Review of three years of Post Authorization Safety Studies (PASS) landscape under the 2010 European Pharmacovigilance

Pierre Engel
Priscilla Velentgas
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Your presenters

**Pierre Engel, Director, Epidemiology, Quintiles Real-world & Late Phase**

Pierre Engel has been involved for seven years on 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 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 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. He joined Quintiles after having held the position of Epidemiologist in a medium-size CRO responsible for scientific oversight of observational studies.

**Priscilla Velentgas, Sr. Director, Epidemiology, Quintiles Real-world & Late Phase**

Dr. Velentgas joined Quintiles in May 2009 and designs and oversees observational studies of drug and vaccine comparative effectiveness and safety, including multiple PASS studies and vaccine PASS. Prior to joining Quintiles, she was a faculty member in the Harvard Medical School Department of Population Medicine, and a Director of Epidemiology for Genzyme. Dr. Velentgas was the senior editor of the Agency for Healthcare Research and Quality publication: “Developing a Protocol for Observational Comparative Effectiveness Research” and is a co-leader of the development and validation of the GRACE initiative checklist for assessment of observational study quality for decision making. Dr. Velentgas received her MS and PhD in Epidemiology from the University of Washington School of Public Health and Community Medicine. She is based in Cambridge, MA.
Agenda

- Understanding EMA Post Authorisation Safety Studies (PASS)
- Applying the EU legislation and regulations in the conduct of post authorisation safety studies
- Lessons learned on the design and the conduct of observational post authorisation safety studies
- Trends in regulatory required post authorisation studies: PAES
Today’s webinar audience

- Academia: 25%
- Biostatistician Qtr: 9%
- Clinical Operations: 17%
- Epidemiology: 7%
- Health Economics/Health Outcomes: 4%
- Market Access: 18%
- Medical Affairs: 12%
- Risk Management: 7%
- Other: 1%
A small number of polling questions have been added to today’s webinar to make the session more interactive.
Understanding EMA post authorisation Safety Studies (PASS)

Pierre Engel
**EU 2010 PV legislation**

*It has been estimated that almost 6000 lives could be saved per year and also a financial saving of up to 237 million euro*

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>EC decision to undertake assessment of PV system</td>
</tr>
<tr>
<td>2005</td>
<td>Independent study completed to map strengths &amp; weaknesses of EU PV system</td>
</tr>
<tr>
<td>2006</td>
<td>2006-2008: Research, consultation, policy development</td>
</tr>
<tr>
<td>2007</td>
<td>Commission strategy to strengthen &amp; rationalise pharma-covigilance</td>
</tr>
<tr>
<td>2008</td>
<td>Pharma Package adopted by Commission</td>
</tr>
<tr>
<td>2009</td>
<td>Final favorable vote in Parliament</td>
</tr>
</tbody>
</table>

A new era of safety putting it into perspective
A new era of safety

Ongoing change and new regulations

Dec 2010
Publication
Regulation (EU) No 1235/2010 and Directive 22010/84/EU

June 2012
Publication
Implementing Regulation on pharmacovigilance activities
Regulation (EU) 520/2012

March 2013
Publication
Regulation introducing a Black Symbol
Regulation (EU) No 198/2013

Feb 2014
Publication Delegated Regulation on post-authorisation efficacy studies
Delegated Regulation (EU) No 357/2014

2010
2011
2012
2013
2014
2015

Jan 2011- July 2012
Implementation period for new 2010 EU PV regulation

July 2012
entry into force new PV legislation

Oct 2012
Publication
Regulation (EC) 1027/2012 & Directive 2012/26/EU

Oct 2013
Publication and entry into force Regulation (EC) 1027/2012 & Directive 2012/26/EU,

May 2015
Entry into force Delegated Regulation (EU) No 357/2014
Good pharmacovigilance practices (GVP) 15 Modules

Module I
Pharmacovigilance systems and their quality systems

Module II
Pharmacovigilance system master file
Rev.1 12/04/2013

Module III
Pharmacovigilance inspections
Rev.1 15/09/2014

Module IV
Pharmacovigilance audits

Module V
Risk management systems
Rev.1 25/04/2014

Module VI
Management and reporting of adverse reactions
Rev.1, 15/09/2014

Module VII
Periodic safety update reports
Rev.1, 12/12/2013

Module VIII
Post-authorisation safety studies
Rev.1, 25/04/2013, Rev 2 imminent

Module IX
Signal management
Rev. 2, 5/04/2013

Module X
Additional monitoring

Module XI
Public participation (Q1-Q2 2015)

Module XII
Continuous pharmacovigilance (Q1-Q2 2015)

Module XIII
No longer under development

Module XIV
International cooperation (Q1-Q2 2015)

Module XV
Safety communication

Module XVI
Risk minimisation measures
Rev.1, 25/04/2014

Published
Under Development

*For more information on the GVP, please refer to the GVP information on the EMA Website. www.ema.europa.eu
Good pharmacovigilance practices (GVP) cont.

