Federal Agency for Medicines and Health Products
(FAMHP)

New Pharmacovigilance Legislation: PSURs & Renewals

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In this presentation …

A. **PSURs: from the preparation of the PSUR to the implementation of European Commission decision/national actions**

1. frequency of submission
2. requirement to submit PSURs for generics, well-established use, traditional herbal and homeopathic (simplified registration procedure) medicinal products
3. EMA PSUR repository
4. assessment procedure
5. new format and content
6. Overview

B. **Renewals:**

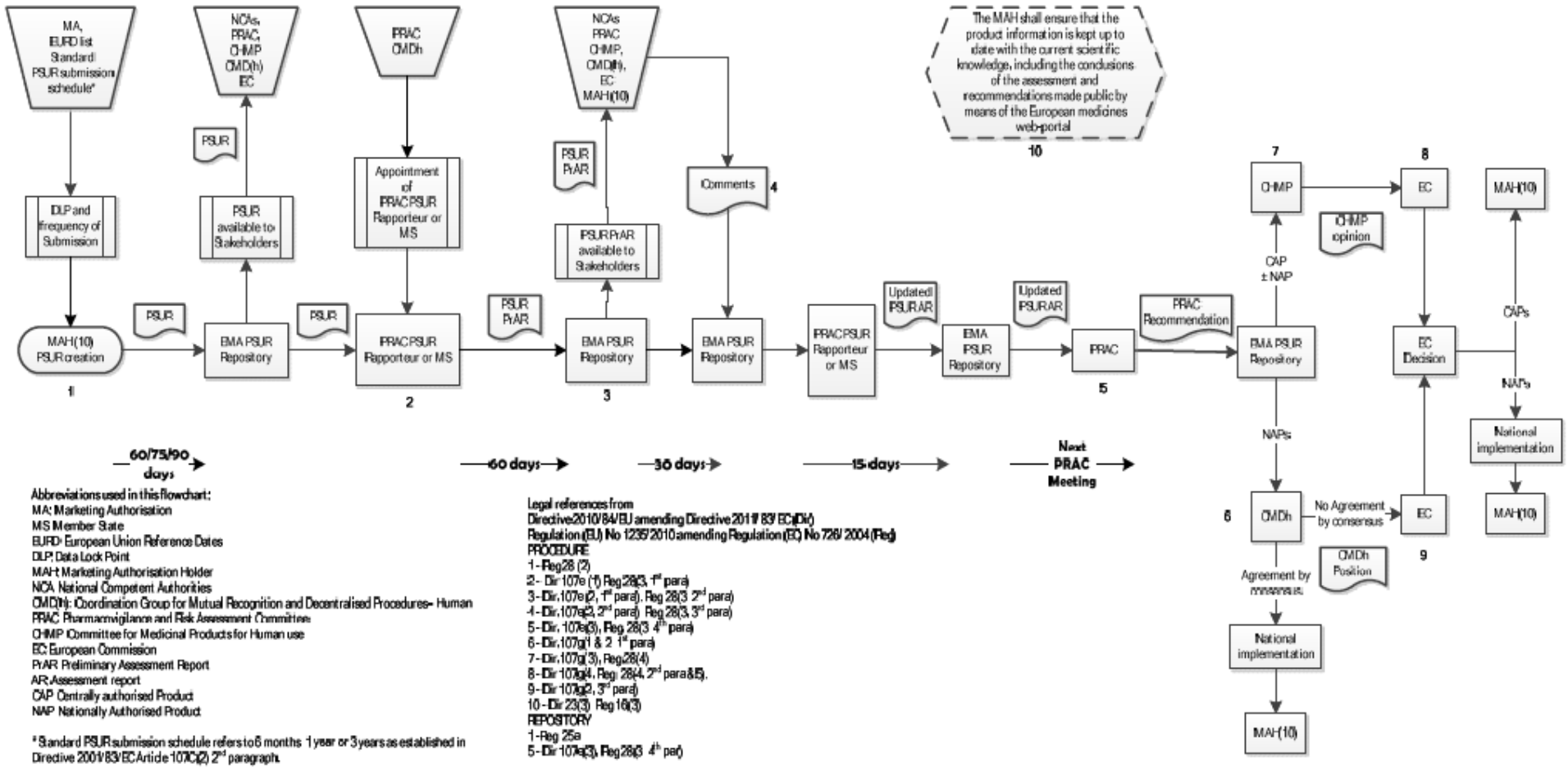
1. What changes in the legislation
2. Data requirements
3. Assessment procedure
4. Overview

Stepwise implementation over the next years,
due to transitional measures and EMA/MS priorities
⇨ Focus on July 2012

PSURs

From the preparation of the PSUR to the implementation of European Commission decision/national actions

Figure VII.1. PSUR procedure - general process



1. PSUR submission frequency

General requirements

- **Possible PSUR cycles > 2/21 July 2012:**

  1. According to the List of Union Reference Dates (URD) and frequency of submission:
     - « New legal provision», although more or less comparable to current "PSUR Work Sharing and Synchronization Lists", which have no formal legal basis
     - public consultation ongoing - target: Sept 2012?
  2. According to condition of the MA
  3. According to "Routine" or "standard" PSUR cycle = every 6 months until 2 years of marketing experience in the EU, once a year for the following 2 years and at 3-yearly intervals thereafter [Dir. 2001/83 Article Art 107c(2)(b) 2 and Reg. 726/2004 Article 28 (2)]

