Lessons Learned on the Design and Implementation of Post-Authorisation Safety Studies (PASS) under the *new* EU 2010 PV Legislation

Michelle Bulliard
Pierre Engel
28 January 2014
Polling Questions

• A small number of polling questions have been added to today’s webinar to make the session more interactive
Your Presenters

Michelle Bulliard  
**Vice President Clinical Operations and Regional Managing Director Europe, Quintiles Real-World & Late Phase Research**

Ms. Bulliard has over 20 years’ experience in running clinical studies, including real world & late-phase studies, patient registries, safety studies, and other specialized real-world programs for orphan drug, disease and medical device studies and studies monitoring effectiveness of risk minimization activities. With an extensive global portfolio, she has conducted many large and successful programs for a wide range of life sciences and healthcare organizations. Michelle is responsible for corporate strategic planning and program development, providing consultation to key clients and oversight for real world and late phase programs.

Pierre Engel  
**Epidemiologist, Quintiles Real-World & Late Phase Research**

Pierre Engel has seven years of experience with international observational studies in various therapeutic areas. Pierre holds a doctorate of Pharmacy, a Master of Public Health and a PhD in Epidemiology. He is a member of the Steering Group and the Health Technology Assessment (HTA) Working Group of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and has been published in various peer-reviewed journals in epidemiology. Pierre previously worked at the French National Institute of Health in charge of developing epidemiological studies on existing data in women’s health.
1. PASS: Review since the EU 2010 PV Legislation first published
2. Practical considerations in the conduct of PASS
3. Methodological considerations when designing a PASS
4. Future trends and perspectives for PASS
5. Q&A
PASS: Review since the EU PV legislation first published

Michelle Bulliard
EU 2010 PV Legislation

Putting it into perspective

Need For PV Change:
• 5% of all hospital admissions are for ADRs
• 5% of all hospital patients suffer an ADR
• ADRs are 5th most common cause of hospital death
• Estimated 197,000 deaths per year in EU from ADRs
• EU societal cost of ADRs € 79 Billion / year

Aim PV Legislation:
• To further strengthen pharmacovigilance
• To promote and protect public health by reducing burden of ADRs and optimising use of medicine

Acronym Key: Pharmacovigilance (PV), Adverse Drug Reaction (ADR)

5910 lives could be save per year
237 mio euro could be saved

Source: The new Pharmacovigilance legislation: an EMA perspective, IPA Conference, Jun11
A New Era of Safety

The Making of the new PV Legislation

Since then: what have we learnt about the design and conduct of post-authorisation studies (PASS) under the new PV legislation; in theory and in practice?
Prioritised Implementation of the PV Legislation by the EMA

PASS & PAES

*www.ema.europa.eu and www.encepp.eu*  *Quintiles Internal Data mining PRAC Minutes July 2012 to January 2014*
Good Pharmacovigilance Practices (GVP)

Module I
Pharmacovigilance systems and their quality systems

Module II
Pharmacovigilance system master file

Module III
Pharmacovigilance inspections

Module IV
Pharmacovigilance audits

Module V
Risk management systems

Module VI
Management and reporting of adverse reactions

Module VII
Periodic safety update reports

Module VIII
Post-authorisation safety studies

Module IX
Signal management

Module X
Additional monitoring

Module XI
Public participation (Q2 2014)

Module XII
Continuous pharmacovigilance (Q2 2014)

Module XIII
No longer under development

Module XIV
International cooperation (Q2 2014)

Module XV
Safety communication

Module XVI
Risk minimisation measures (Closed Aug 2013)

Published  Under Finalisation  Under Development

For more information on the GVP, please refer to the GVP information on the EMA Website.; www.ema.europa.eu
PASS Definition

“Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.”*

PASS initiated, managed or financed by a MAH:

- Pursuant to an obligation imposed by a competent authority
  - as a condition to the granting of the marketing authorisation, or after the granting of a marketing authorisation if there are concerns about the risks of the authorised medicinal product
  - as part of a marketing authorisation granted under exceptional circumstances.

