EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP and the new pharmacovigilance legislation

ENCePP Steering Group meeting with industry associations
22 May 2013

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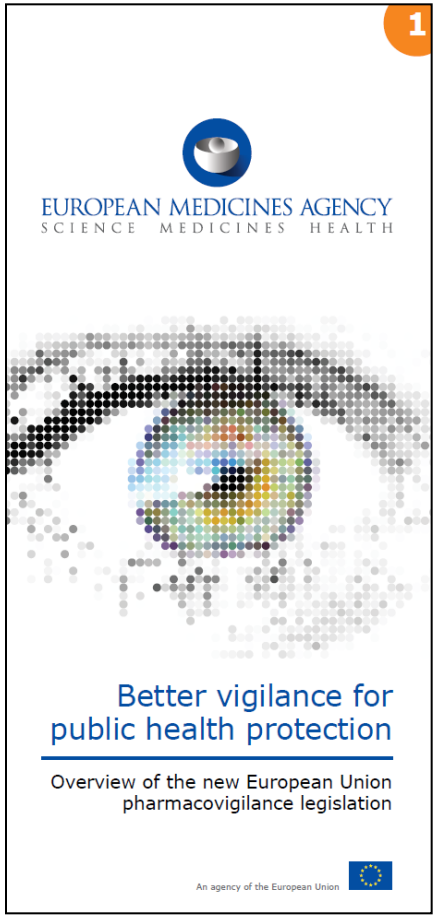
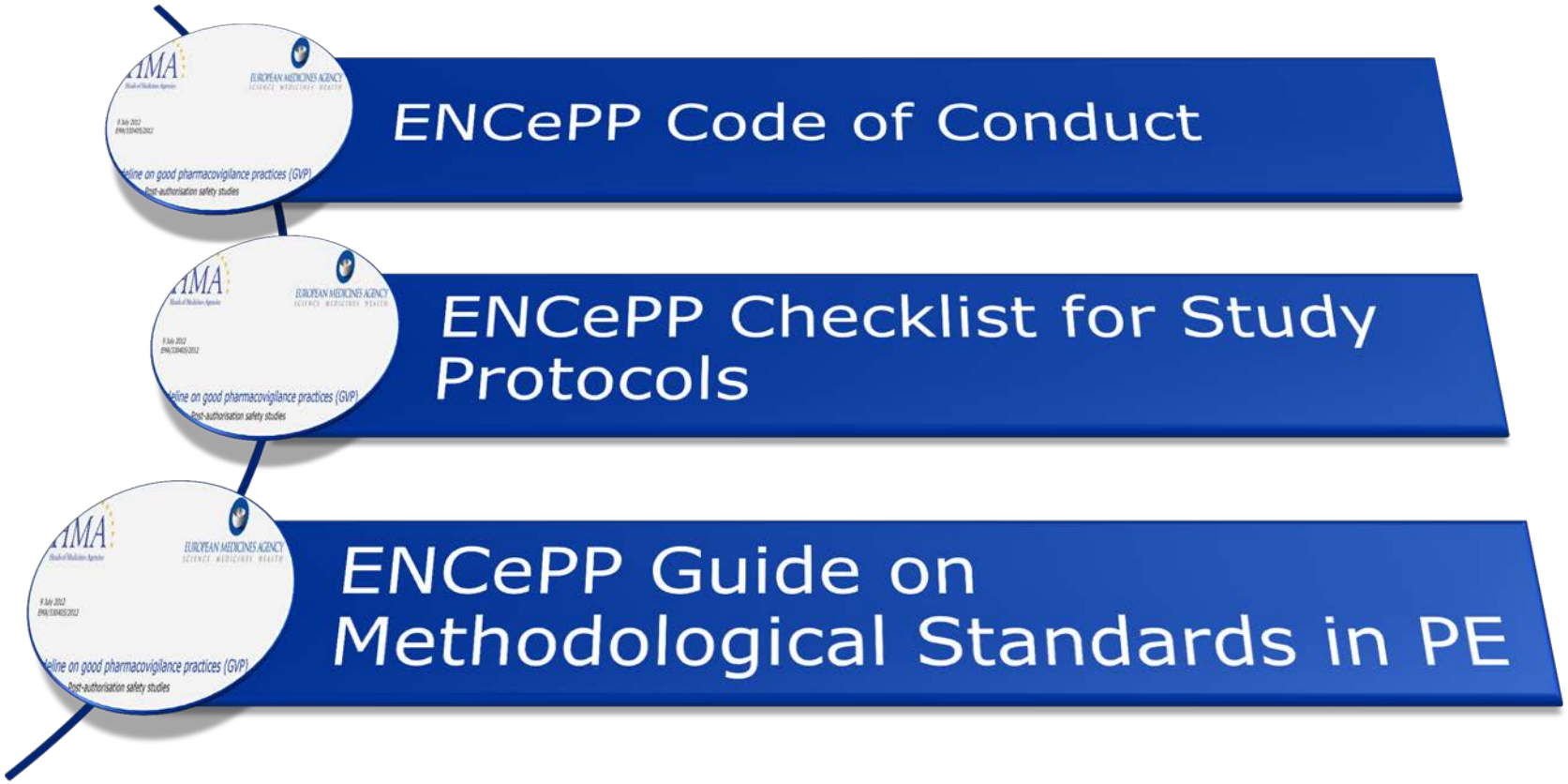
Requirements of new legislation for PAS:



- RMP all new products
- Requirements PASS & PAES
- PASS oversight
- transparency

GVP Module VIII and ENCePP

Included as recommendations/reference documents in GVP M VIII:



GVP Module VIII and ENCePP

- ***VIII.B.3. General principles:***
  For studies that are funded by an MAH and are developed, conducted or analysed fully or partially by investigators who are not employees of the MAH … it is recommended that the research contract takes into account the provisions of the **ENCePP Code of Conduct**.

- ***VIII.B.3. General principles:***
  Relevant scientific guidance includes the **ENCePP Guide on Methodological Standards in Pharmacoepidemiology**, *the ENCePP Checklist for Study Protocols, (…).*

- ***VIII.B.5.1. Format and content of the study protocol:***
  In order to facilitate the review of the protocol, an Annex should include the **ENCePP Checklist for Study Protocols** *signed by the principal investigator*.

GVP Module VIII and ENCePP (2)

- ***VIII.C.2d. Joint 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. A joint PASS may also be necessary where there are limited patients (rare diseases) or the adverse reaction is rare. (…)

  If a joint protocol is not voluntarily agreed and different proposals are submitted, the national competent authority or Agency may define, in consultation with the PRAC, either a common core protocol or key elements (for example, the study design, the study population and the definition of exposure and outcomes) which each marketing authorisation holder will have to implement in the study protocol to be submitted to the national competent authority or the PRAC (…).

EU PAS Register – Legal Basis

- New PhV legislation requires EMA to publish in a **public register** details of **PASS imposed as an obligation** of MA
  - It also specifies that the final report of such studies shall provide the date of registration in this register.
- GVP: **PASS** initiated, managed or financed voluntarily by MAH and **required in the RMP** should also be entered into the EU PAS Register
- The legislation requires Member States (MS) to ensure that the public is given **important information on pharmacovigilance concerns** (this includes information on PASS)
  - For MAH-sponsored PASS requested by a regulatory authority EMA sends an email informing all MS of the study registration with: title, name of sponsor, countries and link to register

EU PAS Register / ENCePP e-Register

The EMA will establish and maintain an EU PAS Register for registration of non-interventional PASS, as described in GVP chapter VIII.B.4. This EU PAS Register will be an upgrade of the existing ENCePP e-Register of studies. Before the EU PAS Register is fully operational, studies should be registered in the ENCePP e-Register to comply with GVP.

→ **ENCePP E-Register acts as 'EU PAS Register'** for all PhEpi and PhV studies

– initiated, managed or financed by a MAH

– conducted by a research centre or network within or outside the EU

PASS Obligations and Requirements

▲ Legal obligation ✓ Recommended in the GVP guideline ★ Optional

Management of study

	PASS with MAH involvement	
	Imposed as an obligation	Conducted voluntarily
Standard format of protocol and study report	▲	✓
Pharmacovigilance Risk Assessment Committee (PRAC) involvement	▲	(if PASS required in RMP)
Registration of study in the EU PAS Register	▲	✓
Study not to promote medicinal product	▲	▲
Restricted payment to healthcare professional	▲	▲
Quality systems	▲	✓
ENCePP methodological standards	✓	✓
ENCePP checklist for study protocol	✓	✓
ENCePP code of conduct	✓	✓
ENCePP study seal	★	★