- **Immediately upon request from a Competent Authority** [Dir. Art 107c(2) second subparagraph]

1. PSUR submission frequency

List of European Union reference dates and frequency of submission of PSURs: "URD List"

- **Objectives:**
  - ✓ Harmonisation PSUR submission for products containing the same active substance or combination in order to allow the preparation of a EU single assessment cfr. current PSUR Work Sharing and Synchronization Lists
  - ✓ Periodicity is defined on the basis of a risk-based approach: limited safety information available, important missing information e.g. children, pregnant women,
  - ✓ Optimisation of the management of PSURs (cfr. spread evenly over time, transparent to all stakeholders, ..)
- **Scope:**
  - ✓ Comprehensive list of substances and combinations of active substances (sources: existing PSUR work sharing and synchronisation lists, EVMPD):
  - ✓ Includes not only chemicals (cfr. current lists), but also biologicals such as vaccines and blood products, ..
  - ✓ Includes also centrally authorised products
  - ✓ Will be updated in accordance to "list of all medicinal products for human use authorised in the Union" as referred to in [Reg. Art 57(b)]

1. PSUR submission frequency

List of European Union reference dates and frequency of submission of PSURs: "URD List"

Public consultation on the list of Union reference dates and frequency of submission of Periodic Safety Update Reports

Related Information:

List of European Union Reference Dates - Introductory cover note for public consultation: http://ema-wip.emea.eu.int/docs/en_GB/document_library/Other/2012/04/WC500124998.pdf

Submission of comments on the EURD list: http://ema-wip.emea.eu.int/docs/en_GB/document_library/Template_or_form/2012/04/WC500125001.xls

ID	Names of active substances or combinations of active substances	European Union reference date (EURD)	Proposed PSUR Submission Frequency	Proposed DLP	Are PSURs required for Generics? Yes/No
1	123i-hippuran	19/01/1996	5 years	19/01/2022	No
2	123i-mibg	31/01/1995	> 5 years	01/01/2020	No
3	125i-human serum albumin	15/12/1989	> 5 years	01/01/2025*	No
4	131i-6-iodo-norcholesterol	21/06/1990	> 5 years	01/01/2025*	No

1. PSUR submission frequency

List of European Union reference dates and frequency of submission of PSURs: "URD List"

- List will be agreed by CMD(h) / CHMP, following PRAC consultation [Dir.Art 107c(4) + (6)]
- Publication URD List on EMA web-portal: Probably Sept 2012 ? [Dir.Art 107c(4) to (7), Reg. Art 26(1)(g)]
  - ✓ Some details regarding rapporteurs will not yet be published
- List will be legally binding following publication, and will replace the current PSUR work sharing and synchronisation lists
- URD list "on top":
  - ⇨ Will overrule the "routine" submission cycle
  - ⇨ MAHs shall vary, if applicable, the condition laid down in their marketing authorisations
  - ✓ Any change to the dates of submission and frequency on PSURs specified in the marketing authorisation shall take effect 6 months after the date of publication [Dir.Art 107c(7)]

List of European Union reference dates and frequency of submission of PSURs: "URD List"

- The URD list will be subject to changes:
  - E.g. following approval new indication, signal detection, …
  - Active substance newly authorised
  - MAH request to the CHMP or the CMDh [Dir. Art 107c(6)] to determine URD / change frequency:
    - for reasons relating to public health;
    - in order to avoid a duplication of the assessment;
    - in order to achieve international harmonisation.

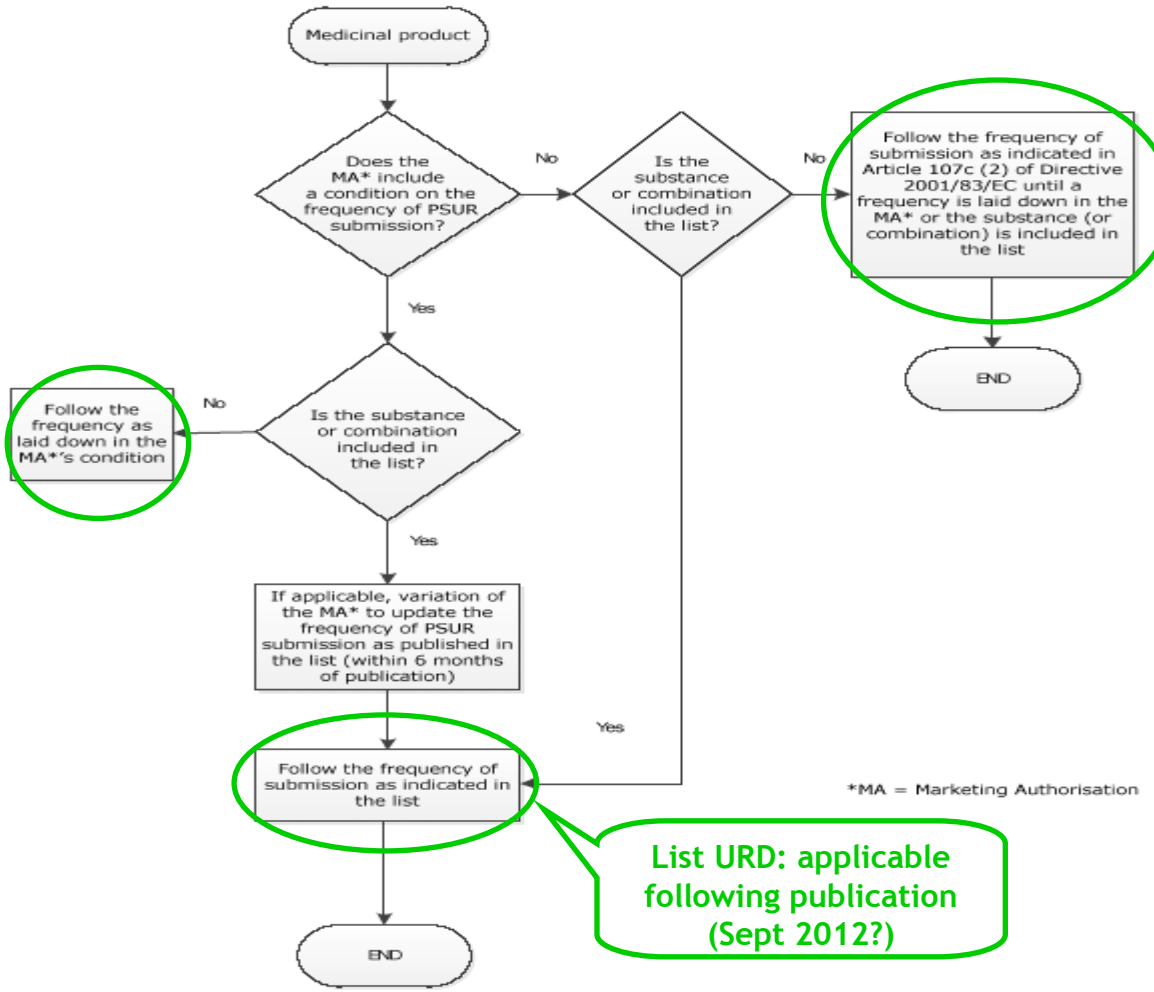
⇨ The URD list is expected to be updated monthly (PRAC recommendation → CHMP/CMDh adoption).

