the sampled medications. Off-label use was most common among cardiac medications (46%, excluding antihyperlipidemic and antihypertensive agents) and anticonvulsants (46%), whereas gabapentin (83%) and amitriptyline hydrochloride (81%) had the greatest proportion of off-label use among specific medications. Most off-label drug mentions (73%; 95% confidence interval, 61%-84%) had little or no scientific support. Although several functional classes were associated with increased off-label use (P<.05), few other drug characteristics predicted off-label prescription.

**Conclusions:** Off-label medication use is common in outpatient care, and most occurs without scientific support. Efforts should be made to scrutinize underevaluated off-label prescribing that compromises patient safety or represents wasteful medication use.

*Arch Intern Med.* 2006;166:1021-1026
Off-label use: particular concern in certain populations

“50-75% of drugs used in pediatric medicine have not been adequately studied to provide appropriate labeling information.”

Drug-drug interactions

Up to 30% of all ADEs are due to drug-drug interactions.

Delayed effects and effects associated with long-term use

In utero exposure of women to DES is associated with a high lifetime risk of a broad spectrum of adverse health outcomes.
Where do we get drug safety data?

Product Life Cycle

Discovery / Preclinical  Clinical Development  Post-Approval

FIM Ph I  Ph II  Ph III  Ph IV

Exposure (Potential Denominator)
Safety is more than dealing with risk
### Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making

Draft PDUFA V Implementation Plan - February 2013
Fiscal Years 2013-2017

#### Figure 1: FDA Benefit-Risk Framework

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
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<tbody>
<tr>
<td>Analysis of Condition</td>
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<td>Current Treatment Options</td>
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<td>Benefit</td>
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<td>Risk</td>
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<td>Risk Management</td>
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**Benefit-Risk Summary Assessment**

CHMP Reflection Paper on Benefit-Risk Methods

European Medicines Agency

London, 19 March 2008

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON BENEFIT-RISK ASSESSMENT METHODS IN THE CONTEXT OF THE EVALUATION OF MARKETING AUTHORISATION APPLICATIONS OF MEDICINAL PRODUCTS FOR HUMAN USE

Key Points:
• Expert judgment expected to remain cornerstone of BR evaluation
• Important benefits and medically serious risks can be identified
• Strengths of evidence and uncertainty are identified and quantified
• Need to further research in BR assessment

ENCePP

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

- Collaborative, scientific network coordinated by EMA to bring together expertise and research resources in pharmacoepidemiology and pharmacovigilance across Europe.
- Brings together >170 academic and hospital-based research centres, providers of healthcare data and specialised networks
- Facilitates the conduct of high-quality, multi-centre, independent studies of medicines focusing on safety and benefit-risk

http://www.encepp.eu
PROTECT

- Funded by the European Community’s Seventh Framework Programme (FP7/2007-2013) for the Innovative Medicine Initiative

- **Goal**: Generate more reliable pharmacoepidemiologic data for proactive pharmacovigilance & risk management of medicines throughout their lifecycle
PROTECT: Classification of benefit-risk approaches

Figure 2. Classifications of benefit-risk assessment approaches

Protect. Review of methodologies for benefit and risk assessment of medication
Prior to new guidelines, PSURs were focused on safety (risk) data.

Module VII – requires new information on efficacy and effectiveness, characterization of benefits, and benefit-risk analysis.

Wide range of sources including:
- Non-clinical and clinical studies
- Observational research
- Patient support programs
- Literature reviews and meta-analyses
Risk Management

An iterative process for balancing risk-benefit profile

Approaches for Assessing Safety in the Post-Marketing Environment
### Safety in the post-marketing setting

*Multiple approaches exist for evaluating safety in the post-marketing environment*

#### Approaches for Evaluating Safety in Post-Marketing

<table>
<thead>
<tr>
<th>“Passive”</th>
<th>“Active”</th>
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<tbody>
<tr>
<td>• Routine pharmacovigilance, AE reporting</td>
<td>• Active AE surveillance (intensive monitoring, PEM)</td>
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<td>• Meta-analysis of existing trial data</td>
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<td></td>
<td>• Additional clinical trials and extension studies</td>
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<td></td>
<td>• Registries &amp; prospective studies with broad eligibility criteria</td>
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<td></td>
<td>• Drug utilization/patterns of use studies</td>
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<td></td>
<td>• Surveys of knowledge, attitudes, and behaviours</td>
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</table>

