



IRISH MEDICINES BOARD



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Periodic Safety Update Reports under the new EU Pharmacovigilance Legislation (and the interface between the Risk Management Plan and the Development Safety Update Report)

SME Information Day, April 19th 2012

Presented by Almath Spooner, Irish Medicines Board and PhVWP





Objective of this presentation

- To highlight key changes to requirements for PSURs under the new EU pharmacovigilance legislation
- To provide an overview of the sources of information and guidance for MAHs.
- To briefly describe possible interfaces with other pharmacovigilance documentation and ongoing work in the area of international harmonisation.



Changes to PSURs

1. Scope
2. Format and Content
3. Submission requirements
4. Assessment procedures
5. Outcome
6. Transparency



Where to get information?

- EC Implementing Measure – legally binding – public consultation by EC complete, draft published, final version by July.
- Good Vigilance Practice Module VII PSURs – draft published for public consultation, closed yesterday, final version to be published by July.
- Union Reference Date List – public consultation accompanied by explanatory document launched April 4th 2012. Comments due June 4th 2012.
- ICH E2C (R2) step 2 guideline – published February 2012, EMA public consultation launched April 15th 2012, comments invited by May 21st 2012.



Objectives of the new legislation – relevance to PSURs?

Promote and protect public health by reducing burden of ADRs and optimising the use of medicines:

- Clear roles and responsibilities
- *Better evidence, more science based*
- *Better link between assessments and regulatory action.*
- *Risk based/proportionate*
- Increased proactivity/*planning*
- *Reduced duplication/redundancy*
- *Integrate benefit and risk where appropriate*
- Ensure robust and rapid EU *decision-making*
- Engage patients and healthcare professionals
- *Increase transparency and accountability*
- Provide better information on medicines



Evolution of the PSUR

1992 CIOMS II guideline

1996 Step 4 ICH E2C Guideline

2003 Step 4 Addendum to ICH E2C (R1)
Published

Initially developed as an interval safety update report.



ICH Pharmacovigilance Documentation

E2C: PSUR

E2E : Safety Specification -> EU RMP

E2F: DSUR



Evolution of post-marketing research activities

Benefits

RCTs (in context of conditional approval)

PAES (where justified)

Risk Management

Spontaneous reporting and signal detection activities

Active surveillance registers
observational studies
Electronic healthcare records
RCTs, LSTs

Integrated assessment of clinical outcomes in the post marketing setting i.e. post marketing benefit-risk assessment → Inform risk management and optimisation of the benefit-risk profile.



Balancing benefits and risks

“In the domain of medical products, it has been said that the FDA has just two speeds of approval — too fast and too slow. Critics concerned about haste point out, accurately, that drugs and other products are generally approved on the basis of relatively small studies and that safety problems often emerge when large populations are exposed to the products. Those worried about delay note, correctly, that people with life-threatening diseases have no time to wait. ***A public health approach recognizes that the potential good of a new medical product or policy must be balanced against the potential harm. Some benefits are not worth the risk; some risks are worth taking.*** Key considerations are the severity of the illness at issue, the availability of alternative treatments or preventive interventions, and the current state of knowledge about individual responses.”

Hamburg and Sharfstein NEJM 2009;360(24):2493-5



Calls for more explicit evaluations of benefit-risk

‘...need to refine... methods of assessing benefit-risk balances and switch from “implicit” to “explicit” decision making—that is, to an approach involving explicit descriptions not only of all decision criteria and interpretations of data but also valuations, such as the weighting factors for potential treatment outcomes’

Eichler, H.-G et al. (2009). Safe drugs and the cost of good intentions. *New England Journal of Medicine*, 360(14), 1378-1380.



Move towards benefit-risk evaluation

Directive 2010/84/EU, Article 107b

PSURs shall contain:

- a) summaries of data relevant to the **benefits and risks** of the medicinal product, including results of **all studies** with a consideration of their potential **impact on the marketing authorisation**;
- b) a **scientific evaluation** of the risk-benefit balance of the medicinal product, which shall be based on **all available data**, including data from clinical trials in unauthorised indications and populations.
- c) All data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of prescriptions, including an **estimate of the population exposed to the medicinal product**.