- ⇨ MAHs shall continuously check the EMA web-portal for any relevant updates
- ✓ Any changes to the list take effect six months after the date of the publication
- ✓ Where appropriate, MAHs shall vary the submission dates in their MA, within 6 months of the publication date

1. PSUR submission frequency

General requirements: potential scenarios July 2012

Figure VII.2. Conditions for PSURs submission as general requirement



« Routine » PSUR cycle: applicable > July 2012

Condition to MA: applicable > July 2012

List URD: applicable following publication (Sept 2012?)

2. PSURs for generics, well-established use, traditional herbal and homeopathic registrations

- **Derogation** to submit "**routine**" PSURs for generics [DIR Art 10(1)], well-established use, traditional herbal and homeopathic (simplified registration procedure) medicinal products [Dir. Art 107b(3)]
- **Except in the following circumstances:**

  Situations where MAHs of Generics, WEU, homeopathics, and traditional herbals can be requested to submit PSURs:

  1. conditions set out in the MA, or [Dir. Art 107b(3)(a)]
  2. request from Competent Authority [Dir. Art 107b(3)(b)] :
     a. on the basis of concerns relating to pharmacovigilance data
     b. or due to the lack of PSURs relating to an active substance

     ⇨ Assessment report ⇨ PRAC: consider whether there is a need for a single assessment ⇨ CMDh / CHMP: List URD

     ⇩

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

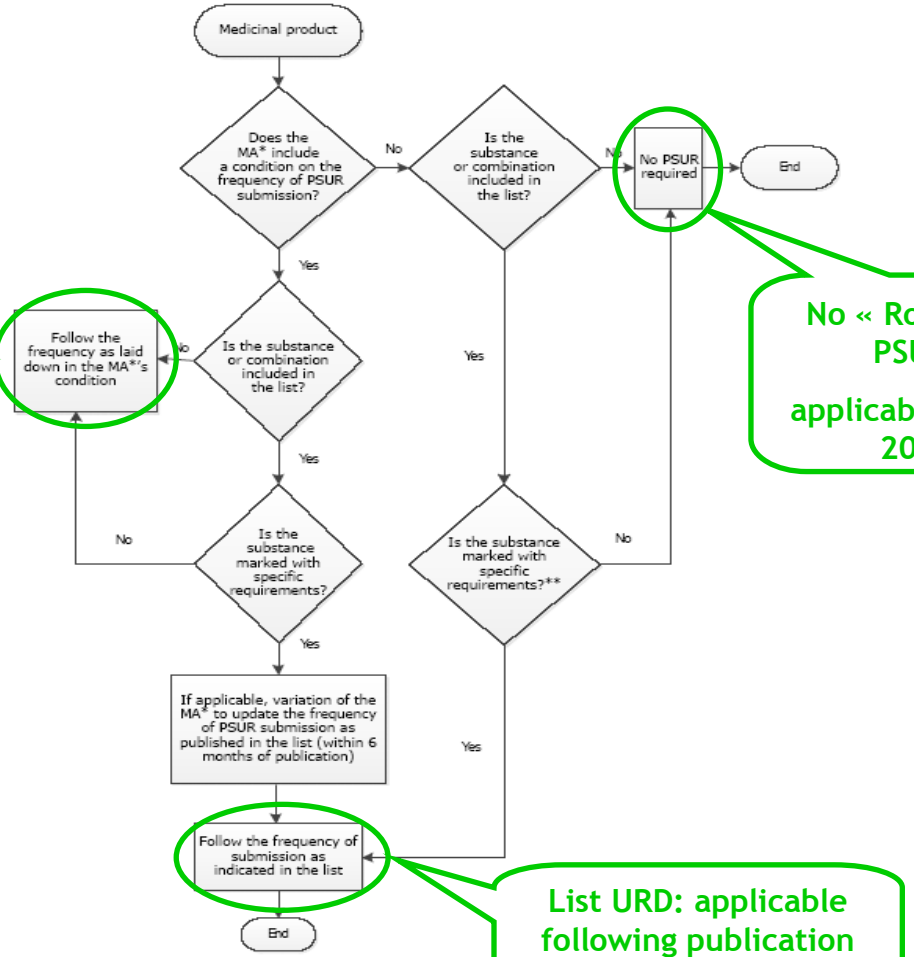
     Rationale: avoid duplication of requests; provide predictability for MAHs

