New PV Legislation: A Call to Arms to the Pharmacoepidemiology Community. Post-Approval Safety Studies

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Disclosure & Perspectives

- Employed at RTI Health Solutions, RTI is an independent non-for-profit research institute working for government and private and other institutions including pharma companies. My work includes research grants, advisory roles and regulatory deliverables, mostly funded by pharma.
- Past employment 1990-2007: R&D Pharma epidemiology in Pfizer, Pharmacia, Novartis, Ciba-Geigy
- Member of the Steering Committee of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and past co-chair of the working group on Research standards & guidance
- Past President and long-time service as officer of International Society for Pharmacoepidemiology (ISPE)

Topics & Key References

- Overview key aspects of guidance
- Challenges & Opportunities
- Focus non-interventional studies, pursuant to an obligation

Key References

- http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c: GPV Modules VIII, VI, V
- http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127658.pdf: Q&A transition aspects (July 2012)

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Risk Management - Cyclical model

Risk Management Framework & Epidemiology

- Risk assessment / measurement
  - estimation and evaluation of risk
- Risk confrontation
  - determining acceptable level of risk
- Risk intervention
  - risk minimization action
- Risk communication
  - interactive exchange of risk information
- Risk management evaluation
  - evaluating effectiveness of activities

➔Epidemiology – population based evidence

➔Epidemiology – population based evidence

➔Public Health perspective

➔Public Health perspective

➔Epidemiology – population based evidence

Mid 2000' - Role of Epidemiology in Transition

"Nice to have"

Regulatory requirement

Strategic advantage

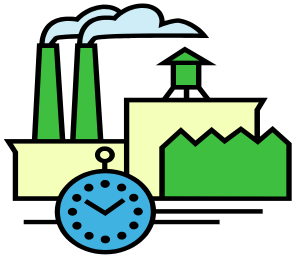
Core discipline for R&D

Critical in filing, peri/post-approval

FDA Sentinel / OMOP

EMA ENCePP / PROTECT

Move to large volume systematic "production mode"



HMA
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22 June 2012
EMA/813938/2011

Guideline on good pharmacovigilance practices (GVP)

Module VIII – Post-authorisation safety studies

Draft finalised 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 finalised 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 finalisation	2 July 2012

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Guideline on good pharmacovigilance practices (GVP)

Module VIII – Post-authorisation safety studies **Table of contents**

Purposes of Module VIII

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).

First impressions

- Based on ISPE Good Pharmacoepidemiology Practice guidance and on concepts, documents, and good practice developed through ENCePP, e.g. Research Standards, Code of Conduct (transparency, independence)
- Detailed technical and conduct guidance 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 in some instances and will require additional resources and impact timelines
- *Language: "shall" = requirement; "should" = guidance*

Non-Interventional

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][1]:

- 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.

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

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

- 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

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. Updates of the study

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. [Q&A July 2012]**

EU PAS register will be an upgrade of the ENCePP registry and will replace the ENCePP registry. All the studies already included in the ENCePP registry will therefore be also included in the EU PAS register [clarification]

The 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 July 2012]**

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 – WG1 plans aligning checklist*
  - B.5.2. Substantial amendments to the study protocol
- 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
  - B.6.2 Reporting of adverse reactions/adverse events
    - *No expedited reporting required for secondary data sources*

Discussion at ISPE – AE reporting process unclear

Reporting of Adverse Reactions (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

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 docs

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

- 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

In conclusion…

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

THANK YOU

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