*Approaches are not mutually exclusive*
# Real-world data for safety studies

<table>
<thead>
<tr>
<th>Primary Data Collection</th>
<th>Retrospective Designs</th>
<th>Prospective Designs</th>
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<tbody>
<tr>
<td>Medical Chart Review</td>
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<td>Pragmatic Trials</td>
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<td>Cohort Studies/Registries</td>
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<td></td>
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<td>Health Surveys</td>
</tr>
<tr>
<td>Secondary Data Collection</td>
<td>Administrative Claims EMR</td>
<td>Automated EMR Data Feeds</td>
</tr>
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Long-term safety study: SCAAR

Long-Term Safety and Efficacy of Drug-Eluting versus Bare-Metal Stents in Sweden

Stefan K. James, M.D., Ph.D., Ulf Stenestrand, M.D., Ph.D., Johan Lindbäck, M.Sc., Jörg Carlsson, M.D., Ph.D., Fredrik Scherstén, M.D., Ph.D., Tage Nilsson, M.D., Ph.D., Lars Wallentin, M.D., Ph.D., and Bo Lagerqvist, M.D., Ph.D., for the SCAAR Study Group*

ABSTRACT

BACKGROUND
The long-term safety and efficacy of drug-eluting coronary stents have been questioned.

METHODS
We evaluated 47,967 patients in Sweden who received a coronary stent and were entered into the Swedish Coronary Angiography and Angioplasty Registry between 2003 and 2006 and for whom complete follow-up data were available for 1 to 5 years...
Real-world drug utilization: RADIUS

- Real world, prospective, 5-year, observational study of 10,000+ patients with RA
- Designed to examine utilization patterns of DMARDs, biologics, and combination therapies
- Safety and effectiveness, including long-term outcomes, also served as study objectives

The Antiretrovirals in Pregnancy Registry: A Fifteenth Anniversary Celebration

Hugh H. Tilson, MD, DrPH,*
Peggy A. Doi, BSMT,† Deborah L. Covington, DrPH,‡ Artist Parker, MD, MPH,§
Kristine Shields, MSN, MPH,¶ and Alice White, PhD∥

the FDA’s review of the registry data resulted in a change in the FDA pregnancy labeling category from FDA pregnancy Category C (risk cannot be ruled out) to Category B (no evidence of risk in humans) (3) and inclusion of the results of the registry in the prescribing information. Additionally, the data was included in the CDC sexually transmitted disease (STD) treatment guidelines (4).
Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release and Long-Acting Opioids

On July 9, 2012, FDA approved a risk evaluation and mitigation strategy (REMS) for extended-release (ER) and long-acting (LA) opioid medications.

ER/LA opioids are highly potent drugs that are approved to treat moderate to severe persistent pain for serious and chronic conditions (list of ER/LA opioid products). The misuse and abuse of these drugs have resulted in a serious public health crisis of addiction, overdose, and death.

The REMS is part of a multi-agency Federal effort to address the growing problem of prescription drug abuse and misuse. The REMS introduces new safety measures to reduce risks and improve safe use of ER/LA opioids while continuing to provide access to these medications for patients in pain.

Key Considerations in Safety Studies

• Formulate a research question(s)
• Identify available resources (sites, clinicians, patients)
• Translate questions of clinical interest into measurable exposures and outcomes
• Choose appropriate study design
• Determine sources of data
• Select patients for study
• Determine duration of follow-up
• Assess threats to internal and external validity
Methodological & Analytical Considerations

Pierre Engel
Polling Questions

- Question: In your opinion what is the most important challenge in conducting post marketing safety studies?
  - Regulatory
  - Operation
  - Scientific
  - Technology
### Validity

**Background**

Validity refers to whether what we are measuring is what we intend to measure.

**Internal Validity**

Internal validity refers to the extent to which the finding of the study accurately represent the causal relationship between an intervention and an outcome in the particular circumstances of an investigation.

**External Validity**

External validity refers to the extent to which the findings obtained from an investigation conducted under parallel circumstances can be generalized to other circumstances.

*Do not compromise internal validity in an effort to achieve generalizability*
Interpretation of Data

**Selection Bias**

- Systematic error from differences in characteristics between those studied and not studied
- Relates to generalizability of the study population
  > Sampling frame should be representative of the target population
- Participation rate needs to be evaluated, along with inclusion/exclusion criteria
  > Differences between participants and non-participants
  > How broad are inclusion/exclusion criteria
Channeling bias, selective prescribing, or confounding by indication/confounding by severity is a form of selection bias where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences. 

> e.g. sicker patients or difficult to treat patients being more likely to receive a new drug

Severe asthmatics were most likely to be switched to inhaled fenoterol from salbutamol, thus creating the appearance of a worse safety profile for fenoterol
Interpretation of Data

Immortal time bias

- Period of cohort follow-up time were outcome cannot be observed
- Can lead to spurious associations *(favours the group including immortal time period)*
- Mitigation
  > Matching
  > Time-dependent exposure
Depletion of susceptibles

• Differential selection of less susceptible subjects overtime

• Impact on results

Example:
Past drug use is a potential risk modifier. Patient staying on a drug more likely to show good tolerance (Moride & Abenhaim 1994)

Follow-up attrition in alcohol treatment studies
According to a report released today...