Format and Content

Format and content needs to be compatible with the objective of benefit-risk evaluation reporting.

- European Commission **Implementing Measure** will implement Article 108(f) i.e. provides the technical detail on the format and content of electronic periodic safety update reports and risk management plans.

- Further guidance in GVP module VII (PSURs)



Draft Implementing Measure (1/2)

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

7. Summaries of significant findings from clinical trials during 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 on signals: New, ongoing or closed



Draft Implementing Measure (2/2)

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



Pharmacovigilance is a global effort ...

Observe – Report – Monitor – Analyse – Evaluate – Act



Patient – Health Care provider – MAH – Regulator

(slide F. Sweeney, EMA)



ICH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

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

Type of Harmonisation Action Proposed

An ICH Expert Working Group (EWG) is proposed to evaluate the ICH pharmacovigilance documentation, conduct a gap and potential improvement analysis of ICH E2C, E2E and E2F and to draft a new ICH Guideline E2C(R2) covering periodic benefit risk evaluation reporting. Furthermore, based on an evaluation of the ICH pharmacovigilance documentation, and a gap and potential improvement analysis of ICH E2C, E2E and E2F, the EWG will deliver a plan to the ICH Steering Committee for review of other ICH Guidelines.

The proposal is in the context of the vision developed at the November 2010 ICH Pharmacovigilance Brainstorming and presented to the ICH Steering Committee:

‘Optimise the lifecycle benefit risk of medicines for the promotion and protection of public



ICH E2C (R2)

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

Comments invited on the ICH E2C (R2) guideline on periodic benefit-risk evaluation report

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News

16/04/2012

Comments invited on the ICH E2C (R2) guideline on periodic benefit-risk evaluation report

The European Medicines Agency is inviting comments on the recently published ICH E2C (R2) guideline on periodic benefit-risk evaluation report (PBRER) from its stakeholders. The guideline reached step 2 of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [\(ICH\)](#) process in February 2012 and now enters step 3, the consultation period.

The focus of the current 'ICH E2C (R1) guideline on periodic safety update report (PSUR) for marketed drugs' is on relevant new safety information in the context of patient exposure, to determine if changes are needed to the medicine information in order to optimise the use of the medicine. The pharmacovigilance environment has evolved, however, prompting reassessment of the role of the PSUR in the

Related information

► [ICH: Efficacy](#)

 [ICH guideline E2C \(R2\): Periodic benefit-risk evaluation report \(PBRER\) \(16/04/2012\)](#)

 [Form for submission of comments on scientific guidelines \(04/02/2010\)](#)

Contact point:

ich@ema.europa.eu



GVP Module VII

Section B – ‘global’ section

- format and content

- broadly consistent with the ICH E2C R2 guideline.

Section C – operation of the EU network

- Submission requirements and the URD list
- Assessment procedures
- Outcomes
- Transparency
- ¹⁹ - Quality Management



Sections of the PSUR – what is new and what is retained?



ICH E2C R2 – retained principles

- A single report for an active substance
- Company Core Data Sheet (version in effect at end of reporting period) as reference information
- International birth date (IBD) and Data lock point (DLP) (with guidance on managing different frequencies of submissions)
- Many of the existing data presentation sections remain but with some amendment (in some cases this will facilitate common modules).



ICH E2C (R2) – What is new?

- ❖ Benefit-risk and cumulative.
- ❖ No routine requirement for line listings,
- ❖ No acceptance of multiple 6 monthly reports, also no summary bridging reports or addendum reports (PBRER = stand alone evaluation document).
- ❖ More structured evaluation based on cumulative data but no mandated (quantitative) methodologies for benefit-risk assessment.
- ❖ Time interval between DLP and submission expanded
- ❖ Modular concept introduced (linked to the gap and improvement analysis for E2E and E2F)
- ❖ PSUR GVP module (section B) is broadly aligned.