- Voluntarily
  - studies required in the risk management plan to investigate a safety concern or evaluate the effectiveness of risk minimisation activities
  - any other PASS

* Directive 2001/83/EC (DIR) Art 1(15) *
## PASS Categories & Supervision

<table>
<thead>
<tr>
<th>Type of activity</th>
<th>In Annex II of Opinion (CAPs only)</th>
<th>Category in Summary table of PhV activities</th>
<th>Status</th>
<th>Supervised under Article 107m</th>
<th>Supervised under Article 107 n-q</th>
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<tbody>
<tr>
<td>Imposed PASS</td>
<td></td>
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<td></td>
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<tr>
<td>“Interventional”*</td>
<td>X</td>
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<td>Mandatory and subject to penalties</td>
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<td>Mandatory and subject to penalties</td>
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<td>Specific Obligation</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Non-interventional</td>
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<td>2</td>
<td>Mandatory and subject to penalties</td>
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<td>X</td>
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<tr>
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<tr>
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<td>3</td>
<td>Legally enforceable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-interventional</td>
<td></td>
<td>3</td>
<td>Legally enforceable</td>
<td></td>
<td>X</td>
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<tr>
<td>Stated</td>
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<td>Not enforced</td>
<td></td>
<td></td>
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<tr>
<td>Non-interventional</td>
<td></td>
<td>4</td>
<td>Not enforced</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Practical considerations in the conduct of PASS
Polling Questions

• Do you have experience in conducting Drug Utilisation Studies and/or Physician/Patient Surveys?
  • Yes
  • No
Examples of types of PASS included in RMPs and/or reviewed by PRAC \(^1, 2\)

- **Drug Utilisation Studies (DUS) and Surveys**
  - e.g. to assess the effectiveness of additional risk minimisation measures such as;
  - Monitoring product use in accordance with the SmPC (off-label use/medication error)
  - Verifying compliance of prescribers re. restricted indication in Controlled Distribution Program
  - Verifying HCP and/or Patient Understanding of Educational Programs
  - Verifying effectiveness of Pregnancy Prevention Program

- **Registries**
  - e.g. product exposure; to assess safety profile of (orphan) drugs
  - e.g. pregnancy registries following a product exposure
  - *Joint disease and product exposure registries*
  - *Joint registries with multiple MAH*

- **Database studies**
  - e.g. for risk characterisation, investigation of targeted AEs

- **Others**
  - e.g. published pharmacoepidemiological studies
GVP Module VIII

**NI PASS**

- **PASS Imposed**
  - Pursuant to an Obligation as a condition for MA

- **Draft protocol reviewed by PRAC if > 1 MS**
  - 60 days

- **Endorsement Letter**

- **Notification to Competent Authorities**
  - Art. 107n.3 of Directive 2010/84/EU

- **Local Requirements**
  - Not homogenized for non-interventional studies
    - Competent Authority requirements
    - Ethics Committees requirements
    - Data Protection Authority requirements

- **Final Study Report submitted to PRAC & NCA within 12 months of end of data collection**

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*Excerpt from PRAC Timetable: PASS Protocols made 27 January, 2014*
**GVP Module VIII**

**NI PASS**

**PASS Voluntarily Initiated and in RMP**

- Draft protocol reviewed by PRAC if > 1 MS
- 60 days
- No Endorsement Letter
- Comments to protocol are provided by PRAC

**Notification to Competent Authorities**

Recommended GVP Module VIII

**Local Requirements**

Not homogenized for non-interventional studies
- Competent Authority requirements
- Ethics Committees requirements
- Data Protection Authority requirements

**Final Study Report submitted to PRAC & NCA within 12 months of end of data collection**

*Excerpt from PRAC Timetable: PASS Protocols made 27 January, 2014*
Guidance for the format and content of the protocol for non-interventional PASS

Objectives

- Consistency in presentation and format of PASS protocols submitted by MAH
- Provision of essential administrative information
- Coverage of all important scientific aspects of a protocol


- Legal obligation for imposed NI-PASS since 10 Jan 2013
- Recommended for all other NI-PASS
PRAC Transparency of Activities

• **Agenda** is published on Day 1 of PRAC by mid-day [next meeting 3rd Feb 2014]

• **Meeting highlights** are published on Friday of PRAC week [next 7th Feb 2014]

• **Safety** referrals are published on Friday of PRAC week [next 7th Feb 2014]

