Adjusting to Effectively Meet the New European Union Pharmacovigilance Requirements

Deirdre McCarthy
Michelle Bulliard
GRP Webinar
31 January 2013
Deirdre McCarthy
Director, Customer Delivery Europe, Quintiles Lifecycle Safety
Ms. McCarthy has more than 10 years experience in pharmacovigilance, previously serving as Pharmacovigilance Officer for the Irish Medicines Board and sitting on the Executive Committee for the International Society of Pharmacovigilance (ISoP) for two terms during which time she was Co-Chair of the ISoP Global Education and Training Programme. Deidre specializes in post-marketing safety management and reporting and European safety regulations. She currently serves in a strategic leadership position within lifecycle safety and infrastructure management and is responsible for customer interface for all post-marketing and clinical trial safety services in Europe.

Michelle Bulliard
Vice President Clinical Operations and Regional Managing Director
Europe, Quintiles Outcome Real-world & Late Phase
Ms. Bulliard has over 20 years’ experience in running clinical studies, including real world & late-phase studies, patient registries, and other specialized real-world programs for orphan drug, disease and medical device studies and studies monitoring 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.
Contents

- Considerations for designing and conducting post authorisation safety studies (PASS) that comply with the new requirements
  - Michelle Bulliard

- Changes to the format, content and submission of Periodic Safety Update Reports (PSURs)
  - Deirdre McCarthy
Today’s Webinar Audience

- Academia: 17.43%
- Biostatistician: 1.97%
- Clinical Operations: 31.91%
- Epidemiology: 4.28%
- Health Economics/Health Outcomes: 14.47%
- Medical Affairs: 18.09%
- Pharmacovigilance: 2.30%
- Regulatory Affairs: 1.97%
- Risk Management: 0.99%
- Other: 5.26%
Polling Questions

- A small number of polling questions have been added to today’s webinar to make the session more interactive
# Acronym Glossary

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Reports</td>
</tr>
<tr>
<td>PASS</td>
<td>Post Authorisation Safety Studies</td>
</tr>
<tr>
<td>PBRER</td>
<td>Periodic Benefit Risk Evaluation Report</td>
</tr>
<tr>
<td>IBD</td>
<td>International Birth Date</td>
</tr>
<tr>
<td>DSUR</td>
<td>Development Safety Update Report</td>
</tr>
<tr>
<td>RMP</td>
<td>Risk Management Plan</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
</tr>
<tr>
<td>MAH</td>
<td>Market Authorisation Holder</td>
</tr>
<tr>
<td>B/R</td>
<td>Benefit Risk</td>
</tr>
<tr>
<td>EURD</td>
<td>European Union Reference Dates</td>
</tr>
<tr>
<td>DLP</td>
<td>Data Lock Point</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>PV</td>
<td>Pharmacovigilance</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>PRAC</td>
<td>Pharmacovigilance Risk Assessment Committee</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA</td>
<td>Marketing Authorisation</td>
</tr>
<tr>
<td>CAP</td>
<td>Central Authorisation Procedure</td>
</tr>
<tr>
<td>NAP</td>
<td>National Authorisation Procedure</td>
</tr>
<tr>
<td>eCTD</td>
<td>Electronic Clinical Trial Dossier</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>LTFU</td>
<td>Lost to Follow-up</td>
</tr>
<tr>
<td>GVP</td>
<td>Good Pharmacovigilance Practice</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>MRP</td>
<td>Mutual Recognition Procedure</td>
</tr>
<tr>
<td>DCP</td>
<td>Decentralised Procedure</td>
</tr>
<tr>
<td>NI</td>
<td>Non-Interventional</td>
</tr>
<tr>
<td>CA</td>
<td>Central Authorisation</td>
</tr>
<tr>
<td>ENCePP</td>
<td>European Network of Centres for Pharmacoepidemiology and Pharmacovigilance</td>
</tr>
<tr>
<td>QPPV</td>
<td>Qualified Person Responsible for Pharmacovigilance at EU Level</td>
</tr>
</tbody>
</table>

Comprehensive listing of Acronyms & Abbreviations ref doc: 5 October 2012 EMA/441950/2012 Patient Health Protection Acronyms and abbreviations used in Pharmacovigilance Risk Assessment Committee (PRAC) Minutes
Disclaimer