Data presentation sections (1)

- **Worldwide marketing approval status**
 - Guideline wording similar to that in ICH E2F
- **Actions taken in the reporting interval for safety reasons**
 - Guideline wording similar to that in ICH E2F
- **Estimated exposure and use patterns**
 - Includes cumulative exposure in CTs (same as in ICH E2F).
 - Cumulative and interval data from marketing experience – common module with RMP



Data presentation sections (2)

Summary tabulations

- Cumulative SAEs from CTs (same as ICH E2F)
- Cumulative and interval tabulations from post marketing sources
 - ❖ **Serious and non serious** adverse reactions from all post marketing sources
 - ❖ Includes post authorization studies
 - ❖ Includes consumer reports
 - ❖ Cumulative and interval data side by side



Data presentation sections (3)

- **Summaries of Significant findings from CTs**
 - Scope similar to ICH E2F
 - Requirement to provide a list of all CTs conducted as PASS
- **Summaries of Findings from non-interventional studies**
 - Relevant safety information
 - List of all non-interventional PASS
 - Information with potential impact on benefit or risk evaluation
 - Progress or final study reports from PASS to be appended.



Data presentation sections (4)

Non clinical data

- new section

Literature

- New and significant safety findings
- Available unpublished manuscripts.
- Information on medicines of the same class.

Lack of efficacy in CTs

- Data from CTs

Late breaking information

- Include actions taken for safety reasons



Data presentation (5) – new section on signals

Overview on Signals: New, Ongoing or Closed

- ❖ Provides an overview of signals detected, under review and evaluated in the reporting period.
- ❖ References a tabulation of new, ongoing and closed signals - format of the tabulation provided in an annex to the E2C R2 guideline.
- ❖ Definitions of new, ongoing and closed signals are provided.
- ❖ Draft Guideline - Option for the MAH to present signals by interval or cumulatively.



Signal Tabulation

APPENDIX C – Tabular Summary of Safety Signals that were New, Ongoing, or Closed during the Reporting Interval

Product Name: _____

Reporting Interval: DD-MMM-YYYY to DD-MMM-YYYY

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	

Explanatory notes

- Signal term



New Evaluation sections (1/3)

1. Signal and Risk Evaluation

- I. Summary of safety concerns
- II. Signal evaluation
- III. Evaluation of Risks and New Information
- IV. Characterisation of Risks
- V. Effectiveness of risk minimisation



New Evaluation sections (2/3)

Benefit Evaluation

1. Important Baseline Efficacy and Effectiveness Information

Summarises information available at the beginning of the reporting period.

2. Newly Identified information on Efficacy and Effectiveness

In approved indications

3. Characterisation of Benefits

Integration of baseline information with any new information.
If significant information or benefit profile is significantly decreased, a concise but critical evaluation needed.



New Evaluation sections – Benefit/Risk (3/3)

Integrated Benefit/Risk Analysis for approved indications.

Benefit-risk Context

- Medical Need and Important Alternatives

Benefit-risk Analysis Evaluation

- For each indication and population.
- Whereas previous sections will include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation. Therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk sections should be carried forward for integration in the benefit-risk evaluation.
- Consider context of use.
- Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation.
- Take into account strengths, weaknesses and uncertainties in the evidence.



Actions and Conclusions

- **Provide a conclusion on Benefit-risk**
 - For each approved indication
 - By subgroups where relevant
- **Assess need to change the CCDS /labelling**
and propose changes where appropriate.
- Include preliminary proposals to optimise or further evaluate Benefit-risk balance (e.g additional **pharmacovigilance or risk minimization activities**).
- Incorporate into the RMP where product has a RMP.



Appendices :

Non-regional:

- Signal tabulation
- Listing of all PASS
- ICH E2C step 2 draft guideline - List of sources of information used (MAH discretion)

Regional (EU requirements):

- Additional PV and risk minimisation activities
- EU marketing authorisation status
- CCSI and draft SmPC
- Summary of ongoing safety concerns
- Reporting of results from PASS



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 GVP module – points to note

- 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.***
- For those medicinal products 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.