Methods to account for confounding

> Design
- Randomization
- Matching
- Restriction

> Analysis
- Stratification
- Multivariable adjustment
  » Traditional multivariable adjustment
  » Inverse probability of treatment weighting
  » Propensity score adjustment (stratification, matching, adjustment)
Ex: Propensity Score Analyses  
Antidepressant Use and Suicide

<table>
<thead>
<tr>
<th>Antidepressant $^b$</th>
<th>Unadjusted</th>
<th>Adjusted for Age, Sex, and Calendar Year</th>
<th>Adjusted for Propensity Score Decile $^c$</th>
<th>Adjusted for High-Dimensional Propensity Score Decile $^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Citalopram</td>
<td>0.63 (0.47-0.85)</td>
<td>0.97 (0.63-1.50)</td>
<td>0.86 (0.56-1.32)</td>
<td>1.00 (0.63-1.57)</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>1.22 (0.83-1.79)</td>
<td>1.28 (0.86-1.90)</td>
<td>1.09 (0.73-1.63)</td>
<td>0.98 (0.63-1.51)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>0.95 (0.74-1.22)</td>
<td>1.12 (0.87-1.46)</td>
<td>0.98 (0.75-1.28)</td>
<td>1.02 (0.77-1.35)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>0.75 (0.55-1.01)</td>
<td>0.86 (0.64-1.17)</td>
<td>0.72 (0.53-0.99)</td>
<td>0.75 (0.53-1.05)</td>
</tr>
</tbody>
</table>

- Compared traditional multivariable, PS adjusted, and hdPS results
- Concluded with increasing adjustment results appeared closer to null, which suggests further control for confounding

Schneeweis, et al. Arch Gen Pysch 2010
Sampling

What does it mean for the sample to be representative?

Study Objective
- Treatment Patterns
- AEs occurrence / Profile

Target Population Level
- Site / Physician
- Patient

Possible Strata
- Physician Specialty
- Geography
- Practice size
- Age, Gender
- Aes & Tx duration
Sample size

Risk minimization survey

- Optimal sample size for surveys has not been specified by regulators. EU GVP module XVI, FDA notes that surveys range from a handful of respondents to ~500.

- Sample size is based on the following assumptions:
  - Proportion of patients who will answer a question incorrectly
  - Acceptable margin of error

<table>
<thead>
<tr>
<th>Proportion of “Fail” responses for each question</th>
<th>10%</th>
<th>25%</th>
<th>50%</th>
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<tbody>
<tr>
<td>95% CI (%) (margin of error +/-5%)</td>
<td>5-15</td>
<td>20-30</td>
<td>45-55</td>
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<tr>
<td>Sample size</td>
<td>138</td>
<td>288</td>
<td>384</td>
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<tr>
<td>Issue</td>
<td>Impact/Solution</td>
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<tr>
<td>Access</td>
<td>• Needs time, approval and quality data in claims such is not typically available.</td>
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<td></td>
<td>• ICF waiver or ad-hoc chart review</td>
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<tr>
<td>Sample size</td>
<td>• Some stratification may be limited due to overall sample size</td>
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<tr>
<td></td>
<td>• Active monitoring/capping for subgroups</td>
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<tr>
<td>External validity</td>
<td>• Sampling frame, patient screen log,</td>
<td></td>
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<tr>
<td></td>
<td>• CALMAR, calibration methods</td>
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<tr>
<td>Confounding and effect modification in longitudinal analyses</td>
<td>• Consideration for time dependent variables and dynamic exposure</td>
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<tr>
<td>Missing data</td>
<td>• Assessment of the pattern of missing data – is it related to exposure, other predictors of outcome</td>
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<td></td>
<td>• Use of sensitivity analyses</td>
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Missing data

- Single imputation methods are not recommended
- Missing at random assumption should be evaluated
- Complete case analysis is simple, may serve as a sensitivity analysis
- If data do not exist (not really “missing”), consider dummy variable adjustment method
- Maximum likelihood methods use all data
- Probability weighting methods can be used to adjust for confounding and account for loss to follow-up (or treatment discontinuation)

Ref: James H. Ware et al. Missing Data NEJM Aug 2012
Conclusion
Summary

1. Need for assessing safety following market approval
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Q&A

Contact Information:

Aaron B. Mendelsohn
Aaron.Mendelsohn@quintiles.com

Pierre Engel
Pierre.Engel@quintiles.com