     This specification is based on the request made by MSs during the creation or maintenance of the URD list, on the basis of a.m. concerns (2. a+b)

2. PSURs for generics, well-established use, traditional herbal and homeopathic registrations

Specific requirements for GEN, WEU, ..: potential scenarios July 2012

Figure VII.3. Conditions for PSURs submission for generic, well-established use, traditional herbal and homeopathic medicinal products



Condition to MA: applicable > July 2012

No « Routine » PSUR:

applicable > July 2012

List URD: applicable following publication (Sept 2012?)

*MA: Marketing Authorisation

**Specific requirements refer to:
- whether marketing authorisation holders for generic, well-established use, traditional herbal and homeopathic medicinal products are requested to submit PSURs following a request of a competent authority in a Member State due concerns relating to pharmacovigilance data or lack of PSUR submission and;
- whether or not the PSUR should cover all the indications, formulations, route of administrations.

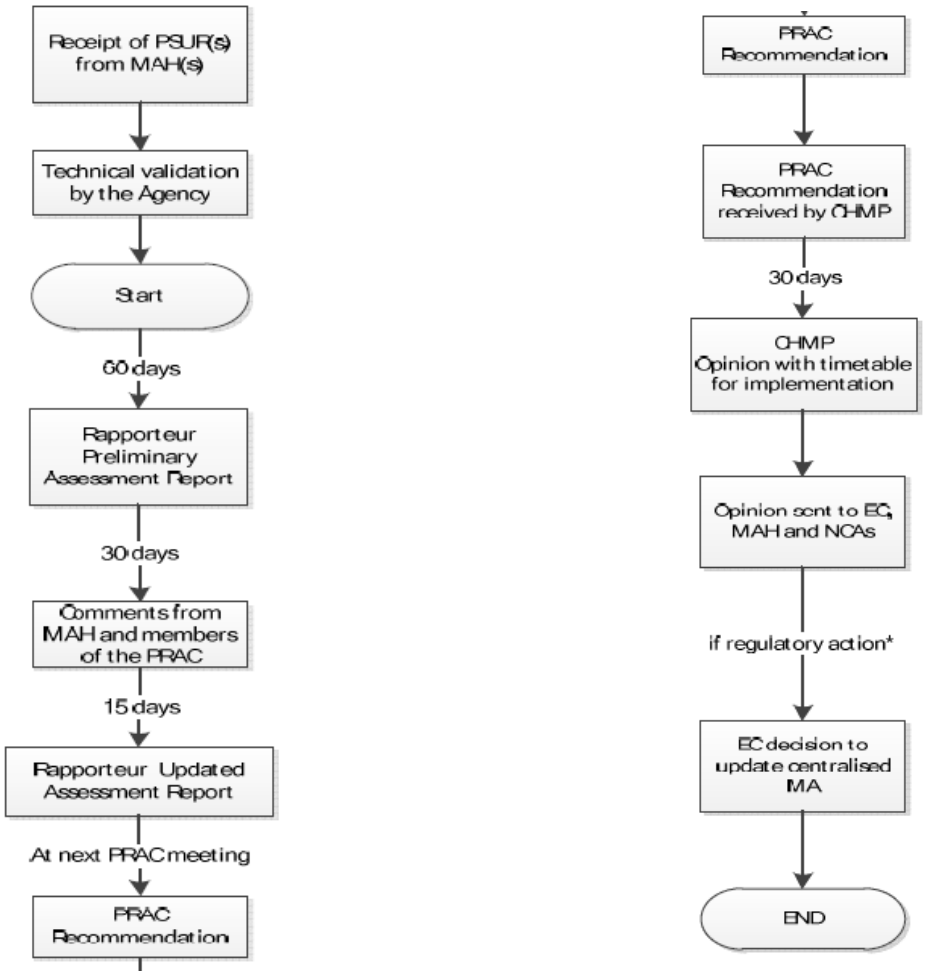
3. EMA PSUR repository

- EMA, in collaboration with the MSs and EC, shall set up and maintain a repository for PSURs and the corresponding assessment reports [Reg. art. 25a]
- MAHs shall submit PSURs electronically to EMA [Dir. Art. 107b]
- Structured electronic format "ePSUR", based on content agreed in the ICH-E2C(R2), submitted via electronic gateway
  - ⇨ Postponed: 2013?
  - ⇨ Transitional provisions in Dir. 2010/84: cover the period from July 2012 till 12 months after the PSUR repository is fully operational
- During transitional period, i.e. until centralised submission to the repository, PSURs will be sent directly to the MSs where the products/substances are authorised:
  - ⇨ EMA will publish the submission requirements of all MSs as regards PSURs (cfr. current Annex 6.2 of Vol. 9 A): media, number of copies, address