GVP product- or population-specific considerations

PI
Vaccines for prophylaxis against infectious diseases

PII – Biologics (Q1-Q2 2015)

PIII – Pregnancy

PIV – Geriatrics

GVP annex I - Definitions

Guideline on GVP Annex I Definitions
Rev 3, 25/04/2013

GVP annex II - Templates

Guideline on GVP Annex II: Templates - DHPC Communication
Rev 1, 25/04/2014

Guideline on GVP Annex II: Templates - PSUR Cover letter
Rev 3, 25/04/2013

Published  Under Development

*For more information on the GVP, please refer to the GVP information on the EMA Website. www.ema.europa.eu
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 risk management measures.*

*Directive 2001/83/EC (DIR) Art 1(15)
Post authorization safety studies

A PASS can be categorised as:

• **Category 1**
  Imposed by a EU competent authority as a condition to the Marketing Authorisation

• **Category 2**
  Imposed by a EU competent authority as a specific obligation for a Marketing Authorisation authorised under exceptional circumstances

• **Category 3**
  Required as part of the Risk Management Plan agreed with a EU competent authority

• **Category 4**
  Voluntary/ not required by the EU or national competent authority
EMA prioritised implementation of the PV legislation

PASS & PAES

Feb & Jul 2012
• EC Q&A on transitional arrangements

May & Nov 2012
• EMA Q&A on practical transitional measures

Jan 2013
• Implementation procedures PASS protocols approval & results management
• EU PAS Register submission for imposed PASS CAPs
• ENCePP Checklist for Study Protocols, rev 2

Oct 2013
• PAES: scientific guidance on methodological aspects (expert workshop)

July 2014
• ENCePP guide on methodological standards in pharmacoepidemiology, rev 3

2015/2016
• Good practice guide on coding and reporting medication errors
• Good practice guide on risk minimisation and prevention of medication errors
• Good practice guide on educational materials
• PAES scientific guidance for public consult November 2015
Applying the EU legislation and regulations in the conduct of post marketing safety studies

Priscilla Velentgas
## PASS categories & supervision

<table>
<thead>
<tr>
<th>PASS Pursuant to an obligation</th>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Imposed PASS</td>
<td>“Interventional”*</td>
<td>X</td>
<td>1</td>
<td>Mandatory and subject to penalties</td>
<td>Supervised</td>
<td>Supervised</td>
</tr>
<tr>
<td></td>
<td>Non-interventional</td>
<td>X</td>
<td>1</td>
<td>Mandatory and subject to penalties</td>
<td>Supervised</td>
<td>Supervised</td>
</tr>
<tr>
<td>Specific Obligation</td>
<td>“Interventional”*</td>
<td>X</td>
<td>2</td>
<td>Mandatory and subject to penalties</td>
<td>Supervised</td>
<td>Supervised</td>
</tr>
<tr>
<td></td>
<td>Non-interventional</td>
<td>X</td>
<td>2</td>
<td>Mandatory and subject to penalties</td>
<td>Supervised</td>
<td>Supervised</td>
</tr>
<tr>
<td>Required</td>
<td>“Interventional”*</td>
<td>X</td>
<td>3</td>
<td>Legally enforceable</td>
<td>Supervised</td>
<td>Supervised</td>
</tr>
<tr>
<td></td>
<td>Non-interventional</td>
<td>X</td>
<td>3</td>
<td>Legally enforceable</td>
<td>Supervised</td>
<td>Supervised</td>
</tr>
<tr>
<td>Stated</td>
<td>“Interventional”*</td>
<td>X</td>
<td>4</td>
<td>Not enforced</td>
<td>Supervised</td>
<td>Supervised</td>
</tr>
<tr>
<td></td>
<td>Non-interventional</td>
<td>X</td>
<td>4</td>
<td>Not enforced</td>
<td>Supervised</td>
<td>Supervised</td>
</tr>
</tbody>
</table>

GVP Module V  Risk Management Systems Table V.2: Attributes of different PhV activities
Methodological approaches to meet NI-PASS objectives

**Retrospective** Designs
- Medical Chart Review
- Administrative Claims
  - EMR

**Prospective** Designs
- Observational Studies/Registries
- Health Surveys
- Automated EMR Data Feeds

Hybrid studies: Studies that leverage different data types

NIS are defined by the methodological approach used and not by its scientific objectives.