• Although this material contains information of a legal nature, it has been developed for informational purposes only and does not constitute legal advice as to the current operative laws, regulations, or guidelines of any jurisdiction. While reasonable efforts have been made to assure the accuracy and completeness of the information provided, researchers should check with authorities and/or EC/IRB before starting Observational/Non-Interventional Studies.
Considerations for Designing and Conducting Post Authorisation Safety Studies (PASS) that Comply with the New Requirements

Part 1

- Introduction New EU PV Legislation
- GVP Module VIII - Non Interventional PASS
- Protocol - Non Interventional PASS
- Safety Reporting - Non Interventional PASS

Acronym Key:
PASS- Post Authorisation Safety Studies
PV – Pharmacovigilance
New EU PV Legislation

Why the Need for PV Change in EU

- 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 Euro 79 Billion / year

Source: The new Pharmacovigilance legislation: an EMA perspective, IPA Conference, Jun11

Acronym Key:
PV – Pharmacovigilance
ADR - Adverse Drug Reaction
New EU PV Legislation
To Further Strengthen Pharmacovigilance

Objective is to promote and protect public health by reducing burden of ADRs and optimising the use of medicines;

- Strengthen EU Network
- Engage patients and healthcare professionals
- Increase transparency and accountability
- Provide better information on medicines

Source: The new Pharmacovigilance legislation: an EMA perspective, IPA Conference, Jun11

Acronym Key:
PV – Pharmacovigilance
ADR - Adverse Drug Reaction
New EU PV Legislation
To Further Strengthen Pharmacovigilance

Regulation
(EC) No 726/2004: for CAPs
Chapter. 3
(EU) No 1235/2010 entered into force 2 July 2012

Directive
2001/83/EC: for NAPs incl. MRP/DCP
Title IX
2010/84/EU: entered into force 21 July 2012

Guideline
Volume 9A of the Rules Governing Medicinal Products in the EU

Good Pharmacovigilance Practices*

*Volume 9A remains reference as applicable until transition period ends or until that specific GVP module published

Acronym Key:
PV – Pharmacovigilance
CAP – Central Authorisation Procedure
NAP – National Authorisation Procedure
MRP – Mutual Recognition Procedure
DCP – Decentralised Procedure
# Good Pharmacovigilance Practices

**GVP Finalisation**

<table>
<thead>
<tr>
<th>Module</th>
<th>Module Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pharmacovigilance systems and their quality systems</td>
</tr>
<tr>
<td>II</td>
<td>Pharmacovigilance system master file</td>
</tr>
<tr>
<td>III</td>
<td>Pharmacovigilance inspections</td>
</tr>
<tr>
<td>IV</td>
<td>Pharmacovigilance system audits</td>
</tr>
<tr>
<td>V</td>
<td>Risk management systems</td>
</tr>
<tr>
<td>VI</td>
<td>Management and reporting of adverse reactions to medicinal products</td>
</tr>
<tr>
<td>VII</td>
<td>Periodic safety update report</td>
</tr>
<tr>
<td>VIII</td>
<td>Post-authorisation safety studies</td>
</tr>
<tr>
<td>IX</td>
<td>Signal management</td>
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<tr>
<td>X</td>
<td>Additional monitoring</td>
</tr>
<tr>
<td>XI</td>
<td>Public participation in pharmacovigilance</td>
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<tr>
<td>XII</td>
<td>Continuous PV, ongoing benefit-risk evaluation, regulatory action &amp; planning of public communication</td>
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<td>Incident management no longer under development. All topics originally intended in this module now to be included in module XII.</td>
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<td>International cooperation</td>
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<td>XV</td>
<td>Safety communication</td>
</tr>
<tr>
<td>XVI</td>
<td>Risk-minimisation measures: selection of tools and effectiveness indicators</td>
</tr>
</tbody>
</table>

**Acronym Key:**
GVP– Good Pharmacovigilance Practice
RMP vs. PSURs

Tools to be used differently at stages in the product lifecycle

RMP:
Main focus is planning
- Risk minimisation
- Data collection
- Ensuring effectiveness of measures

PSUR:
Main focus is benefit-risk evaluation:
- Ensure benefit risk balance remains favourable
- Signal detection and evaluation
- Ensure product information up to date
- Establish and publish the known risks of a substance

Acronym Key:
RMP – Risk Management Plan
PSUR - Periodic Safety Update Reports
RMP