4. PSUR: Assessment procedure

A. Assessment of PSUR for single centrally authorised medicinal product [Reg. art. 28]

⇨ New procedure with PRAC involvement implemented from July 2012



4. PSUR: Assessment procedure

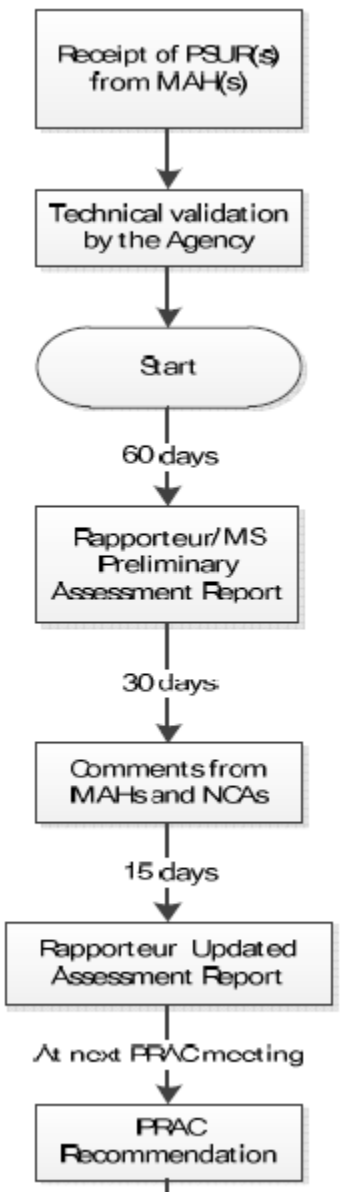
B. EU Single assessment [Dir. Art 107e to 107g]

- ✓ medicinal products, containing an active substance authorised in more than one Member State (i.e. on List URD)
- ✓ could be a mixture of centrally authorised products, MRP / DCP, purely nationally authorised products

- ⇨ New procedure with PRAC involvement postponed: 2013?
- ⇨ Will replace current «informal PSUR work sharing », MRP / DCP assessment, ..