• **Minutes** are published on the following month after adoption [next approx 6 weeks after meeting]

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**EMA website serves as the EU Medicines Web-portal**

www.ema.europa.eu
PRAC Volumes & Time

- EMA 7th Stakeholders forum on the implementation of the new Pharmacovigilance legislation 27 Sep, 2013

% PRAC plenary discussion time 2013 based on total hours:

- Signals: 10%
- Referrals: 33%
- PSURs: 16%
- RMPs: 19%
- Other: 14%

Graph showing volumes and time for different categories from Sep-12 to Jul-13:
- Other safety issues - MS
- Other safety issues - CHMP
- PhVig
- Inspections
- PASS
- PSURs
- RMPs
- Art.5(3) referrals

Graph indicating the distribution of PRAC plenary discussion time with respective percentages for each category.
The EU PAS Register

- The 2010 PV legislation requires that protocols and abstracts of results of PASS imposed as an obligation are published in a publicly available register*
- It also specifies that the final report of such studies must provide the date of registration in this register
- Registration must be made prior to the start of data collection
- For imposed studies: does not replace regulatory submission
- For studies conducted voluntarily: accepted by MS as means for submitting study information.**

Transitional period:
- ENCePP E-Register of Studies to be used
- Guide for study registration was amended for MAH-sponsored NI-PASS required by a regulatory authority:
  - Acknowledgment email sent by EMA to MAH
  - All Member States informed by EMA of the registration with: title, name of sponsor, countries, link to registry
- EU PAS Register is being developed as upgrade of ENCePP E-Register of Studies and will include already

* Articles 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC ** (Annex 1 of GVP Module VIII)

PAS=Post-authorisation Studies
EU PAS REGISTER
Meeting Goals of Transparency

Registered in E-Register of Studies

<table>
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<tr>
<th></th>
<th>06/06/2013</th>
<th>29/10/2013</th>
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<tbody>
<tr>
<td>Total no. of studies</td>
<td>111</td>
<td>165</td>
</tr>
<tr>
<td>ENCePP Seal Studies</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Studies registered by ENCePP centres</td>
<td>52</td>
<td>64</td>
</tr>
<tr>
<td>Studies requested by a regulator</td>
<td>n/a</td>
<td>83</td>
</tr>
</tbody>
</table>

Keys to Success
Right Operational Model for a PASS

- RIGHT SITES
- RIGHT PATIENTS
- RIGHT DATA

The Right Approach for The Right Question™
Methodological considerations when designing a PASS

Pierre Engel
# The Right Approach for the Right Question™

<table>
<thead>
<tr>
<th>Primary Data Collection</th>
<th>Retrospective Designs</th>
<th>Prospective Designs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Chart Review</td>
<td>Pragmatic Trials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cohort Studies/Registries</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Health Surveys</td>
<td></td>
</tr>
<tr>
<td>Administrative Claims EMR</td>
<td>Automated EMR Data Feeds</td>
<td></td>
</tr>
</tbody>
</table>
Polling Questions

- Does your organization plan to conduct PASS using secondary data collection?
  - Yes
  - No
Lessons learned from dialogue with PRAC and meetings minutes*

• Among the main reasons of rejection during the first round of review by priority
  • Inadequate study design to meet study objectives
  • Sample size and statistical analyses not enough detailed
  • Missing timelines
  • Lack of enrolment strategy, representativeness and geographical scope
  • Selection bias and confounding bias not addressed

• Need to include detail
  • Patient facing questionnaires,
  • Algorithms for event adjudication,
  • Data Management Aspects

# Design Mitigation Plan

**GPP (ISPE), Guide of Methodological Standards (ENCePP), GVP module VIII**

<table>
<thead>
<tr>
<th>Topic/Challenge</th>
<th>Impact/Solution</th>
</tr>
</thead>
</table>
| Exposure and outcomes | • Retrospective/prospective  
                      • New user designs, coding scheme, validate events |
| Sample size | • Subgroup of interest?  
               • Active monitoring/capping for subgroups |
| External validity | • Sampling frame, patient screen log  
                           • Calibration methods |
| Confounding and effect modification in longitudinal analyses | • Time dependent variables, use of propensity scores |
| Access to secondary source data | • Time, Data quality, ICF waiver |
| Missing data | • Pattern of missing data  
                • Use of sensitivity analyses |

