Update regarding PSUR and RMP for herbal and homeopathical medicinal products

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Legal basis


AMG
StF: BGBl. Nr. 185/1983, BGBl. I Nr. 162/2013

Pharmakovigilanz-Verordnung (2006)

GVP-Module
Guidelines on good pharmacovigilance practices
Legal basis

EMA has published the following modules:

**Module I:** Pharmacovigilance systems and their quality systems
**Module II:** Pharmacovigilance system master file
**Module III:** Pharmacovigilance inspections
**Module IV:** Pharmacovigilance audits
**Module V:** Risk management systems
**Module VI:** Management and reporting of adverse reactions to medicinal products
**Module VII:** Periodic safety update report
**Module VIII:** Post-authorisation safety studies
**Module IX:** Signal management
Legal basis

Module X: Additional monitoring
Module XV: Safety communication
Module XVI: Risk minimisation measures

Further planned modules:
Modul XI: Public participation in pharmacovigilance
Modul XII: Cont. pharmacovigilance, ongoing benefit-risk evaluation
Modul XIV: International cooperation

General changes

- PSURs – not obligatory for all products
- Planned electronic transmission to a PSUR repository
- Information over the internet websites: AGES and EMA ("transparency")
- RMP obligatory for nearly all new applications
- PASS and PAES as risk minimisation measures
- Evaluation of the imposed/agreed risk minimisation measures
General changes

- Changes of the product information, „additional monitoring“
- Establishing of the PRAC (Pharmacovigilance Risk Assessment Committee)
- Signal detection under inclusion of the PRAC
- Compilation of Pharmacovigilance System Masterfile (PSMF) by MAH and regular audits
- Adverse event reporting: non serious cases, reporting by the patients
Objectives of a risk management plan

- characterise the safety profile of the medicinal product(s)
- document measures to prevent or minimise the risks
- assess the effectiveness of those interventions;
- document post-authorisation obligations that have been imposed as a condition of the marketing authorisation
- describe what is known and not known about the safety profile
- Use in medical practice, document the need for studies on efficacy in the post-authorisation phase
- include a description of how the effectiveness of risk minimisation measures will be assessed
Situations when a risk management plan should be submitted

- for all new marketing applications
- with an application involving a significant change to an existing marketing authorisation:
  - new dosage form, new route of administration;
  - new manufacturing process of a biotechnologically-derived product;
  - paediatric indication or other significant change in indication;
- at the request of the agency or national competent authority when there is a concern about a risk affecting the risk-benefit balance;
- with a submission of final study results impacting the RMP.
Overview of the parts and modules of the RMP

**Part I** Product(s) Overview

**Part II** Safety Specification

- Module SI: Epidemiology of the indication(s) and target population(s)
- Module SII: Non-clinical part of the Safety Specification
- Module SIII: Clinical trial exposure
- Module SIV: Populations not studied in clinical trials
- Module SV: Post-Authorisation Experience
- Module SVI: Additional EU requirements for the Safety Specification
Overview of the parts and modules of the RMP

Module SVII: Identified and potential risks
Module SVIII: Summary of the safety concerns

Part III Pharmacovigilance Plan
Part IV Plans for post-authorisation efficacy studies
Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)
Part VI Summary of the RMP
Part VII Annexes
Identified risk

An untoward occurrence having an adequate evidence of an association with the medicinal product of interest

For example an adverse reaction:

- from non-clinical studies, confirmed by clinical data;
- from well-designed clinical trials or epidemiological studies suggesting a causal relationship;
- suggested by a number of well-documented spontaneous reports (temporal relationship and biological plausibility), such as anaphylactic reactions or application site reactions
Potential risk

An untoward occurrence with some basis for suspicion of an association with the medicinal product of interest but not confirmed

For example:

- toxicological findings seen in non-clinical safety studies, not observed in clinical studies;
- adverse events observed in clinical trials or epidemiological studies, suspicion of an association,
- signal from a spontaneous adverse reactions
- an event known to be associated with other active substances within the same class
Missing information

Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations

Examples of missing information include populations not studied, high likelihood of off-label use.