Risk Management Plans firmly embedded in new legislation

- All new products to have RMP – clear legal basis
- Proportionate to identified and potential risks
- Transparent to public
- Key measures to be made conditions of MA
- Obligation to monitor effectiveness of risk minimisation – EMA / MS / MAH. Studies will be done to ensure;
  - safety messages are understood,
  - safety messages change prescribing and dispensing behavior of health professionals and
  - adverse reactions are reduced (health outcomes).
- Safety & Efficacy studies included - move towards integrated Benefit-Risk

Acronym Key:
RMP – Risk Management Plan
MA - Marketing Authorisation
MAH - Market Authorisation Holder
Post-Authorisation Safety Studies (PASS)
Polling Questions

- What is your experience in conducting non-interventional post-authorisation safety studies in the past 5 years?
  - No experience
  - Less than 2 studies
  - 3 or more studies
# Good Pharmacovigilance Practices

*GVP  Focus on NI PASS*

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**Acronym Key:**
- GVP – Good Pharmacovigilance Practice
- NI - Non-Interventional
- PASS - Post Authorisation Safety Studies
GVP Module VIII

Post-authorisation safety studies

Guideline on good pharmacovigilance practices (GVP)
Module VIII – Post-authorisation safety studies

Guidance and requirements for the conduct of any non-interventional PASS (NI PASS)

Guidance for Study Protocol Content section by section

Guidance for Study Report section by section

Guidance for EMA regulatory procedure for NIS PASS pursuant to a regulatory obligation

Acronym Key:
-GVP– Good Pharmacovigilance Practice
-NI- Non-Interventional
-PASS - Post Authorisation Safety Studies

## NI PASS Regulatory Requirements

### Key changes between Vol.9A & GVP Module VIII

<table>
<thead>
<tr>
<th></th>
<th>EudraLex Volume 9A</th>
<th>GVP Module VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY START-UP</strong></td>
<td>PASSE mandated by the Authority</td>
<td>PASS pursuant to an obligation</td>
</tr>
<tr>
<td></td>
<td>PASS performed at the MAH’s initiative</td>
<td>PASS voluntarily initiated by the MAH</td>
</tr>
<tr>
<td>Terminology</td>
<td>PASSE mandated by the Authority</td>
<td>PASS pursuant to an obligation</td>
</tr>
<tr>
<td></td>
<td>PASS performed at the MAH’s initiative</td>
<td>PASS voluntarily initiated by the MAH</td>
</tr>
<tr>
<td>Draft Protocol</td>
<td>Via CHMP</td>
<td>Via PRAC</td>
</tr>
<tr>
<td>reviewed by EMA</td>
<td></td>
<td>• = Pharmacovigilance Risk Assessment Committee</td>
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<tr>
<td>EMA review timelines</td>
<td>Not mentioned</td>
<td>60 days</td>
</tr>
<tr>
<td>After EMA</td>
<td>• Recommendation: CA notification</td>
<td>• Legislation: if letter of endorsement, CA notification</td>
</tr>
<tr>
<td>approval/Conduct of</td>
<td>• Annual report</td>
<td>• Progress reports predefined basis</td>
</tr>
<tr>
<td>the study</td>
<td>• Recommendation post study on public register</td>
<td>• Obligation to post study on EU PAS Register [interim arrangements in ENCePP Register]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local regulatory requirements for NI PASS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### STUDY AMENDEMENT

| Protocol review      | Not mentioned                                          | • PRAC review                                    |
|                      | In practice: reviewed by CHMP                          | • Timelines = 30 days                            |

### END OF STUDY

| Final study report   | Submitted to CA                                       | • Submitted to PRAC within 12 months of the end of data collection unless waiver granted |
NI PASS Protocol
Introduction

10 January 2013, MAH have obligation to comply with format & content of the study protocol for PASS

Guidance for the format and content of the protocol of non-interventional PASS (NI PASS)

Guidance for Study Protocol is to support consistency of presentation & information provided

Art 36 to 38 and Art 40 of the Commission Implementing Regulation (EU) No 520/2012

26 September 2012 EMA/623947/2012 Patient Health Protection

Template based on Art 38 of Implementing Regulation No 520/2012 with additional instructions of GVP Module VIII

Acronym Key:
NI - Non-Interventional
PASS - Post Authorisation Safety Studies
MAH - Market Authorisation Holder
Guidance on Protocol NI PASS

Notes on Format

✓ All headings & sub-headings of the format presented in the guidance should always be included
  - The same numbering should be used
  - Additional sub-headings can be added as necessary
  - Where a heading or sub-heading does not apply to the study “Not applicable” should be stated with a short justification

✓ All dates should be indicated in the format “DD Month YYYY” (e.g. 31 January 2013).

