Introducing Patient-Reported Outcomes into EMA-mandated Post-Authorization Safety Studies and FDA-Mandated Post-Marketing Safety Commitments

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Chair Overview

- My perspective: as qualified person for pharmacovigilance (QPPV)
- US and EU perspectives:
  - What can we learn from patient outcomes research and real-world post-market studies?
  - What constraints, if any, contribute to differences in the design and/or operations of post-market studies in the EU versus the US.
- Emphasis is on:
  - Practical application rather than regulatory policy
  - Identifying and predicting hurdles
  - Suggesting solutions

Workshop Topics

- Workshop Key Questions
- Background and Current Landscape
- Mandated post-authorization studies – Definitions and Outcomes of Interest
  - Post-authorization Safety Studies (PASS)
  - Post-authorization Efficacy Studies (PAES)
  - Post-marketing Requirement Studies (PMR)
- Expanding Objectives and Outcomes Beyond Safety
- Case Study
- PASS + HEOR Design Overview and Scientific Approach
  - Hypothetical Design
    - Overview of common design parameters
- Opportunities and Challenges
- Summary of Recommendations
Workshop Key Questions

- What are the market forces contributing to the need for multi-faceted post-market study designs?
- How are mandated post-market studies defined?
  - What is a PASS? What is a PAES? What is a PMR?
- When and how can PRO and other HEOR outcomes be incorporated into safety studies such as a PASS or PMR?
  - What evidence needs can the inclusion of these outcomes address?
- What new trade-offs or considerations must be addressed when collecting both patient-reported safety as well as HEOR Outcomes of interest?
- Will studies in the US be applicable to EU requirements and vice versa?
- How could these new mandates and increased post-market evidentiary requirements affect the sponsor’s internal processes?

Background and Current Landscape

- Current environment presents formidable challenges:
  - Likely that authorities will continue to tighten regulatory processes in relation to market access and pricing
  - Evidentiary requirements increasing but research dollars decreasing
  - Market is increasingly study design astute
    - Acceptability of some features of design vary between EU and US
  - Peer review of studies extremely rigorous - publication in top tier journals can be challenging
- Convergence of Regulator and Payer Evidence Needs warrants:
  - Early planning and alignment of Sponsor internal stakeholders
  - Efficient study designs and operational execution
  - Coordinated, strategic approach to post-market evidence gathering
    - Critical review, organization, and prioritization of research questions is paramount
Convergence of Regulators & Payers (Eichler, 2010)

Paradigm Shift (Prof. Mondher Toumi, MD, Lyon)

"Decision Point to Decision Window..."
Strategic Area 3: Optimising the Safe Use of Medicines

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<tr>
<th>Objectives</th>
<th>Impact/Result Indicators</th>
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<tr>
<td>Strengthen the evidence base in the post-authorization phase to enable better regulatory decision-making.</td>
<td>A regulatory model which facilitates the post-authorization collection of data on benefits and risks of medicinal products is put at the disposal of the Regulatory System.</td>
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<td>Enhance patient safety by avoiding unnecessary risks to patients as a result of the use of medicines.</td>
<td>A revised risk management concept, which targets both novel pharmacovigilance methodologies as well as a risk minimisation toolbox better adapted to reduce harm, is available.</td>
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<td>Become a reference point on information for medicines evaluated by the Agency.</td>
<td>A high-quality, informative and targeted set of information on medicines, falling within the sphere of the Agency’s responsibilities, is proactively put at the disposal of the EU Regulatory System Network at the moment of licensing/updating of the marketing authorisation.</td>
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<td>Improve the decision-making process by taking due account of patient experience, hence contributing to the rational use of medicines.</td>
<td>Conclusions from outcome research projects analysing the impact of the regulatory decisions on public health are used to provide input in future regulatory policy decision-making.</td>
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Post-authorization Safety Studies (PASS)

- Defined in Directive 2001/83/EC (DIR) Art 1(15) as any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of work management measures
  - EMA/813938/2011 GVP Module VIII with revision 1 on 19 April 2013
- Possible methodologies
  - Retrospective Drug Utilization studies (DUS)
    - Databases
    - Primary data collection
  - Prospective Studies and Registries
  - Other observational studies including surveys
  - Pragmatic trials
- Scientific guidance should be considered for design, conduct and reporting
  - ENCePP, ISPE GPP
- PASS should be registered electronically with EU PAS Register

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Defining a PASS...