Methodological Challenges

**Recent case studies**

- Selection/definition of comparator group for comparative study may be questioned:
  - must be justified based on expected mechanism of action for possible increase in risk and what is known about risk for currently available products
  - powering the sample size* as it often relates to minimum detectable relative risk (need for bigger sample size, lower detectable relative risk)

- Off label Use

Methodological Challenges

Sample size: risk minimisation survey

- Optimal sample size for surveys has not been specified by regulators. Upcoming GVP module XVI dedicated to risk minimisation evaluation to be published.
- 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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</thead>
<tbody>
<tr>
<td>95% CI (%) (margin of error +/-5%)</td>
<td>5-15</td>
<td>20-30</td>
<td>45-55</td>
</tr>
<tr>
<td>Sample size</td>
<td>138</td>
<td>288</td>
<td>384</td>
</tr>
</tbody>
</table>

Future trends and perspectives for PASS

Pierre Engel
Recent EU development in DUS

Claims data

Research question and objectives: The primary objectives of the DUS are the following:

- To describe the characteristics of new users of cilostazol according to (1) demographics, (2) baseline comorbidity including conditions listed in the SmPC and the risk management plan (RMP) as potential or identified safety concerns, (3) baseline and concurrent use of medications potentially interacting with cilostazol, and (3) specific comorbidity
- To describe the duration of the use of cilostazol and discontinuation patterns
- Secondary objectives of the DUS are to (1) quantify and describe off-label prescribing, (2) describe dosage patterns of the use of cilostazol, (3) to assess the proportion of patients who are hospitalised for any cause while treated with cilostazol, and (4) identify the medical specialties of physicians prescribing cilostazol.

Data sources: The study is proposed to be conducted in the following databases:

- The Aragón Institute of Health Sciences (Instituto Aragonés de Ciencias de la Salud [IACS]) database, Spain
- The Information System for the Advancement of Research in Primary Care (Sistema d’Informació per el Desenvolupament de la Investigació en Atenció Primària [SIDIAP]) database in Catalonia, Spain
- The German Pharmacoepidemiological Research Database (GePaRD ), Germany
- The Health Improvement Network (THIN), United Kingdom (UK)
- The Swedish National Databases.

Incorporating patient perspective
Support PRO-AEs in PASS

PROSPER Initiative:
PROSPER seeks to support the wider use of PRO-AEs. The scope of this guidance document, which was completed between July 2011 and November 2012, considered a host of domains related to PRO-AEs including definitions and suitable taxonomies, the range of datasets that could be used, data collection mechanisms, and suitable analytical methodologies.

++ Patient community involvement
• ENCePP
• EMA
2014 and beyond...

PASS Perspectives

• Encouraging use of disease registries, joint studies
• PASS – meta-analyses
• Data integration: multinational DB studies
• PAES, Pragmatic trials

Early dialogue with industry

• EMA workshops
• ENCePP surveys
• Adaptive registries
• Increasing transparency
Summary

Lessons Learned on the Design and Implementation of Post-Authorisation Safety Studies (PASS) under the new EU 2010 PV Legislation
Ensuring Success with your PASS

- Ensure robust governance in place
- Implement procedures, guidelines, and tools
- Assign the right multidisciplinary skill sets
- Staff training
- Collaboration & Communication
This is fine, I can see all the evidence I need from here.
Speaker Information

Contact Information:

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• Michelle.Bulliard@quintiles.com

Pierre Engel
• Pierre.Engel@quintiles.com
Upcoming Events

Real-World and Late Phase Research Webinars

Quintiles experts run regular webinars on Real-World & Late Phase services.

Topics include:

- DIABETES VALUE DEMONSTRATION
- ONCOLOGY VALUE DEMONSTRATION
- RARE DISEASE REGISTRIES
- EUROPEAN PHARMACOVIGILANCE LEGISLATION
- REGISTRIES 101
- MARKET ACCESS
- MAXIMIZING VALUE AND QUALITY IN PHASE IV

To register or view previous webinars please go to

www.quintiles.com/real-world-late-phase-webinars
Thank you

Questions?