Post-Approval Safety Studies: Impact of 2012 PV Legislation & Guidance

7th European Forum for QPPV

London, April 18, 2012

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Topics & Key References

- Focus: Impact of the 2012 GPV legislation & guidance on the planning, registration and conduct of non-interventional PASS

- Key References
  - GPV Modules VIII, VI
    http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c
  - Q&A transition aspects. Section 4, Update November 2012
    http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127658.pdf
  - EU PAS Register Guide, October 2012
    http://www.encepp.eu/publications/documents/EUPASRegisterGuide.pdf
  - EMA presentation on Registration, X. Kurz, October 2012
    http://www.encepp.eu/publications/documents/3.1_EUPASRegister.pdf

Perspectives & Disclosures

- Researcher, RTI Health Solutions & formerly R&D pharma
- ISPE, past President & past chair of Public Policy Committee, maintains Good Pharmacoepidemiology Practice
- ENCePP, member Steering Committee & past chair Research Standards Working Group

Guideline on good pharmacovigilance practices (GVP)

Module VIII – Post-authorisation safety studies
22 June 2012
EMA/813938/2011

Draft finalized by the Agency in collaboration with Member States and submitted to ERMS FG	19 January 2012
Draft agreed by ERMS FG	24 January 2012
Draft adopted by Executive Director	20 February 2012
Start of public consultation	21 February 2012
End of consultation (deadline for comments)	18 April 2012
Draft finalized by the Agency in collaboration with Member States	20 June 2012
Draft agreed by ERMS FG	21 June 2012
Draft adopted by Executive Director	22 June 2012
Anticipated date for coming into effect after finalization	2 July 2012

Module VIII & QPPV

- “In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the **qualified person responsible for pharmacovigilance** (QPPV) or his/her delegate (see Module I) should be involved in the **review and sign-off of study protocols** conducted in the EU.”

Key changes

- Studies need to be registered in the EU PAS registry
- New/revised structure study protocols and reports
- Expanded procedures for protocol and study report review
- Independent publication of study results agreed in advance between marketing authorization holder and research group.
- Companies will be encouraged to run “joint studies” for safety concerns involving more than a single medicinal product
- *Epidemiology protocols and reports are in EU legislation*

Guideline on good pharmacovigilance practices, Module VIII - Table of Contents

Guideline on good pharmacovigilance practices, Module VIII — Table of Contents (II)

Purposes of Module VIII

— VIII.A. Introduction

- "The purposes of this Module are to:
  - provide general guidance for the **transparency**, **scientific standards and quality standards** of non-interventional PASS conducted by marketing authorisation holders voluntarily or pursuant to an obligation imposed by a competent authority (VIII.B);
  - describe procedures whereby competent authorities may impose to a marketing authorisation holder an obligation to conduct a clinical trial or a non-interventional study (VIII.C.2), and the impact of this obligation on the risk management system (VIII.C.3);
  - describe procedures that apply to non-interventional PASS imposed as an obligation for the protocol oversight and reporting of results (VIII.C.4) and for changes to the marketing authorisation following results (VIII.C.5)."

Overall impressions

- Based on existing guidance:
  - International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practice guidance
  - Concepts, documents, and good practice developed through the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), e.g. Research Standards, Code of Conduct on transparency and independence
- Detailed guidance on methods and conduct in line with state of the art in the field
- Detailed guidance on documentation and procedural requirements, some in the public domain, which are beyond current practice and will require additional resources and impact timelines

Definition of Non-Interventional - Still a Challenge (VIII.A. Introduction)

"A PASS is non-interventional if the following requirements are cumulatively fulfilled [Volume 10 of The Rules Governing Medicinal Products in the European Union, Questions and Answers, Version 9.0, August 2011, Question 1.9]:

- the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
- the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- **no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data."**

"Non-interventional studies are defined by the methodological approach used and not by its scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort or other study designs making secondary use of data). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met. In these studies, **interviews, questionnaires and blood samples may be performed** as part of normal clinical practice.

VIII.B.2. Definitions - Good clarification

- "Date at which a study commences: date of the start of data collection."
- "Start of data collection: the date from which information on the first study subject is first recorded in the study dataset or, in the case of **secondary use of data**, the date from which data extraction starts [IR Art 37]. Simple counts in a database to support the development of the study protocol, for example to inform the sample size and statistical precision of the study, are not part of this definition."
- "End of data collection: the date from which the **analytical dataset is completely available** [IR Art 37]."
- "Analytical dataset: the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study."