Common examples:

- Use in pregnant and lactating women
- Children
- Patients with hepatic / renal impairment
## RMP modules for new applications

### Figure V.3. Requirements for new marketing applications

| Type of new application                      | Part I | Part II-Module SI | Part II-Module SII | Part II-Module SIII | Part II-Module SIV | Part II-Module SV | Part II-Module SVI | Part II-Module SVII | Part II-Module SVIII | Part III | Part IV | Part V | Part VI | Part VII |
|---------------------------------------------|--------|-------------------|--------------------|--------------------|--------------------|-------------------|-------------------|-------------------|---------------------|-----------------|---------|-------|-------|--------|---------|
| New active substance                        | ✓      | ✓                 | ✓                  | ✓                  | ✓                  | ✓                 | ✓                 | ✓                 | ✓                   | ✓               | ✓       | ✓     | ✓     | ✓      | ✓       |
| Similar biological                          | ✓      | ✓                 | ✓                  | ✓                  | ✓                  | ✓                 | ✓                 | ✓                 | ✓                   | ✓               | ✓       | ✓     | ✓     | ✓      | ✓       |
| Informed consent¹                           | ✓      | ✓                 | ✓                  | ✓                  | ✓                  | ✓                 | ✓                 | ✓                 | ✓                   | ✓               | ✓       | ✓     | ✓     | ✓      | ✓       |
| Generic medicine                            | ✓      | ✓                 | ✓                  | ✓                  | ✓                  | ✓                 | ✓                 | ✓                 | ✓                   | ✓               | ✓       | ✓     | ✓     | ✓      | ✓       |
| Hybrid medicinal products                    | ✓      | ✓                 | ✓                  | ✓                  | ✓                  | ✓                 | ✓                 | ✓                 | ✓                   | ✓               | ✓       | ✓     | ✓     | ✓      | ✓       |
| Fixed combination                           | ✓      | ✓                 | ✓                  | ✓                  | ✓                  | ✓                 | ✓                 | ✓                 | ✓                   | ✓               | ✓       | ✓     | ✓     | ✓      | ✓       |
| “Well established use”                      | ✓      | ✓                 | ✓                  | ✓                  | ✓                  | ✓                 | ✓                 | ✓                 | ✓                   | ✓               | ✓       | ✓     | ✓     | ✓      | ✓       |
| “Same active substance”                     | ✓      | ✓                 | ✓                  | ✓                  | ✓                  | ✓                 | ✓                 | ✓                 | ✓                   | ✓               | ✓       | ✓     | ✓     | ✓      | ✓       |

¹ Application under Article 10(c) of Directive 2001/83/EC

[^]: May be omitted under certain circumstances

[*: Modified requirement]
How to write a Risk Management Plan?

- Use the structure as provided in the Guidance on format of the risk management plan (RMP) in the EU - in intergated format (structure and tables)
- Write from a risk-based view
- Observe that the RMP is an alone standing document
How to write a Risk Management Plan?

• For a well-established use application („bibliographische Zulassung“) all sections with the exception of Part II module SII-IV have to be completed
• For herbal applications hypersensitivity is a common identified or potential risk
• Content of alcohol should be considered
• SmPC is not the Summary of safety concerns
RMP required for:

- New applications since 2012
- For significant changes (new dosage, new application form, new indication, new studies etc.)
- When requested by EMA or AGES

Waiver from RMP submission

Traditional herbal application (AMG §12) and homeopathic products registered according to AMG §11

No RMP needed, waiver is sufficient
PSUR - PBRER

- Format and content of PSURs based on Periodic Benefit Risk Evaluation Report (PBRER) described in the ICH-E2C(R2) guideline. PBRER replaces format described in ICH-E2C(R1).
- Risk based periodicity
- European Union Reference Date list (EURD)
- Single assessment – PSUSAs – *under preparation*
- Electronic reporting to EU repository at EMA – *not in place yet*
- Not routinely required for low risk/old products
  - generic medicinal products (DIR Art 10(1))
  - well-established use medicinal products (DIR Art 10a)
  - homeopathic medicinal products (DIR Art 14)
  - traditional herbal medicinal products (DIR Art 16a)
- Changes to safety information might lead to safety variation -
Contents:
Part I: Title page including signature
Part II: Executive Summary
Part III: Table of Contents
1. Introduction
2. Worldwide marketing authorisation status
3. Actions taken in the reporting interval for safety reasons
4. Changes to reference safety information
5. Estimated exposure and use patterns
6. Data in summary tabulations
7. Summaries of significant findings from clinical trials during the reporting interval
8. Findings from non-interventional studies
9. Information from other clinical trials and sources
10. Non-clinical Data
11. Literature
12. Other periodic reports
13. Lack of efficacy in controlled clinical trials
14. Late-breaking information
15. Overview of signals: new, ongoing or closed
16. Signal and risk evaluation
17. Benefit evaluation
18. Integrated benefit-risk analysis for authorised indications
19. Conclusions and actions
20. Appendices to the PSUR
PSUR - PBRER

A PSUR is required for drugs with

- Full MA (Vollzulassung)
- Condition in the MA
- „Yes“ in the EURD list, even if no full MA