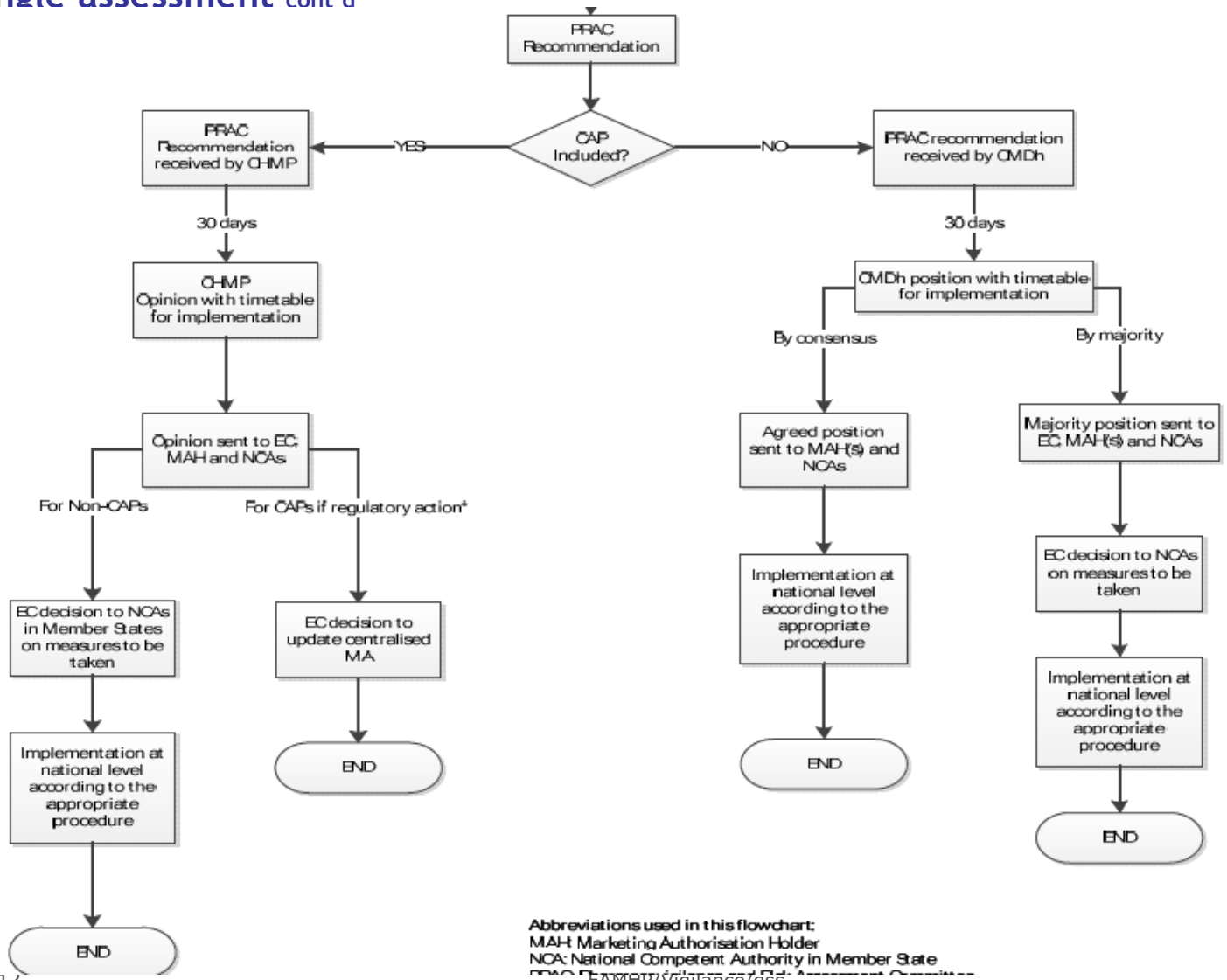
4. PSUR: Assessment procedure

B. EU Single assessment cont'd



4. PSUR: Assessment procedure

B. EU Single assessment cont'd



4. PSUR: Assessment procedure

B. EU Single assessment cont'd

- **Key differences with current "informal PSUR work sharing":**
  - Extended scope: will include centralised products, biologicals, ..
  - In general, PSURs will not be required for generics, WEU , ..
  - Procedure: PRAC recommendation, involvement of CMD(h) and CHMP
  - Short timetable: 60 + 30 + 15 days without clock-stop
  - Clear legal basis for single assessment ⇨ the outcome is legally binding (maintain, vary, revoke, suspend)

- **Until the "EU single assessment procedure" is in place (2013?), PSURs for MRP/DCP/NAPs will follow procedures currently in place (without formal PRAC involvement):**
  - Informal PSUR work sharing (possibly with "new" timetable??)
  - Mutual Recognition Procedures
  - Purely national procedures

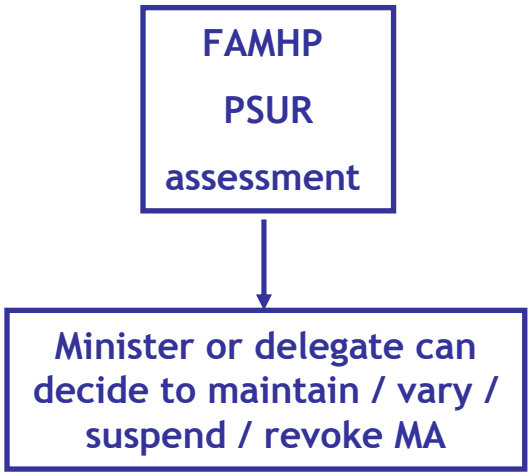
  ⇨ Update of Generic product information where no PSURs are submitted?
  - With the "single EU assessment", outcomes will be published on the EMA webportal [Dir. Art. 23]
  - European discussion on process for informing MAHs - no longer involved in work sharing assessments - of the outcome is ongoing.

4. PSUR: Assessment procedure

C. purely nationally authorised medicinal products not on URD list [Dir. Art. 107 d + f]

- ✓ medicinal product authorised in only one Member State
- ✓ and substance not on URD List

⇨ Applicable > July 2012



5. PSUR: New format and content

- **PSUR definition** [Dir. 2010/84/EU art. 107b]

✓ summaries of data relevant to the benefits and risks, including results of all studies with a consideration of their potential impact on the marketing authorisation
✓ a scientific evaluation of the risk-benefit balance, based on all available data, including data from clinical trials in unauthorised indications and populations
✓ estimate of the population exposed

⇨**Changed objective**

✓ a tool for post-marketing benefit risk evaluation, based on the available data at a defined time point in the lifecycle of the product

⇨**New PSUR format and content: addition of "benefit and risk benefit evaluation" sections**

- Implementing Measure [draft] sets out the new format and content
- GVP module VII [draft]

Interface with ICH E2C(R2):
Periodic benefit-risk evaluation report (PBRER)

5. PSUR: New format and content

Implementing measure / GVP: electronic PSUR format and content (draft)

- **Content: structured evaluation rather than data presentation**

✓ Detailed listings of individual cases not routinely included: upon request during assessment for ADRs of special interest?
Reason: EudraVigilance [once fully operational] will contain serious + non-serious ADRs
✓ Summaries of significant safety and efficacy information from all data sources: spontaneous data, literature, clinical trials and studies, …
✓ PSUR shall contain cumulative data, whilst retaining focus on new information: some modules will include both cumulative and interval data/information
✓ Scientific evaluation of the risk-benefit balance, based on all available data
✓ Results of assessments of the effectiveness of risk minimisation activities

- **Format (structure)**

✓ Modular structure: a more flexible modular format, can easily be updated
✓ Minimise duplication with other regulatory documents: common content of particular sections to be utilised interchangeably across different PSURs, DSURs and RMPs

- **Relationship PSUR / RMP**

✓ PSUR = post-authorisation risk benefit assessment
RMP = pre-and post-authorisation risk-benefit management and planning
✓ When both PSURs and RMPs are required for a product, routine updates to the RMP should be submitted at the same time as the PSUR
✓ MAH should consider whether any identified or potential risks discussed within the PSUR is important and requires an update of the RMP

5. PSUR: New format and content

Implementing measure / GVP: electronic PSUR format and content (draft)

- Title Page including signature
- Executive Summary
- Table of Contents

1. Introduction
2. Worldwide Marketing Approval Status
3. Actions Taken in the Reporting Interval for Safety Reasons
4. Changes to Reference Safety Information
5. Estimated Exposure and Use Patterns
   - 5.1. Cumulative Subject Exposure in Clinical Trials
   - 5.2. Cumulative and Interval Patient Exposure from Marketing Experience
6. Data in Summary Tabulations
   - 6.1. Reference Information
   - 6.2. Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials
   - 6.3. Cumulative and Interval Summary Tabulations from Post-marketing Data Sources