✓ Annex 1 should be used to list stand-alone documents not included in the protocol,
  - e.g. contact details of responsible parties and all investigators. In this case, a summary should be provided in the corresponding section of the protocol and reference should be made to Annex 1

✓ Annexes can be added to provide documents referred to in the protocol

✓ MAH(s)) should keep a copy of the protocol signed by the QPPV or his/her delegate (with the date of the signature) available for any future request or inspection

Acronym Key:
NI - Non-Interventional
PASS - Post Authorisation Safety Studies
MAH - Market Authorisation Holder
QPPV - Qualified Person Responsible for Pharmacovigilance at EU Level

Guidance for the format and content of the protocol of non-interventional PASS (NI PASS) 26 September 2012 EMA/623947/2012 Patient Health Protection
# Guidance on Protocol NI PASS

**PASS Information** - Table to be provided on Title Page

<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>Informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protocol version identifier</strong></td>
<td>Number</td>
</tr>
<tr>
<td><strong>Date of last version of protocol</strong></td>
<td>Date</td>
</tr>
<tr>
<td><strong>EU PAS register number</strong></td>
<td>Registration number in the EU PAS register; indicate “Study not registered” if the study has not been registered in the EU PAS register.</td>
</tr>
<tr>
<td><strong>Active substance</strong></td>
<td>List of pharmacotherapeutic group(s) (ACT codes) and active substance(s) subject to the study</td>
</tr>
<tr>
<td><strong>Medicinal product</strong></td>
<td>List of centrally authorised medicinal product(s) and/or, if possible, of nationally authorised products subject to the study</td>
</tr>
<tr>
<td><strong>Product reference</strong></td>
<td>Reference number(s) of centrally authorised products and/or, if possible, of nationally authorised products subject to the study</td>
</tr>
<tr>
<td><strong>Procedure number</strong></td>
<td>If applicable, Agency or national procedure number(s), e.g. EMA/X/X/XXX</td>
</tr>
<tr>
<td><strong>Marketing authorisation holder(s)</strong></td>
<td>Marketing authorisation holder(s) which initiate(s), manage(s) or finance(s) the study</td>
</tr>
<tr>
<td><strong>Joint PASS</strong></td>
<td>“Yes” or “No”</td>
</tr>
<tr>
<td><strong>Research question and objectives</strong></td>
<td>Summary of the research question and main objectives</td>
</tr>
<tr>
<td><strong>Country(-ies) of study</strong></td>
<td>List of countries where the study is to be conducted; if countries have not been identified yet, or if the list is not complete, this should be stated</td>
</tr>
<tr>
<td><strong>Author</strong></td>
<td>Name and contact details of the main author of the study protocol</td>
</tr>
<tr>
<td><strong>Marketing authorisation holder(s)</strong></td>
<td>Name, address and contact details of the marketing authorisation holder(s).</td>
</tr>
<tr>
<td><strong>MAH contact person</strong></td>
<td>Contact person for this PASS protocol submission (if this a joint PASS, only one person should be mentioned)</td>
</tr>
</tbody>
</table>

*Text in green italics is intended to guide reader on principal points to be considered for writing that section of protocol. It should be deleted if this guidance is used as a template.*
Guidance on Protocol NI PASS

PASS Information - Table of Contents

1. Table of contents
2. List of abbreviations
3. Responsible parties
4. Abstract
5. Amendments and updates
6. Milestones
7. Rationale and background
8. Research question and objectives
9. Research methods
   9.1. Study design
   9.2. Setting
   9.3. Variables
   9.4. Data sources
   9.5. Study size
   9.6. Data management
   9.7. Data analysis
   9.8. Quality control
   9.9. Limitations of the research methods
   9.10. Other aspects
11. Management and reporting of adverse events/adverse reactions
12. Plans for disseminating and communicating study results
13. References

Annex 1. List of stand-alone documents
Annex 2. ENCePP checklist for study protocols

3. List of all responsible parties can be kept in a stand alone document - Annex 1
4. Stand alone summary
6. Planned dates for study milestones should be indicated in a table..
9.1 The strength of the study design to answer the research question explained in this section.
9.2 Setting and study population defined in terms of persons, place, study time period, and selection criteria.
9.4 Strategies & data sources for determining exposures, outcomes and all other variables relevant to objectives..
12. Any plans for submission of progress reports & final reports; any arrangements made between MAH(s) for disseminating & communicating study results of Joint PASS.