EURD list column:
Are PSURs required for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended?
Generics (Article 10(1) Dir. 2001/83/EC) and Well-established use (Article 10a Dir. 2001/83/EC), Homeopathic (Article 14 Dir. 2001/83/EC) and Traditional Herbal (Article 16a Dir. 2001/83/EC) medicinal products are exempted from submitting PSURs unless:

- The MA provides for the submission of PSURs as a condition (PSUR period has to be included in MA) or

- Requested by a Competent Authority in a Member state due to:
  
  o Concerns relating to pharmacovigilance data
  o Lack of PSURs relating to an active substance after the MA has been granted.
Directive 2001/83/EC:

Article 10a: Active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years

Article 14: Only homeopathic medicinal products which satisfy a set of conditions (orally or externally, no specific therapeutic indication, sufficient degree of dilution)

Article 16a: Traditional herbal medicinal product
A submission of a PSUR for a generic drug or a well established use drug (§ 10a) is not necessary when a substance (or a combination of substances) is not mentioned on the EURD list.

Cave: changes in the EURD list!

Questions regarding EURD list (EMA-Homepage) mailto: eurdlist@ema.europa.eu.

Marketing authorisation holders for products authorised before 02 July 2012 (centrally authorised) and 21 July 2012 (nationally authorised)

- frequency and dates of submission of PSURs not laid down as a condition to the MA or in EURD list shall submit PSURs according to the following submission schedule
  - at 6 months intervals once the product is authorised, even if it is not marketed;
  - once a product is marketed, 6 monthly PSUR submission should be continued following initial placing on the market in the EU for 2 years, then once a year for the following 2 years and thereafter at 3-yearly intervals.
PSURs for homeopathic drugs

- Only needed for authorised drugs (nur für zugelassene und nicht für registrierte) starting with the number „3“
- For those drugs starting with HOM- no PSUR has to be submitted.
## EURD list

<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>Submission date</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>Procedure number of the PSUR single assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>capsaicin</td>
<td>15.05.2009</td>
<td>1 year</td>
<td>24.7.2014</td>
<td>yes</td>
<td>PSUSA/000 00533/201 405</td>
</tr>
</tbody>
</table>
PSUR - PBRER

PSUR submission to PSUR repository

- EU-single assessment (PSUSA)
- Non-EU-single assessments: authorised only in one country and those substances which do not appear on the EURD list
  → Repository for PSURs of both types, to support the same process of submission, storage and retrieval
  Currently under preparation (testing phase), also MAHs may participate in testing
  Purely national authorised products not subject to single assessment will have to be submitted to the repository, too
Timelines:

- within 70 calendar days of the DLP (day 0) for PSURs covering intervals up to 12 months
- within 90 calendar days of the DLP (day 0) for PSURs covering intervals in excess of 12 months;
- ad hoc PSURs requested by competent authorities: normally specified in the request, otherwise the ad hoc PSURs should be submitted within 90 calendar days of the data lock point.
How to write a PSUR (PBRER)?
• Use the structure as provided in the GVP Module VII
• Write from a risk-based view
• Please observe that the PSUR (PBRER) is an alone standing document

How to submit a PSUR (PBRER)?
• On CD with a cover letter to AGES or over CESP, not as a paper copy; submission to the repository as soon as available
Pharmacovigilance system / Pharmakovigilanz-System
A pharmacovigilance system is defined as a system used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.

Pharmacovigilance system master file
Detailed description of the pharmacovigilance system, which is established by the MAH for one or more authorised medicinal products.

QPPV / Pharmakovigilanzverantwortliche/r
Individual named by a pharmaceutical company as the main person responsible for ensuring that the company (MAH) meets its legal obligations for the monitoring of the safety of the product/s on the market.
New application: Only a submission of the PSMF summary is required. It has to include the following statement:

- proof for a qualified person responsible for pharmacovigilance;
- the Member States in which the qualified person resides and carries out his/her tasks;
- the contact details of the qualified person;
- a statement signed: applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX;
- a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.
• QPPV has to both reside and operate in the Union (+ NO, IS, FL)
• Details of keeping have to be entered in the Extended Medicinal Product Dictionary (XEVMPD), including changes
• All MAHs have to register
• Unique code will be assigned
• PSMF not part of the marketing authorisation (MA) dossier and is maintained independently from the MA
• It should be permanently available for inspection and should be provided within 7 days to the Competent Authorities if requested
• Name and contact details of a QPPV and each change of these data have to be reported to AGES and agency

• National authorisation:
  Change of a PSMF summary has to be done as variation type IA

• At the latest until 02 July 2015 (for CAP) and 21 July 2015 (for all other registrations) a PSMF has to be submitted either in the frame of a renewal or as an extra submission