PASS Obligations and Requirements - Reporting

▲ Legal obligation

✓ Recommended in the GVP guideline

Reporting of study information

	PASS with MAH involvement	
	Imposed as an obligation	Conducted voluntarily
Protocol and progress reports to be submitted upon request to national competent authority (NCA) of Member State (MS) where study is conducted	▲	▲
Final report to be sent to NCA of MS where the study is conducted, within 12 months of the end of data collection	▲	▲
Data generated in the study to be monitored	▲	▲
Any information that may influence the benefit-risk balance to be reported to NCAs of MSs where the product is authorised	▲	▲
Reporting of suspected adverse reactions in studies with primary data collection	▲	▲
Final manuscript of article to be transmitted to NCAs within 15 days after acceptance by journal editor	✓	✓

ADR Reporting Requirements

Orientations for forthcoming revision of GVP Module VI guidance

(final wording to be finalised before public consultation)

Non-interventional PAS based on secondary use of data:

- Reporting of suspected adverse reactions as ICSRs is not required.
- Reports of AEs/ARs to be summarised in interim/final study report.

Non-interventional PAS based on primary data collection directly from HCPs, patients, consumers:

- Sponsor should specify in protocol any adverse events which should be actively sought and reported by investigators, patients or consumers.
- Death and fatal outcomes are events that need to be actively collected by sponsors unless justified.
- From these collected AEs, only valid ICSRs of ARs suspected to be related to the medicinal product should be reported as solicited events.
- Other events should not be actively collected; if spontaneously reported by HCPs, patients or consumers in the course of the study, they should not be reported as ICSRs but included only in the interim/final study report.

ENCePP supporting Committees: referrals

- Provision of (pharmaco)epidemiology expertise for Ad-hoc expert groups [e.g. re-examination of calcitonin Art 31, cyproterone-EE Art 107i]
- Provision of data in response to an invitation from EMA e.g. tetrazepam Art 107i (RegiSCAR data), CHC Art 31, Diane Art 107i (IMS drug utilisation data)
- Final studies feeding into referrals e.g. SOS consortium NSAIDs study and NSAIDs Art 5.3 + Art 31 (diclofenac), and an EMA-funded ENCePP study on COC utilisation.

ENCePP supporting Committees: safety issues

- Provision of information/data in response to a request from EMA e.g. hypnotics and risk of death, fluoroquinolones and retinal detachment
- Discussion of scope of existing/ongoing studies regarding further endpoints/exposures and/or confounders as new issues arise e.g. SAFEGUARD/CARING consortium and safety of insulin/oral T2DM therapies, EpoCAN and epoetins
- EMA Call for Expressions of Interest for Drug Safety Studies
  - ✓ *Requirement in each call for tender that an ENCePP Study Seal is applied for.*
  - ✓ *7 studies complete/on-going: new call about to be launched for metformin safety study*

EMA funded ENCePP studies

Name of study	Timeframe
Isotretinoin and the effectiveness of the Pregnancy Prevention Programme in Europe *http://www.encepp.eu/encepp/viewResource.htm?id=2706	19/12/2011 - 19/06/2013
Impact of risk minimisation in patients treated with rosiglitazone-containing products http://www.encepp.eu/encepp/viewResource.htm?id=2236	15/10/2010-17/10/2011
A/H1N1 pandemic vaccines and pregnancy outcomes http://www.encepp.eu/encepp/viewResource.htm?id=2758	18/10/2010-30/06/2013
Patterns and determinants of use of oral contraceptives in the EU http://www.encepp.eu/encepp/viewResource.htm?id=2914	02/12/2011-22/03/2013
Monitoring the effectiveness of risk minimisation in patients treated with pioglitazone-containing products http://www.encepp.eu/encepp/viewResource.htm?id=2918	20/01/2012-20/03/2013
Risk of cardiac valve disorders associated with the use of biphosphonates http://www.encepp.eu/encepp/viewResource.htm?id=2772	02/12/2011-02/10/2013
Association between anxiolytic or hypnotic drugs and total mortality http://www.encepp.eu/encepp/viewResource.htm?id=3786	17/09/2012-17/09/2013

** Entry in ENCePP Register*

References

- ENCePP Code of Conduct (http://www.encepp.eu/code_of_conduct/index.shtml)
- ENCePP Checklist for Study Protocols (http://www.encepp.eu/standards_and_guidances/documents/ENCePPChecklistforStudyProtocols.doc)
- ENCePP Guide on Methodological Standards in PE (http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE_2.pdf)
- GVP Module VIII (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf)
- 2010 pharmacovigilance legislation (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000492.jsp&mid=WC0b01ac058033e8ad)
- Q&A to support the implementation of the Pharmacovigilance legislation (http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500127658)
- EU PAS Register Guide (http://www.encepp.eu/publications/documents/EUPASRegisterGuide.pdf)