5. PSUR: New format and content

Implementing measure / GVP: electronic PSUR format and content (draft)

7. Summaries of Significant Findings from Clinical Trials in the Reporting Interval
    - 7.1. Completed Clinical Trials
    - 7.2. Ongoing Clinical Trials
    - 7.3. Long-term Follow-up
    - 7.4. Other Therapeutic Use of Medicinal Product
    - 7.5. New Safety Data Related to Fixed Combination Therapies
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

Implementing measure / GVP: electronic PSUR format and content (draft)

15. PSUR section "Overview of signals: new, ongoing, or closed"

- high level overview of signals detected, under review and evaluated during the reporting interval
- brief description on the specific signal detection methods used, as well as the sources screened for signals

Signal term	Date detected	Status (new, ongoing or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
stroke	month/ year	new	month/ year	Spontaneous, animal	brief summary of key data and rationale for further evaluation	review cases; epidemiological studies	

5. PSUR: New format and content

Implementing measure / GVP: electronic PSUR format and content (draft)

16. Signal and Risk Evaluation
    - 16.1. Summaries of Safety Concerns
    - 16.2. Signal Evaluation
    - 16.3. Evaluation of Risks and New Information
    - 16.4. Characterisation of Risks
    - 16.5. Effectiveness of Risk Minimisation (if applicable)
17. Benefit Evaluation
    - 17.1. Important Baseline Efficacy and Effectiveness Information
    - 17.2. Newly Identified information on Efficacy and Effectiveness
    - 17.3. Characterisation of Benefits
18. Integrated Benefit-risk Analysis for Authorised Indications
    - 18.1. Benefit-risk Context – Medical Need and Important Alternatives
    - 18.2. Benefit-risk Analysis Evaluation
19. Conclusions and Actions
20. Appendices to the PSUR

Implementing measure / GVP: electronic PSUR format and content (draft)

16. PSUR section "Signal and risk evaluation"

16.1 "Summary of safety concerns"

- baseline summary of important safety concerns against which new information and evaluations within the PSUR can be made:
  - ✓ important identified risks;
  - ✓ important potential risks;
  - ✓ important missing information.

⇨ For products with a safety specification (cfr. RMP): equal to safety specification summary

16.2 "Signal evaluation"

- summarise results of evaluations of safety signals, closed during the reporting interval

⇨ potential or identified risk: to be discussed in "Evaluation of risks and new information"

⇨ rejected as false signals

16.3 "Evaluation of risks and new information"

- critical appraisal of new information from the reporting interval on new or previously detected risks:
  - ✓ new potential risks;
  - ✓ new identified risks;
  - ✓ new information on previously detected risks (potential or identified);
  - ✓ update on important missing information

5. PSUR: New format and content

Implementing measure / GVP: electronic PSUR format and content (draft)

16.4 "Characterisation of risks"

- characterize important identified risks and important potential risks based on cumulative data (i.e. not restricted to the reporting interval) and describe important missing information

18. PSUR section "Integrated benefit-risk analysis for authorised indications"

18.1 "Benefit-risk context - medical need and important alternatives"

- brief description of the medical need for the medicinal product in the authorised indications and summarised alternatives

18.2 "Benefit-risk analysis evaluation"

- specific to an indication and population
- With respect to benefit: consider its nature, clinical importance, duration, and generalisability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments. Consider the effect size. ..
- With respect to risk: consider its clinical importance, (e.g. nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients), and whether it arose from off-label use, a new use, or misuse.
- The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation.

Implementing measure / GVP: electronic PSUR format and content (draft)

Regional appendix: EU-specific requirements for PSURs

- scientific evaluation of the risk-benefit balance detailed in VII.B.5. shall be based on all available data, including data from clinical trials in unauthorised indications and populations
- PSUR EU regional appendix, sub-section "Reporting of results from post-authorisation safety studies":
  - ✓ Findings from both interventional and non interventional post-authorisation safety studies (PASS) should be reported in the PSUR: the PSUR should provide comprehensive information on the findings of all PASS, both interventional and non-interventional, in PSUR sections 7 and 8 respectively.
  - ✓ For studies falling within the scope of GVP Module VIII on PASS, that guidance is applicable and progress reports and final study reports should be included in the PSUR for studies ongoing or completed in the reporting period (Region-specific information) in accordance with EU specific requirements for PASS.

6. PSUR: overview

Current legislation	New legislation	Transitional provisions?	Situation July 2012
PSUR requirement: for all MAs	Derogation: no routine PSUR for generics, WEU, THMP, homeopathic registration	No	derogation for routine PSURs applicable
PSUR frequency: routine PSUR cycle for most MAs	1) Risk based PSUR cycle, through comprehensive URD List 2) Condition to MA 3) Routine PSUR cycle	No	1) List URD legally binding as soon as published (Sept. 2012) 2) July 2012 3) July 2012
PSUR submission: to MS / EMA (centralised) [Annex 6.2 of Vol. 9 A]	E-submission to EMA PSUR repository	From 12 months after repository is operational	PSUR submission to MS / EMA (centralised)

6. PSUR: overview

Current legislation	New legislation	Transitional provisions?	Situation July 2012
Assessment: ▪ centralised procedure ▪ informal PSUR work sharing ▪ MRP ▪ Purely national procedures	Clear legal basis for: ▪ Assessment of single centrally authorised medicinal product ▪ Single EU assessment ▪ Purely national procedure	No	▪ Assessment of centralised products following new procedure (PRAC) ▪ Informal PSUR work sharing ▪ Mutual Recognition Procedures ▪ Purely national procedures
Content: ▪ Focus on presentation of safety data	▪ Structured risk evaluation ▪ Benefit evaluation ▪ Integrated benefit risk evaluation module	Transitional period of 6 months in Implementing Measures - draft	Between July 2012 and January 2013 old and new formats will co-exist