VIII.B.3. General principles Δ

- "What is a PASS? A post-authorisation study should be classified as a PASS when the study includes any of the following objectives:
  - to quantify potential or identified risks, e.g. to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another drug or class of drugs, and investigate risk factors and effect modifiers;
  - to evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment);
  - to provide evidence about the absence of risks;
  - to assess patterns of **drug utilisation** that add knowledge on the safety of the medicinal product (e.g. indication, dosage, co-medication, medication errors);
  - to **measure the effectiveness of a risk minimisation activity**."

- "Research contract provisions and clear roles and responsibilities for MAH, and researcher"

2. Obligations and requirements

▲ legal obligation ✓ recommended in the GVP ★ optional

Management of study

	PASS with MAH involvement	
	Imposed as an obligation	Conducted voluntarily
Standard format of protocol and study report	▲	✓
PRAC oversight	▲	(if in RMP)
Registration of study in EU PAS register	▲	✓
Study not to promote medicinal product	▲	▲
Restricted payment to HCP	▲	▲
Quality systems	▲	✓
ENCePP methodological standards	✓	✓
ENCePP checklist for study protocol	✓	✓
ENCePP CoC	✓	✓
ENCePP seal	★	★

VIII.B.4. Study Registration

"VIII.B.4. Study registration
In order to support transparency on non-interventional PASS conducted voluntarily or pursuant an obligation and to facilitate exchange of pharmacovigilance information between the Agency, Member States and marketing authorisation holders, the marketing authorisation holder should make study information available in the EU electronic register of post-authorisation studies (EU PAS Register) maintained by the Agency and accessible through the European medicines web-portal. The study protocol should be entered in the register before the start of data collection."

"The Agency EMA will have to make **public on the European medicines webportal, protocols and public abstracts of PASS** falling within the scope of the new procedures involving the PRAC. **[Q&A November 2012 Section 4.6]"**

"The EMA will establish and maintain an EU PAS (Post-Authorisation Studies) register allowing to register non-interventional PASS studies, as described in GVP Module VIII. Before the EU PAS register is fully operational, **studies should be registered in the ENCePP register of studies.** All the studies already included in the ENCePP registry will therefore be also included in the EU PAS register **" [Q&A November 2012 Section 4.7]**

EU PAS Register to be developed as upgrade of ENCePP E-Register of studies and will include already registered studies, including ENCePP seal

Transitional period:

- ENCePP E-Register of studies to be used
- Guide for study registration amended
- for MAH-sponsored non-interventional 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

Study Protocol and Reports

- B.5 Study Protocol
  - B.5.1 Format and content of the study protocol
    - Annex with **ENCePP checklist** for study protocols *signed by principal investigator*
  - B.5.2. Substantial amendments to the study protocol
  - Template & Guidance: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133174.pdf
- B.6 Reporting of PV data to competent authorities
  - B.6.1 Data relevant to risk-benefit
  - B.6.3 Study reports (progress, final) – Format and content
  - Template & Guidance: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2013/01/WC500137939.pdf

Reporting of Adverse Reactions Δ

- B.6.2 Reporting of adverse reactions/adverse events
  - "No expedited reporting required for secondary data sources"

Clarification

- Term "expedited reporting" not used anymore: both serious and non-serious reports of suspected adverse reaction need to be reported either within 15 days or 90 days timelines (Module VI)
  - Terminology: "reporting of cases of suspected adverse reactions"
- Non-interventional PASS with secondary use of data:
  - Reporting of adverse reactions is required neither within 15 days nor within 90 days.
  - Adverse reactions should be summarised in the final study report (note the difference between "reporting" and "summarising").

VIII.B./ Publication of study results

VIII.B.7. Publication of study results

"For studies that are fully or partially conducted by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder and the investigator should agree in advance a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The marketing authorisation holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication."

VIII.B.7.1. Regulatory submission of manuscripts accepted for publication

"In order to allow national competent authorities to review in advance the results and interpretations to be published, the marketing authorisation holder should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication."