Annex 2. A copy of the ENCePP Checklist for Study protocols completed and signed by the main author of the study protocol should be included in Annex 2.
GVP Module VIII

NI PASS Pursuant to an Obligation

Draft protocol reviewed by PRAC
if > 1 MS

Endorsement Letter

60 days

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

Local Requirements

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

Acronym Key:
GVP – Good Pharmacovigilance Practice
NI- Non-Interventional
PASS - Post Authorisation Safety Studies
PRAC- Pharmacovigilance Risk Assessment Committee
GVP Module VIII

NI PASS  Pursuant to an Obligation other correspondence with PRAC

Progress reports
- Timing should be specified in protocol
- Progress also reported in PSURs & RMP updates

Protocol amendment
- PRAC review required
- Review timelines = 30 days
- Applicable local requirements

End of study report
- Must be submitted within 12 months of the end data collection

Acronym Key:
GVP – Good Pharmacovigilance Practice
NI - Non-Interventional
PASS - Post Authorisation Safety Studies
PSUR - Periodic Safety Update Reports
RMP - Risk Management Plan
PRAC - Pharmacovigilance Risk Assessment Committee
Safety Reporting During a PASS
Drug Adverse Reaction

EU Legislation Definition

ICH E6

A response to a drug
which is noxious and unintended [...] at doses normally used [...]

EU Directive – NEW LEGISLATION

A response to a drug
which is noxious and unintended [...] at doses normally used [...] + from medication errors and + uses outside the terms of the marketing authorisation (including misuse and abuse)
**Safety Reporting**

**Prospective post-authorisation studies – EU requirements**

Until July 2012, before new EU PV Legislation

OLD

- EU
  - Serious AR
  - MAH
  - CA of MS where reaction occurred

Non-EU

- Serious AR
  - MAH

NEW

- EU
  - Non-serious AR
  - MAH
  - NS-ADR 90 Days
  - S-ADR 15 Days

- Non-EU
  - Serious AR
  - MAH

Acronym Key: AR – Adverse Reaction; CA - Central Authorisation; MAH - Market Authorisation Holder

New safety reporting requirements when new functionalities of the EudraVigilance database are validated by the EMA (approximately in 2015)

➢ GVP Module VI
Safety Reporting

Prospective post-authorisation studies - interim arrangements

- **GVP Module VI**
  - New safety reporting requirements in EU
  - Interim arrangements for non-serious Adverse Reactions¹

### Region where Adverse Reaction occurred

<table>
<thead>
<tr>
<th></th>
<th>Expedited Time Frames</th>
<th>Interim safety requirements until EudraVigilance new functionalities set up (2015)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious AR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occurring in the EU / countries</td>
<td>Report within 15 days</td>
<td>All countries</td>
</tr>
<tr>
<td>Occurring outside the EU</td>
<td>Report within 15 days</td>
<td>Germany, UK</td>
</tr>
<tr>
<td><strong>Non serious AR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occurring in the EU</td>
<td>Report within 90 days</td>
<td>Austria, Germany (vaccine only), Denmark, Poland, Romania</td>
</tr>
</tbody>
</table>

¹Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period, EMA/321386/2012 Rev. 4,5 December, 2012
Retrospective studies

GVP Module VI
VI.C.1.2.1.
Non-interventional studies

- For non-interventional study designs which are based on secondary use of data, adverse reactions reporting is not required.
- Reports of adverse events/reactions should only be summarised in the study report, where applicable.

Acronym Key:
GVP – Good Pharmacovigilance Practice
Polling Questions

- How ready is your company to address the new legislative changes described in order to conduct NI PASS today?
  > No action taken yet
  > Staff resources, processes/technology in progress
  > Staff resources, new processes/technology fully in place
Changes to the Format, Content and Submission of Periodic Safety Update Reports (PSURs)

History and rationale

Objectives

Periodicity, EU Reference Dates List

Overview of main changes

Top tips

Region-Specific Appendices

Relationship with other PV documents
Polling Questions

What is your experience in the submission of Periodic Safety Update Reports (PSURs)?