- Study is defined a PASS on the basis of study objectives not methodology employed
  - Not constrained by type of design selected
- Non-interventional
  - Protocol does not mandate particular treatments, nor medical interventions
    - Usual care treatment decision made prior to PASS enrollment
- Main aim must include one or more of the following objectives:
  - Quantify potential or identified risks
  - Evaluate risks of drug in populations where safety information is limited or missing
  - Evaluate risks of drug after long-term use
  - Provide evidence of absence of risks
  - Assess patterns of drug use that add information related to drug safety
  - Measure effectiveness of a risk minimization activity

Post-authorization Efficacy Studies (PAES)

- The PV legislation refers to the possibility of requesting the marketing authorization holder to conduct post-authorization efficacy studies (PAES)
  - Articles 9(4)(cc) and 10a(1) of Regulation (EC) 726/2004
  - Articles 21a and 22a(1) of Directive 2001/83/EC
- Aim is to complement efficacy data that are available at the time of the initial authorization
  - Effectiveness and relative effectiveness data often warranted
  - Legislation opens door to opportunities for pragmatic trials and effectiveness outcomes
- Public consultation open until February 18, 2013. Specific questions posed to public and private stakeholders
  - See PCPAES/12/01 – Public Consultation on PAES
PAES Methods Development for Real-World Studies...

- EMA Workshop 607/212/2013: While it is recognized that interventional explanatory trials may not answer all questions related to efficacy in everyday medical practice, the experience of pragmatic trials and observational studies for measuring it is limited.
- Differing design options and analytical techniques need to be addressed with consideration of methodological aspects such as:
  - Most appropriate study design for the research question and hypotheses to be tested
  - Frequency of exposure as occurring without intervention in the study population
  - Endpoint(s) in terms of frequency, time to onset and measurement accuracy
  - Biases and confounding factors, measured and unmeasured, and their control
  - Inferences about effectiveness relating to particular interventions
  - Feasibility, efficiency and timelines
  - Definition and quality of data sources on exposure, outcomes and covariates in the context of the research question
  - Generalizability of findings
- Incorporation of PROs that measure effectiveness not explicitly highlighted

FDA Amendments Act of 2007 Regarding Post Marketing Requirement Study (PMR)

- A post approval study or clinical trial can be required on the basis of scientific data, including information regarding chemically-related or pharmacologically-related drugs.
  - To assess a known serious risk
  - To assess signals of a serious risk
  - To identify an unexpected serious risk when available data indicate the potential for a serious risk
- Or if there is new safety information for a marketed product
Study Design Options under FDAAA

- FDA weighs various options
  - The active post market risk identification and analysis system (i.e., database analysis)
  - A post approval observational study
  - Randomized clinical trial (RCT)

- This is a hierarchy, with RCT considered only if the other 2 options are not feasible to achieve the objectives

PASS / PMR - Expanding **Objectives** Beyond Safety!

- Meet post-market regulatory and payer requirements
- Understand value of new product
- Observe disease, including heterogeneity
- Understand current care patterns, outcomes and identify unmet needs in routine medical care
- Understand relationship between treatments and outcomes
- Understand facilitators/barriers to initial use and appropriate adherence
- Monitor "off label" uses and other unknown usage issues
- Provide continuous source of data for benefit-risk & value dissemination with publications and presentations
- Establish Sponsor as a credible player in this therapeutic area
- Build and maintain relationships with key practitioners
PASS / PMR - Expanding Outcomes Beyond Safety!

Population characteristics
- Real-world versus RCT / external versus internal validity

Treatment Patterns and Resource Utilization
- Medications
  - Duration of treatment;
  - Line of therapy
- MD consults (Specialist versus GP / In-patient versus Out-patient
- Home nursing care
- ER visits and hospitalizations by ward type and LOS
- Procedures and diagnostics
- Medications: Rx & OTC

Lost productivity / opportunity costs

Quality of Life (QOL) / PROs
- Health status: Generic / Disease specific; Utilities

Treatment satisfaction

Persistence / compliance

Case Study

Haemophilia

ORIGINAl Article Treatment
The relative burden of haemophilia A and the impact of target joint development on health-related quality of life: results from the ADVATE Post-Authorization Safety Surveillance (PASS) study

R. KLAMROTH,* H. POLLMANN,* C. HERMANS,‡ A. FARADJI,§ A. S. YARLAS,* J. D. EPSTEIN,** and R. M. EWENSTEIN***

... “These data may be of significant interest to political or medical decision makers who have the ability to make broad policy changes that can affect haemophilia patients in their community.” (Page 419)
Hypothetical Design: PASS + HEOR Outcomes