VIII.C. Operation of the EU network

- VIII.C.4 – Regulatory supervision of non-interventional PASS
  - MAH develops draft protocol
  - Pharmacovigilance Risk Assessment Committee (PRAC) rapporteur writes protocol assessment report
  - PRAC or NCA issues letter of endorsement/objection
  - EMA provides scientific secretariat to the PRAC
  - Presubmission meetings

- Increased review of protocols and documents

Member state requirements transmission of study documents

Table 1. Studies imposed as an obligation by a competent authority

	Study protocols, updated study protocols following substantial amendments, final study reports[1]		Progress reports, if requested[1]
	Direct transmission by MAH to MS[2]	Transmission by MAH to MS via PRAC[3]	Direct transmission by MAH to MS[2]
Member States where the study is conducted	**All**		**All**
Member States acting as Rapporteur or RMS for the medicinal product		**All**	**All**
Member States where the medicinal product is authorised, but not acting as Rapporteur of RMS for the medicinal product*		**All**	**DE**

[1] Study information should also be entered and maintained in the EU PAS Register.

[2] Final study protocols, substantial amendments to study protocol, any progress reports, abstracts of final study report, and final study reports to be transmitted by marketing authorisation holders to Member States according to national procedures.

[3] Information to be transmitted by marketing authorisation holders to the Agency and all PRAC members in the context of the oversight of post-authorisation safety studies by the PRAC as described in Directive 2001/83/EC Art 107 n-p.

* even if study not conducted in the Member State

http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129147.pdf

VIII.C. Operation of the EU network

d. Joint post-authorisation safety studies

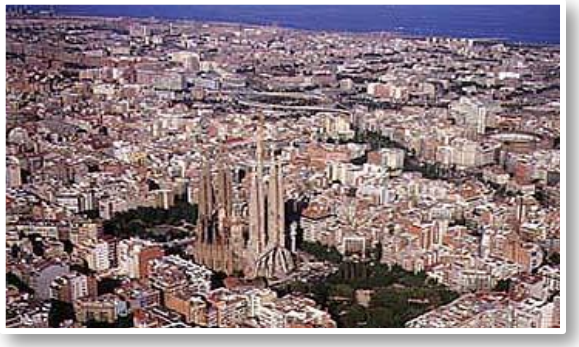
"If safety concerns apply to more than one medicinal product, the Agency or the national competent authority shall, following consultation with the PRAC, encourage the marketing authorisation holders concerned to conduct a joint PASS [DIR Art 22a, REG Art 10a]. A joint PASS may also be necessary where there are limited patients (rare diseases) or the adverse reaction is rare. Requests to the marketing authorisation holders should contain the justification for the request of a joint study and the elements of the study design that support a joint protocol."

Key changes for PASS

- Studies need to be registered in the EU PAS registry
  - Materials posted include the study protocol prior to study initiation (start data collection) and the final study report
- New/revised structure study protocols and reports
  - Revise internal templates
- Expanded procedures for protocol and study report review by EMA, national authorities and the PRAC
  - Keep in mind for timelines and budgets
- Requirement for independent publication of study results agreed in advance between marketing authorization holder and research group.
  - Keep in mind in contracts and timelines
- Companies will be encouraged to run “joint studies” for safety concerns involving more than a single medicinal product

In conclusion…

- Detailed guidance on quality, scientific standards, transparency. Allows for better planning of activities for MAA/MAH, regulators, researchers and stakeholders
- Changes in format (revise templates for protocols, reports) and process (input by more stakeholders)
- Increased transparency (study registration, public posting of protocol, abstract report) is a major change
- Increased collaborative work and opportunity to learn



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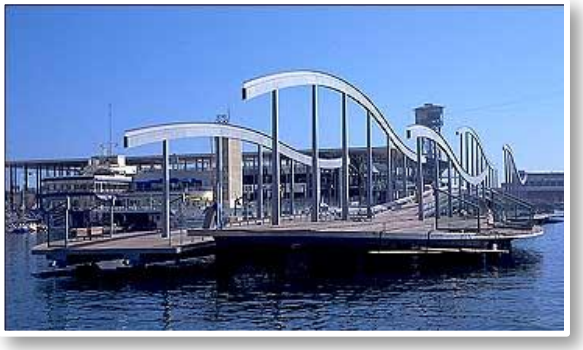

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