> No experience
> Some experience
> Significant experience
History of PSURs and rationale for new format
History

1992 CIOMS II Guideline on PSURs

1996 Step 4 - ICH E2C Guideline Published:
Clinical Safety Data Management – Periodic Safety Update Reports for Marketed Drugs

2003 Step 4 - Addendum to ICH E2C (R1) Published

1996 - 2010 Variously Adopted in the 3 ICH Regions

2003 – 2010 Business as usual until...

Acronym Key:
PSUR – Periodic Safety Update Reports
EU Legislative Changes

DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 15 December 2010
amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to
medicinal products for human use

of 15 December 2010
amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of
medicinal products for human and veterinary use and establishing a European Medicines Agency,
and Regulation (EC) No 1394/2007 on advanced therapy medicinal products
Rationale & Vision

Rationale

- ICH E2C originally created in 1990s
  - Guideline has not kept pace with regulatory/technology advances
- Overlap of content of ICH Guidelines E2C(R1), E2E and E2F
- Lack of modular approach
- Resources diverted away to duplicative document production, rather than focusing on risk management activities that could promote public health

Vision

- New ICH guideline will ensure that the reports have the role of being periodic benefit-risk evaluation reports.
  - Safety evaluation
  - Evaluation of all relevant available information (all use)
  - Benefit-risk evaluation
ICH Milestones

Draft ICH Concept Paper for the Review of ICH E2C
March 2010

Final Concept Paper
Periodic Safety Update Reports for Marketed Drugs E2C(R2) and gap and potential improvement analysis of ICH E2C, E2E and E2F
15 December 2010
Endorsed by the ICH SC on 16 December 2010

Periodic Benefit-Risk Evaluation Report (PBRER)
E2C(R2)

Current Step 4 version
dated 17 December 2012
Current Legal Basis in EU

COMMISSION IMPLEMENTING REGULATION (EU) No 520/2012
of 19 June 2012

Effective 10 January 2013

Guideline on good pharmacovigilance practices (GVP)
Module VII – Periodic safety update report

HMA
Heads of Medicines Agencies

22 June 2012
EMA/816292/2011
Objective of the PSUR

- To present a comprehensive and critical analysis of new or emerging information on the risks and, where pertinent, new evidence of benefit to enable an appraisal of overall benefit risk.

- To contain an evaluation of new relevant information that became available to the MAH during the reporting interval, in the context of cumulative information:
  - Examine whether new information is in accord with previous knowledge of the benefit risk profile
  - Summarises relevant new safety information that may impact the benefit risk profile
  - Summarises any important new efficacy and effectiveness information
  - Conduct an integrated B/R evaluation (where new important safety information has emerged)

Acronym Key:
PBRER - Periodic Benefit Risk Evaluation Report
MAH - Market Authorisation Holder
B/R – Benefit Risk
‘All drugs are dangerous, Some may also be useful’

N. Moore, BMJ, 2005, 330;539-40
Periodicity, EU Reference Dates and Data Lock Points
PSUR must be prepared at the following intervals:

- Immediately upon request
- Every six months from authorisation until product placed on the market
- Every six months for first two years on the market
- Annually for the next two years
- Thereafter every 3 years
- Exception – frequency and dates of submission are laid down as a condition of the MA or determined otherwise in the list of Union Reference Dates.

Submit:
- By day 70 for intervals up to 12 months
- By day 90 for intervals in excess of 12 months
What is the EURD List?
A comprehensive list of active substances and combinations of active substances for which PSURs shall be submitted:

- Legally binding
- Periodicity defined on a risk-based approach

Why was it put in place?
In order to facilitate the harmonisation of Data Lock Points (DLPs) and frequency of submission of PSURs for medicinal products containing the same active substance or the same combination of active substances subject to different marketing authorisations, authorised in more than one Member State.