* Cross-sectionnal design
2. Quintiles RWLPR Managed PASS

Examples of types of PASS included in RMPs\(^1,\)\(^2\)

**Registries**
- Product exposure to assess safety profile of drugs
- Pregnancy registries following product exposure
- Disease + product exposure registry
- Joint registries with multiple MAH

**Drug Utilisation Studies (DUS) and Surveys**
- e.g. to assess effectiveness of additional risk minimisation measures;
- 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

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

**Others**
- e.g. published pharmacoepidemiological studies
NI-PASS regulatory framework in EU

When do I submit my protocol to the PRAC?

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

- Legal requirement to submit protocol
  - Article 107(n-q) of Directive 2001/83/EC
  - Submit protocol no later than 2-3 months following MA

- Endorsement Letter

**PASS Voluntarily Initiated**
and in RMP

- Recommended to submit protocol
  - GVP Module VIII B1

- No Endorsement Letter
  - Comments to protocol are provided by PRAC

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**Notification to Competent Authorities & Local Requirements**

- Legal requirement
  - Article 107n.3 of Directive 2001/83/EC

**Local Requirements**

- Study registration on EU PAS Register
  - GVP Module VIII B4

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

Keys to success

Right operational model for a PASS

- Right sites
- Right patients
- Right data

The Right Approach for The Right Question™
Lessons learned on the design and the conduct of PASS

Pierre Engel
Lessons learned on the design and the conduct of European Post Authorisation Safety Studies (PASS)

Review of 3 years of PRAC oversight

Why did we choose to study trends in PASS?
- July 2012 -> biggest change in EU Pharmacovigilance legislation* since 1995

Two of the main objectives
- Increase proactivity/ planning: Emphasis on Risk Management
- Increase transparency and accountability

Increased demand for conducting PASS

European Regulators publish more data

Pool of scientific and practical insights on how to best conduct and implement PASS
Lessons learned on the design and the conduct of European Post Authorisation Safety Studies (PASS)

Review of 3 years of PRAC oversight

How did we go about the research?

1. Exhaustive review of PRAC* monthly meeting minutes (July 2012 - July 2015):
   353 PASS protocol submissions corresponding to 189 different PASS

2. Methodological and regulatory data to characterise each PASS retrieved from:
   ENCePP EU PAS Register
   93 of the 189 PASS were registered (49% overall)
   Of those 40 had protocol available (21% overall)
   Quintiles had 18 additional protocols available
   EMA‡ website: review of public documents (e.g. EMA Assessment Reports)

*PRAC: EMA Pharmacovigilance and Risk Assessment Committee
‡EMA: European Medicines Agency
Lessons learned on the design and the conduct of European Post Authorisation Safety Studies (PASS)
Review of 3 years of PRAC oversight

What did we find out?

A post-authorisation study should be classified as a PASS when the main aim for initiating the study includes:

• To quantify risks or provide evidence about the absence of risks
• To evaluate risks in populations with limited/missing safety data
• To assess patterns of drug utilisation that informs on the safety profile
• To measure the effectiveness of a risk minimisation activity

*Adapted from Directive 2001/83/EC (DIR) Art 1(15)

Main aim for initiating PASS

- 74% Investigate safety concerns
- 34% Drug utilisation
- 25% Effectiveness of risk minimisation

35% also included effectiveness endpoint
Lessons learned on the design and the conduct of European Post Authorisation Safety Studies (PASS)  
Review of 3 years of PRAC oversight

What did we find out?

- 71% of PASS defined study population (patients/healthcare professionals) based on the exposure of interest
- 20% of PASS targeted a specific population (healthcare professionals/pregnant women/paediatric patients)

*Directive 2001/83/EC (DIR) Art 1(15)

Inclusion criteria (All PASS, N=189)

- Single drug: 71%
- Multiple drugs: 8%
- Disease: 21%

65% with no comparator

Note: Missing data excluded from the denominators
Lessons learned on the design and the conduct of European Post Authorisation Safety Studies (PASS)
Review of 3 years of PRAC oversight

What did we find out?

