EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

GVP Module VII – Periodic Safety Update Report

Fourth Stakeholders Forum on the implementation of the new Pharmacovigilance legislation, 27th February 2012

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Points to note for PSURs

- PSUR format and content
- Requirements for PSUR submissions and the URD list
- New procedure with PRAC involvement
- Single EU assessment
- Outcomes and implementation
- Transparency
- Quality Management System
- Transitional arrangements

1. Format and Content (1/2)

- Implementing Measure sets out the requirements (including period for transition to new format).

- Interface with ICH E2C(R2) (*Annexes referenced in the module*)

- Summary information, scientific safety evaluation and integrated benefit-risk evaluation

- Some modules will include both cumulative and interval data/information.

-No routine requirement for line listings. However, line listings may be requested during the assessment.

- Summary tabulations (serious and non serious) will be included. Case narratives to be provided where relevant to the scientific analysis of a signal or safety concern.

Possibility for common modules with RMP

Modules of the Safety Specification

1. PSUR Exposure and Use Patterns (+Actions taken in the reporting period for safety reason) ~ RMP Post Authorisation experience.
2. Summary of safety concerns (PSUR input)
3. Characterisation of risks (PSUR output)

and

4. Evaluation of the effectiveness of risk minimisation

- DSUR mapping not addressed in GVP module.

2. PSUR submissions - general requirements (1/3)

1. Submitted in accordance with Article 107c paragraph 2 and Article 28 (2) of Regulation (EU) 1235/2010:

   "*every 6 months during the first 2 years following the initial placing on the market, once a year for the following 2 years and at three-yearly intervals thereafter*"

2. According to the condition of the MA
3. According to the List of Union Reference Dates (URD) and frequency of submission.
4. PSURs also need to be submitted immediately upon request from a Competent Authority.

Generics, well established use, homeopathic and THMPs

As per Article 107b (3), by way of **derogation**, Generics (Article 10(1) Dir. 2001/83/EC), 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 the routine requirement for submitting PSURs ***unless***:

1) The MA provides for the submission of PSURs as a condition or
2) Requested by a Competent Authority in a Member state due to:

- **Concerns relating to pharmacovigilance data**
- **Lack of PSURs relating to an active substance after the MA has been granted.**

Requests for PSURs

The substances for which PSURs for generic, WEU,THMP and homeopathic medicinal products are required will be specified on the URD list.

Rationale:

- Facilitate and optimise the single EU assessment process
- Avoid duplication of requests for PSURs
- Support transparency
- Provide predictability for MAHs

❖ Public consultation on the draft URD list envisaged for April 2012.

3. Role of PRAC in decision-making process

Centrally authorised medicine is involved

Assessment report by a rapporteur appointed by PRAC

↓

PRAC: adoption and recommendations

↓

CHMP: opinion on regulatory action, based on PRAC recommendations

↓ *CHMP=PRAC*

Decision transmitted to **EC**

↓ *CHMP≠PRAC*

Written explanation together with a decision

4. Single EU assessment

Key Differences from current PSUR-WS:

- Legal basis
- Different scope and submission requirements (e.g. no routine requirement for generics)
- PRAC involvement with payments to Rapporteurs
- Timelines for procedure defined in legislation.
- Benefit-risk evaluation based on cumulative data.
- Assessment will lead to legally binding outcomes (maintain, vary, revoke, suspend).
- Annex to the CHMP opinion/CMDh position with recommendations for product information (new safety information/key risk minimisation measures).

5. Single EU assessment – binding outcomes

No CAP

CG position based on recommendations from the PRAC + TT for implementation

By consensus — 30 days — **No consensus**

NEW

CG agreement + TT for implementation sent to MAH(s) and all NCAs

NCAs to implement action/MAH(s) to submit variation to NCAs

Majority position sent to EC

EC decision (Art. 33, 34) to MS

30 days

National implementation

At least 1 CAP

CHMP opinion based on recommendations from the PRAC + TT for implementation

For non CAP — 30 days — **For CAP**

EC decision (Art. 33, 34) to MS

30 days

National implementation

EC decision (incl. Art. 127a decision to MS, if applicable)

RA Action = maintain / vary / revoke or suspend MA(s)

6. Transparency

The following documents must be made publicly available by means of the European medicines web-portal:

- Final assessment conclusions of the adopted assessment reports.
- PRAC recommendations including relevant annexes
- CMD(h) position
- CHMP opinion
- European Commission Decision.

7. Stepwise implementation of changes for PSURs

July 2012:

- New format and content (legal transitional period to be defined in the Implementing measure).
- List of EU reference dates and frequency of submission will be published
- PRAC involvement in assessment of PSURs for CAPs.

Postponed until after 2012:

- Single EU assessment procedure
- Development of a PSUR repository

Discussion and questions.

EU Specific requirements – regional annexes

1. Additional pharmacovigilance and risk minimisation activities
2. EU marketing authorisation status
3. Company core safety information and summary of product characteristics
4. Summary of ongoing safety concerns
5. Reporting of results from post-authorisation safety studies in PSURs

PSUR section	RMP section
Section 2 – "Worldwide marketing approval status" EU marketing approval status included in the EU Regional Appendix	Sub-section of part I – "Product overview"
Section 3 – "Actions taken in the reporting period for safety reason"	Part II, module SV – "Post-authorisation experience", section "Regulatory and marketing authorisation holder action for safety reason"
Sub-section 5.2 – "Cumulative and interval patient exposure from marketing experience"	Part II, module SV – "Post-authorisation experience", section "Non-study post-authorisation exposure"
Sub-section 16.1 – "Summaries of safety concerns"	Part II, module SVIII – "Summary of the safety concerns" (as included in the version of the RMP which was current at the beginning of the PSUR reporting interval)
Sub-section 16.4 – "Characterisation of risks"	Part II, Module SVII – "Identified and potential risks"
Sub-section 16.5 – "Effectiveness of risk minimisation (if applicable)"	Part V – "Risk minimisation measures", section "Evaluation of the effectiveness of risk minimisation activities"

Quality Management System (MAH)

1. Submissions - Check regularly the URD list, procedures in place to follow the requirements established by the Agency for the submission of PSURs to the repository
2. Production of PSURs according to legal requirements.
3. Where the submission of a risk management plan (RMP) is not required, the marketing authorisation holder should maintain on file a specification of important identified risk, important potential risks and important missing information in order to support the preparation of the PSURs.
4. QPPV responsibilities re production and submission, quality, responses, awareness of conclusions, PRAC recommendations, CHMP opinions, CG positions and actions to be implemented.
5. Record management

Outcome of the single EU assessment (variation)

Implementation of recommendations for nationally authorised products:

- Annex to the CHMP opinion/CG position will include

  - the new safety warnings and

  - key risk minimisation recommendations

  to be included in the relevant sections of the product information.

- This annex should also include timelines for implementation by the marketing authorisation holder to submit a variation.