6. PSUR: overview

Legal framework
▪ Directive 2001/83 art. 107b – 107g ▪ Regulation 726/2004 art. 25a, art. 28 ▪ Implementing measures "format and content of electronic PSURs" - DRAFT ▪ GVP module VII provides guidance on the preparation, submission and assessment of PSURs - DRAFT ▪ ICH guideline E2C (R2): Periodic benefit-risk evaluation report - step 3
Transitional provisions
▪ Directive 2010/84 art. 2(7) ▪ Implementing measures "format and content of electronic PSURs" - DRAFT ▪ Q&A on transitional arrangements [http://ec.europa.eu/health/files/pharmacovigilance/2012_02_qa_phv.pdf]

1. Renewal: what changes in the legislation?

Directive	Regulation	New/Amendments
Direct Provision:		
Art 24(2,3)	Art 14(2,3)	AMENDMENT - Renewal: ▪ Deadline for renewal submission: at least 9 months in advance of the MA expiry date ⇨ Applies to products for which the MA ceases after 2/21 April 2013 ▪ Content of renewal re PSUR ⇨ renewal application submissions have to comply with the new data requirements after 2/21 July 2012 ▪ Ground for requesting an additional renewal: justified grounds relating to phvig, including exposure of an insufficient number of patients ⇨ 2/21 July 2012
Indirect Provisions:		
Art 23(3)	Art 16(3)	NEW : ▪ Obligation for MAH to keep the PI up-to-date with current scientific knowledge incl. assessment conclusions /recommendations on EU medicines web-portal
Art 107b(3)		▪ No routine PSURs for generics, WEU, homeopathics and traditional herbals
Art 116		AMENDMENT: ▪ grounds to vary, suspend, revoke -> extended to non fulfilment of conditions to MA

2. Renewal: data requirements

GL on processing of renewals - centralised procedure [under revision]: what changes?

1. **Module 1**

- 1.8.1 summary of the phvig system, if applicable
- 1.8.2 update of the RMP, for products which have a RMP (or justification, if MAH considers that there is no need to change the latest RMP)

2. **Module 2**

- Addendum to Clinical Overview:
  - ✓ critical discussion on current benefit/risk balance, taking into account PSURs submitted, suspected ADRs, additional phvig activities and the effectiveness of risk minimisation measures contained in the RMP …
  - ✓ make reference to any relevant new information in the public domain e.g. literature references, clinical trials and clinical experience, new treatments available; The information shall include both positive and negative results of clinical trials and other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation [cfr. Dir. Art. 23]
  - ✓ should contain an expert statement; the statement should confirm that the product information has been kept up to date with current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal
  - ✓ Inspection status

2. Renewal: data requirements

2. Module 2 Cont'd

- Addendum to Clinical Overview (relevant sections of PSUR integrated in clinical overview)
  - ✓ Worldwide marketing approval status
  - ✓ Actions taken for safety reasons
  - ✓ Significant changes made to the Company Core Safety Information
  - ✓ Meaningful differences between the CCSI and the proposals for the SmPC
  - ✓ Estimated exposure
  - ✓ Data in summary tabulations
  - ✓ Summaries of significant findings from clinical trials and non-interventional studies
  - ✓ Literature
  - ✓ Risk evaluation
  - ✓ Benefit evaluation
  - ✓ Benefit/risk balance

** MAHs are advised to consider the GVP Module on PSURs as guidance for the preparation of the above sections of the clinical overview.

3. Module 5

- no PSUR submission within renewal application

GL on processing of renewals - centralised procedure [under revision]: what changes?

- Review of MA conditions within renewal
- check whether the MAH complies with his obligation to keep the product information up to date in the light of current scientific knowledge taking into account conclusions of assessments and recommendations which are made public on the EMA web-portal
- PRAC involvement
- Opinion can include:
  - ✓ Conditions or restrictions regarding supply and use (Annex II)
  - ✓ Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the MSs

4. Renewal: overview

Current legislation	New legislation	Transitional provisions?	Situation July 2012
Deadline for renewal submission: 6 months	Deadline for renewal submission: 9 months	No	"9 months deadline" applies to products for which the MA ceases after 2/21 April 2013
consolidated version of the file in respect of quality, safety and efficacy, incl. all variations	New data requirements: … including the evaluation of data contained in suspected adverse reactions reports and PSURs …	No	renewal application submissions have to comply with the new data requirements after 2/21 July 2012

4. Renewal: overview

Legal framework
▪ Directive 2001/83 art. 24 (2,3) ▪ Regulation 726/2004 art. 14 (2,3) ▪ CMDh Best Practice Guide on the processing of renewals in the MRP/DCP - UNDER REVISION ▪ Guideline on the processing of renewals in the centralised procedure - UNDER REVISION (public consultation finalised) ▪ Reflection Paper "Criteria for requiring one additional five-year renewal for Centrally Authorised Medicinal Products" - UNDER REVISION
Transitional provisions
▪ Q&A on transitional arrangements [http://ec.europa.eu/health/files/pharmacovigilance/2012_02_qa_phv.pdf]

Thank you!