- Rev 3 List published 21 Dec 2012 – comes into effect six months after publication

Acronym Key:
EURD- European Union Reference Dates
PSUR - Periodic Safety Update Reports
DLP – Data Lock Points
## EU Reference Dates List

### List of Union reference dates and frequency of submission of periodic safety update reports

<table>
<thead>
<tr>
<th>Active substances and combinations of active substances</th>
<th>European Union reference date (EURD)</th>
<th>PSUR Submission Frequency</th>
<th>DLP</th>
<th>Are PSURs required for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended?</th>
<th>Publication Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>(18f) fludeoxyglucose</td>
<td>14/11/94</td>
<td>3 years</td>
<td>30/11/14</td>
<td>No</td>
<td>01/10/12</td>
</tr>
<tr>
<td>1,3-butanediol, cinchocaine hydrochloride, dexamethasone</td>
<td>23/09/83</td>
<td>13 years</td>
<td>15/05/25</td>
<td>No</td>
<td>01/10/12</td>
</tr>
<tr>
<td>125i-human serum albumin</td>
<td>15/12/1989</td>
<td>13 years</td>
<td>15/12/25</td>
<td>No</td>
<td>01/10/12</td>
</tr>
<tr>
<td>131i-6-iodo-norcholesterol</td>
<td>21/06/1990</td>
<td>13 years</td>
<td>21/06/25</td>
<td>No</td>
<td>01/10/12</td>
</tr>
<tr>
<td>13C-urea</td>
<td>14/08/97</td>
<td>5 years</td>
<td>15/01/18</td>
<td>No</td>
<td>01/10/12</td>
</tr>
<tr>
<td>5 fluorouracil (i.v. application)</td>
<td>16/12/77</td>
<td>3 years</td>
<td>16/12/14</td>
<td>Yes</td>
<td>01/10/12</td>
</tr>
<tr>
<td>5 fluorouracil (topical application)</td>
<td>Not Available*</td>
<td>3 years</td>
<td>16/12/14</td>
<td>Yes</td>
<td>01/10/12</td>
</tr>
<tr>
<td>5 fluorouracil, salicylic acid</td>
<td>25/05/94</td>
<td>3 years</td>
<td>25/05/15</td>
<td>No</td>
<td>01/10/12</td>
</tr>
<tr>
<td>5-aminolevulinic acid (glioma)</td>
<td>07/09/07</td>
<td>3 years</td>
<td>07/03/15</td>
<td>Yes</td>
<td>01/10/12</td>
</tr>
<tr>
<td>5-aminolevulinic acid (keratosis)</td>
<td>07/09/07</td>
<td>6 months</td>
<td>14/06/13</td>
<td>No</td>
<td>01/10/12</td>
</tr>
<tr>
<td>abacavir</td>
<td>29/06/98</td>
<td>3 years</td>
<td>31/12/13</td>
<td>Yes</td>
<td>01/10/12</td>
</tr>
<tr>
<td>abacavir, lamivudine</td>
<td>14/11/03</td>
<td>3 years</td>
<td>31/12/13</td>
<td>Yes</td>
<td>01/10/12</td>
</tr>
</tbody>
</table>
Generics/Well-Established Use

1) Generics, well-established use, and traditional herbal medicinal products are exempted from submitting PSURs except in the following circumstances:

- The marketing authorisation provides for the submission of PSURs as a condition.
- PSURs is (are) requested due to concerns relating to PV data or due to the lack of PSURs relating to an active substance after the MA has been granted (e.g. when the “reference” medicinal product is no longer marketed).

2) For the products where PSURs are no longer required to be submitted routinely, it is expected that marketing authorisation holders will continue to:

- Evaluate the safety of their products on a regular basis and
- Report any new safety information that impacts on the benefit-risk profile or the product information.

Acronym Key:
PSUR - Periodic Safety Update Reports
PV – Pharmacovigilance
MA - Marketing Authorisation
Polling Questions

Which one new section of the PSUR do you anticipate most difficulty in preparing?

- Signal and Risk Evaluation
- Benefit Evaluation
- Integrated Benefit-Risk Analysis for Approved Indications
- New Format and Requirements for Summary Tabulations