- In general slightly more PASS used a primary data collection approach
- Those using secondary data sources (among available protocols, N=58):
  - 42% Chart abstraction
  - 37% Claims, database, Health Electronic Records
  - 21% Existing registries

Note: Missing data excluded from the denominators

Among PASS aiming to assess drug utilisation (N=65)

- 58% Secondary
- 42% Primary
What did we find out?

PRAC comments were available for only 1/3 of the 353 PASS protocol submissions: 76 PRAC comments corresponded to requests for protocol revision (22% of the 353 PASS protocol submissions)
What did we find out?

- Pool of protocols to consult when designing a new PASS
- This is the first comprehensive review of three years of PASS protocol submissions since the inaugural PRAC meeting in July 2012.
- Although the EMA and the PRAC have significantly improved the availability of PASS information, public transparency on PRAC feedback and guidance on how to best design and implement those studies could be further improved.
- Our results also indicate the lack of adherence of the MAHs to the EU PAS Register
- Perspectives:
  - Analyse the trends in PASS reports (as they become available)
  - Are PASS consistent with, and taking enough advantage of the Risk Management Plan (RMP)?
Polling questions

How have you most often utilized the PAS Register?

• Register a study(ies)
• Find information on other studies within indication of interest
• Other
Trends in regulatory required post marketing studies: PAES
The legislation enables the competent authority to require post authorisation “efficacy” studies (PAES).

<table>
<thead>
<tr>
<th>Pre-Authorization</th>
<th>Post-Authorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>…where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed.</td>
<td></td>
</tr>
<tr>
<td>…when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly.</td>
<td></td>
</tr>
</tbody>
</table>
Commission delegated regulation (EU) 357/2014
Rationale for requiring a PAES

• Initial assessment based on surrogate endpoints which require verification
• Products used in combination with other medicinal products
• Uncertainty of efficacy in certain subpopulations which couldn’t be resolved prior to MA
• Potential lack of long-term efficacy which could mean B/R balance no longer positive
• Benefits seen in clinical trials may be significantly affected by use under real world conditions
• For vaccines, where protective efficacy studies have not been feasible
• Change in understanding of the standard of care for a disease and hence the appropriate criteria assessing therapeutic efficacy
Part IV of the Risk Management Plan

Discussion on any gaps in the knowledge about benefit:

• Applicability of efficacy data to all patients in target population
• Studied patients vs target population
• Factors which might affect efficacy in everyday medical practice
• Hospital vs community setting
• Long term efficacy
• Any evidence of variability in benefits in sub populations
Polling questions

Have you designed or conducted a PAES?

- Yes
- No
Other recent developments to support planning and conduct of post-authorisation studies*

• New systems and services for stakeholders:
  – New EMA literature monitoring service to reduce burden on industry – May 2015
  – EU dictionary of medicines to better monitor safety data, to coordinate regulation – now operational
  – Repository for industry periodic product reports – to simplify reporting for industry – in pilot
  – Improved EudraVigilance to 1. detect safety issues more quickly; 2. reduce duplicative reporting for industry – in testing 2016

• Evidence-based improvements:
  – Improved processes for PAS (joint studies + scientific advice)
  – Improved scientific methods and guidance for PAS (ENCePP methods guide, GVP, PAES)

• Opportunities: leverage new science (epidemiology) and new technologies (electronic health records, apps, social media) – to monitor real-world use of medicines and support market entry and health protection

• New EU CTR
New Clinical Trial Regulation

*With New Definitions per Art. 2*

**Regulation (EU) no 536/2014**

Of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing directive 2001/20/EC

- Entry into law - 16 Jun 2014
- Official date of application - earliest 28 May 2016
- Application date is linked to technical aspects being in place (+6 months)
Previous and upcoming events

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

Topics include:

- Observational research & registries
- Safety & risk management
- HTA & Market Access
- Maximizing value and quality in phase iv
- Rare disease registries
- Comparative effectiveness research
- Clinical outcome assessments

Visit Quintiles to learn more at one of the following upcoming meetings:

- ISPOR 21st Annual International Meeting
- The 8th European Conference on Rare Diseases & Orphan Products (ECRD 2016)
- BIO International Convention
- Optimizing Real-World Evidence Programs for Emerging Biopharma
- 10th Euro Global Summit and Expo on Vaccines & Vaccination
- Real-World Evidence Seminar: Evolving Landscape in Japan

To register or view previous webinars please go to http://www.quintiles.com/landing-pages/real-world-and-late-phase-research-webinars
Thank you

Questions?

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