Enrollment period: Eligibility screening

Follow-up Data Collection Period

Identification of eligible patients

- Usual Care Treatment Decision
- Identification of potentially eligible patients
- Enrollment of consenting and eligible patients
- Hypothetical routine care visit schedule
- Site-based data collection time points
- Direct to patient data collection time points (PROs, Treatment Satisfaction, self-reported Resource Use)

Overview of Key Opportunities and Challenges

- Data collection and the usual care paradigm
- Hawthorne Effect
- Patient-reported Outcomes
  - Non-Interventional study status and patient questionnaires
  - Direct to patient data collection
  - HRQoL: Impact of side effects / drug tolerability for safety reporting
- Health Economic Outcomes
  - Payers and need for post-market resource use patterns and costs of care
    - Focus on hospitalizations for costing and implications for safety monitoring
Data Collection and the Usual Care Paradigm

- Challenge is to balance need for some control (e.g., patient consent and enrollment) with need for data that reflect usual care and real-world outcomes
  - No mandated study visits
  - Visit frequency as per routine medical care
    - Data can be collected at each visit, or retrospectively at specified time points by abstracting from chart
    - If PROs should be collected at specific intervals, can consider direct to patient approach where feasible
- Studies should:
  - Minimize Hawthorne effect by limiting intrusion into usual care
  - Include a broad range of subjects
  - Reflect patients in actual practice
  - Include a variety of physician specialties
- The data are the data!
  - Must accept implications of naturalistic design particularly in terms of:
    - QC and data management processes
    - Response rates

PASS / PMR + PROs

- Non-Interventional study status and patient questionnaires
  - Interviews, questionnaires, and blood samples may be considered normal clinical practice
- Direct to patient: mode of data collection
  - Mail, phone, internet?
- PRO validation?
  - Must determine instrument properties in terms of how data are collected
    - Paper, phone interview, internet
  - PROs not a primary endpoint in PASS / PMR, but studies are mandated
    - The more important the data, the greater the need for high quality data
      - Site-based data collection versus direct to patient
- Treatment satisfaction
  - Side effects/Non-serious Adverse Events
- Implementation of sub-studies as an operational tactic to achieve flexibility
PASS + Health Economic Outcomes

- Payers need evidence including post-market resource use patterns and costs of care
  - Frequently focus of Health Economics data collection is on hospitalizations and related variables
    - Admission and discharge dates
    - Length of stay by ward type
    - ER visits
- Hospitalizations and ER visits are also safety variables requiring operational follow-up and reporting
  - Care must be taken to:
    - Avoid duplicate variables on Resource Use and SAE pages of the CRF
    - Ensure alignment between Sponsor Safety and HE professionals

PASS + HEOR: Process Issues

- Conduct of study design activities in collaboration with Sponsor internal stakeholders across a variety of disciplines
  - Epidemiology
  - Safety and Pharmacovigilance
  - Medical Affairs
  - Health Economics
  - Marketing
  - Local affiliates
- External stakeholders
  - KOLs
  - Regulators
  - Payers
  - Patient Advocacy groups
- Competing evidence requirements
  - Less is more
    - Balancing the “Must-haves” versus the “Nice-to-haves”
    - Substudies
To Succeed in this Evolving Landscape...

- Increasing evidence requirements and decreasing research dollars
  - Sponsors must begin planning early in drug development for safety and value demonstration evidence gathering *
  - Peri-approval Disease Registries
  - PRO Validations
- Critical to optimize study designs and streamline evidence development efforts
- Significant investments made by time of marketing
  - Achieve cost and timeline efficiencies by re-purposing study materials and operational observational study infrastructures from earlier product life-cycle
- Late Phase trends and evidence requirements can be anticipated

Strategies and Recommendations

- Build a value strategy to help streamline and prioritize post-market data collection initiatives
  - Aim is to employ the right design(s) for the purpose
- Efficiency is important but one design may not fulfill all objectives
- Involvement of internal and external stakeholders early in design phase adds quality and validity
  - Senior authorship will require early participation in design activities including direct contributions by KOLs
- Methodology must be balanced with practicality
  - A rigorous design includes feasible and practical logistics
Strategies and Recommendations

- Multi-national and multi-faceted evidence gathering in the context of PASS and PMR activities and timelines is feasible
  - Challenges can be foreseen and resources applied proactively
  - Set expectations appropriately
- Those at the helm of study design activities must offer leadership with respect to:
  - Scientific rigor
  - Operational efficiencies and streamlining
  - Transparency re: consequences of trade-offs between science and logistics

Q&A