Acronym Key:
PSUR - Periodic Safety Update Reports
Overview of Selected Main Changes/New Requirements
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Updates</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td><strong>Signal and Risk Evaluation</strong></td>
<td><strong>Subsection 16.1:</strong> Summary of safety concerns (same as safety specification as per ICH E2E).</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Subsection 16.2:</strong> Signal evaluation. Summarise the results of signal evaluation (refuted signals or potential/identified risk).</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Subsection 16.3:</strong> Evaluation of risks and new information. Critical appraisal of new information (e.g. new information may change a potential risk to an identified risk). Based on interval data.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Subsection 16.4:</strong> Characterisation of risks (based on cumulative data). Describe limitations and missing information.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Subsection 16.5:</strong> Effectiveness of risk minimisation (if applicable).</td>
</tr>
<tr>
<td>Section</td>
<td>Title</td>
<td>Updates</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>17</td>
<td>Benefit Evaluation</td>
<td><strong>Subsection 17.1:</strong> Baseline efficacy and effectiveness information.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Subsection 17.2:</strong> Newly identified information on efficacy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Subsection 17.3:</strong> Characterisation of benefits.</td>
</tr>
<tr>
<td>18</td>
<td>Integrated Benefit Risk Analysis for Approved Indications</td>
<td><strong>Subsection 18.1:</strong> Benefit risk context &amp; medical need.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Subsection 18.2:</strong> Benefit risk analysis evaluation.</td>
</tr>
</tbody>
</table>
A lot to consider!
Top Tips for Preparing the new PSUR
How to Prepare

Implementing the changes - practical considerations

- Revise SOPs and templates to account for changes
- Provide staff training
- Thoroughly review data requirements
  - Exposure data
  - Data tabulations
- Review resource required to write/review PSURs
- Review ex-EU reporting requirements
  - Regional requirements
  - Waivers
- Ensure Regulatory dept are aware of changes
  - Change in periodicity
- Ensure signals are tracked and evaluated for inclusion in PSUR
- Multiple functions contribute to PSUR
  - Ensure various contributors are aware of roles & responsibilities
  - Use PSUR KO checklist

Acronym Key:
SOP- Standard Operating Procedure
PSUR - Periodic Safety Update Reports
PBRER Process Flow

Acronym Key:
PBRER- Periodic Safety Update Reports
Polling Questions

- What type of staff resource do you think will need to be directly involved with preparing the new-style PSUR (choose multiple if required)?

  > Physicians
  > Pharmaco-epidemiologists
  > Statisticians
  > Safety Scientists/PV Experts

Acronym Key:
PSUR - Periodic Safety Update Reports
PV - Pharmacovigilance
Appendices – What to Note (Region-Specific Overview)
PSUR Regional Requirements

EU Specific Appendices
- Proposed product information
- Reference information comparison
- Proposed additional PV and risk minimisation activities
- Summary of ongoing safety concerns
- Reporting of results from post-authorisation safety studies
- Effectiveness of risk minimisation

US Specific Appendices
- Index case line listings
- Medwatch forms

Acronym Key:
PSUR - Periodic Safety Update Reports
PV - Pharmacovigilance
Link with RMPs and DSURs
### PSUR, DSUR and RMP

*Common Ground-sections of documents that can be shared*

<table>
<thead>
<tr>
<th>PSUR section</th>
<th>Share with RMP</th>
<th>Share with DSUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide MA Status</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Action taken for safety reasons</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cumulative exposure in clinical trials/postmarketing</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cumulative tabulations of SAEs from Clinical Trials</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Completed/ongoing clinical trials, LTFU, Other therapeutic use, new data related to combo therapies</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Finding from non-interventional studies</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Information from other sources</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Non clinical data</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Literature</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Lack of efficacy in clinical trials</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Late breaking information</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Conclusions &amp; actions</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Acronym Key:**
- PSUR - Periodic Safety Update Reports
- DSUR - Development Safety Update Report
- RPM - Risk Management Plan
- MA - Marketing Authorisation
- SAE – Serious Adverse Event
- LTFU - Lost to Follow-up
Summary

- Changes to the format, content and submission of Periodic Safety Update Reports (PSURs)
  - Deirdre McCarthy

- Considerations for designing and conducting post authorisation safety studies (PASS) that comply with the new requirements
  - Michelle Bulliard
Questions?

Q&A

- If you are interested in asking a question, you may either:
  - Click on the hand icon located in the webinar control panel on your screen and we will unmute your line
  - Type a question in the question box and we will ask the question on your behalf

Upcoming Events

- **Post-Approval Summit**
  - May 7-8, 2013
  - Conference Center at Harvard Medical School, Boston, MA
  - [www.postapproval.org](http://www.postapproval.org)

- **GRP Webinar: Generating Evidence for Medical Devices for Supporting Market Approval and Monitoring Safety Post-Approval**
  - February 27, 2013, 11am-12pm EST
  - [https://www1.gotomeeting.com/register/605902273](https://www1.gotomeeting.com/register/605902273)