New Concepts for format and content

Modular approach

- ICH E2C R2 step 2 draft guideline has been drafted so that the content of some sections of the PSUR/PBRER could be identical to the corresponding sections of other documents.
- Allows sections or modules to be submitted at different times to multiple authorities across separate documents i.e. PSUR, DSUR and RMP.
- Maximizes utility and minimises duplication

Cumulative report

- Multiple six monthly reports will not be accepted
- Summary Bridging reports and Addendum reports will not be accepted.



Other new concepts for PSURs

Link to regulatory action

- New assessment procedure involving PRAC will start for CAPs in 2012.
- Single EU assessment including NAPs will start after 2012.
- Assessment leads to automatic regulatory action: variation, suspension, revocation.
- Likely to replace some referrals.
- Increased transparency



Other new concepts for PSURs

Rationalization and simplification

- Concept of Worksharing developed under the PSUR WS project.
- Single EU assessment procedure will have difference but builds on the principle.
- Development of the PSUR repository postponed until after 2012.
- When functional, centralised reporting.



Other new concepts for PSURs

Risk Proportionality

Submission frequency will be:

- variable
- based on a risk based approach
- Controlled by a legally binding list of substances published by EMA with submission dates (Union Reference Dates and periodicity of submissions (URD) list).

Public consultation on URD list – 4th April 2012, closes 4th June 2012.



PSUR submissions - general requirements

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.



Managing different frequencies

04/04/2012

Feedback requested on the draft list of EU reference dates for periodic safety update reports in preparation for introduction of the new pharmacovigilance legislation

The European Medicines Agency, on behalf of the European Union (EU) medicine regulatory network, is inviting marketing-authorisation holders and other stakeholders to review and provide comments on the [draft list of European Union reference dates](#) (referred to as the 'EURD list') for periodic safety update reports (PSURs) in preparation for the introduction of the new pharmacovigilance legislation in July 2012.

The Union reference date is the earliest known date of the marketing authorisation for a medicinal product containing the same active substance or the same combination of active substances.

The EURD list includes the active substances and combinations of active substances contained in medicinal products subject to different marketing authorisations, together with the corresponding Union reference dates, frequencies for submission of PSURs and related data lock points.

The purpose of the consultation is to ensure completeness and correctness of the information before the list is adopted later this year by the [Committee for Medicinal Products for Human Use \(CHMP\)](#) and the [Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human](#) [☞], (CMDh) following consultation with the new Pharmacovigilance and Risk Assessment Committee (PRAC) from July 2012.

The consultation is open until 4 June 2012. Those submitting comments on the draft EURD list are asked to read the [introductory cover note](#) and use the Excel template [submission of comments on the EURD list](#) to provide comments. Responses should be sent to eurdlist@ema.europa.eu.



Managing different submission requirements

- ICH E2C R2 draft guideline - practical advice for MAHs on managing different frequencies of submissions i.e. when preparing reports covering different reporting periods to different authorities.
- Each report should be stand alone and in accordance with the format and content defined in the Implementing Measure and elaborated on in guidance.
- Each report should include interval data for the whole period



Variable reporting periods

For PSURs (PBRERs) with DLPs based on the IBD but covering different reporting periods, the following will apply:

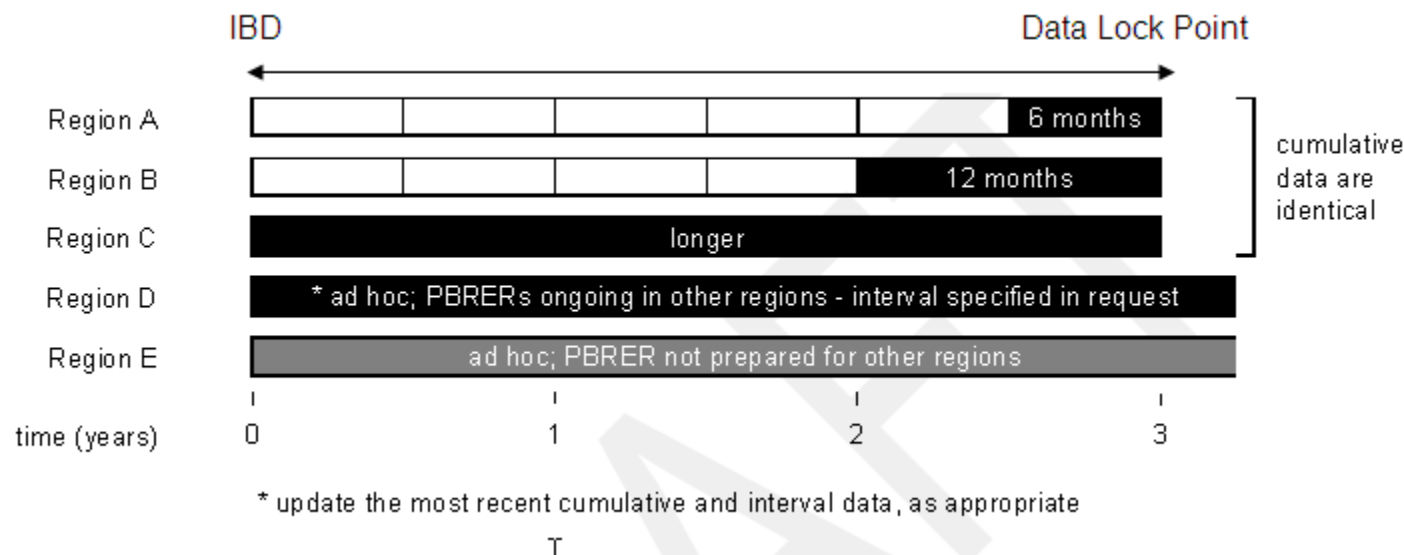
- Cumulative sections are likely to be similar
- Interval sections will need to be updated
- Newly identified information on risk, efficacy and effectiveness - sections need to be reviewed and evaluation of new information needs to be meaningfully incorporated.
- New information may require a new integrated benefit-risk evaluation



ICH E2C R2 Submission of PBRERs based on the same DLP with various reporting periods

Shading indicates period of interval data.

For all reports, the cumulative data reflect all data from the IBD





Time Interval between Data Lock Point and the Submission

PBRERs covering intervals of 6 or 12 months:
within 70 calendar days

PBRERs covering intervals in excess of 12 months:
within 90 calendar days

Ad hoc PBRERs:
90 calendar days, unless otherwise specified in the ad hoc
request.



Interface with the RMP

- ❖ European Commission **Implementing Measure** will implement Article 108(f) i.e. provides the technical detail on the format and content of **electronic periodic safety update reports and risk management plans**.
- ❖ Detail in GVP modules V (RMPs) and VII (PSURs)



PSUR and RMP

PSUR = Evaluation of the benefit risk profile and signal evaluation and updates to product information

RMP = Planning of data collection and risk minimization Activities

- There is some overlap (mainly safety specification).
- Not all products have RMPs.
- Not all products will have PSURs.
- Each document must be standalone.
- Modular approach will not eliminate unavoidable overlap but should improve the utility of sections of each document.



Possible common sections between PSUR and RMP

Table VII.1. Common sections between PSUR and RMP

PSUR section	RMP section
Section 2 – “Worldwide marketing approval status” and EU marketing approval status included in the EU Regional Appendix	Sub-section of part I – “Product overview”
Section 3 – “Actions taken in the reporting interval for safety reasons”	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 – “Summary 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”



Module SV of the RMP /PSUR 3.5.2 Estimated exposure and Use Patterns

3.5.1 Cumulative Subject Exposure in Clinical Trials (common to DSUR)

3.5.2 Cumulative and Interval Patient Exposure from Marketing Experience (common to RMP)

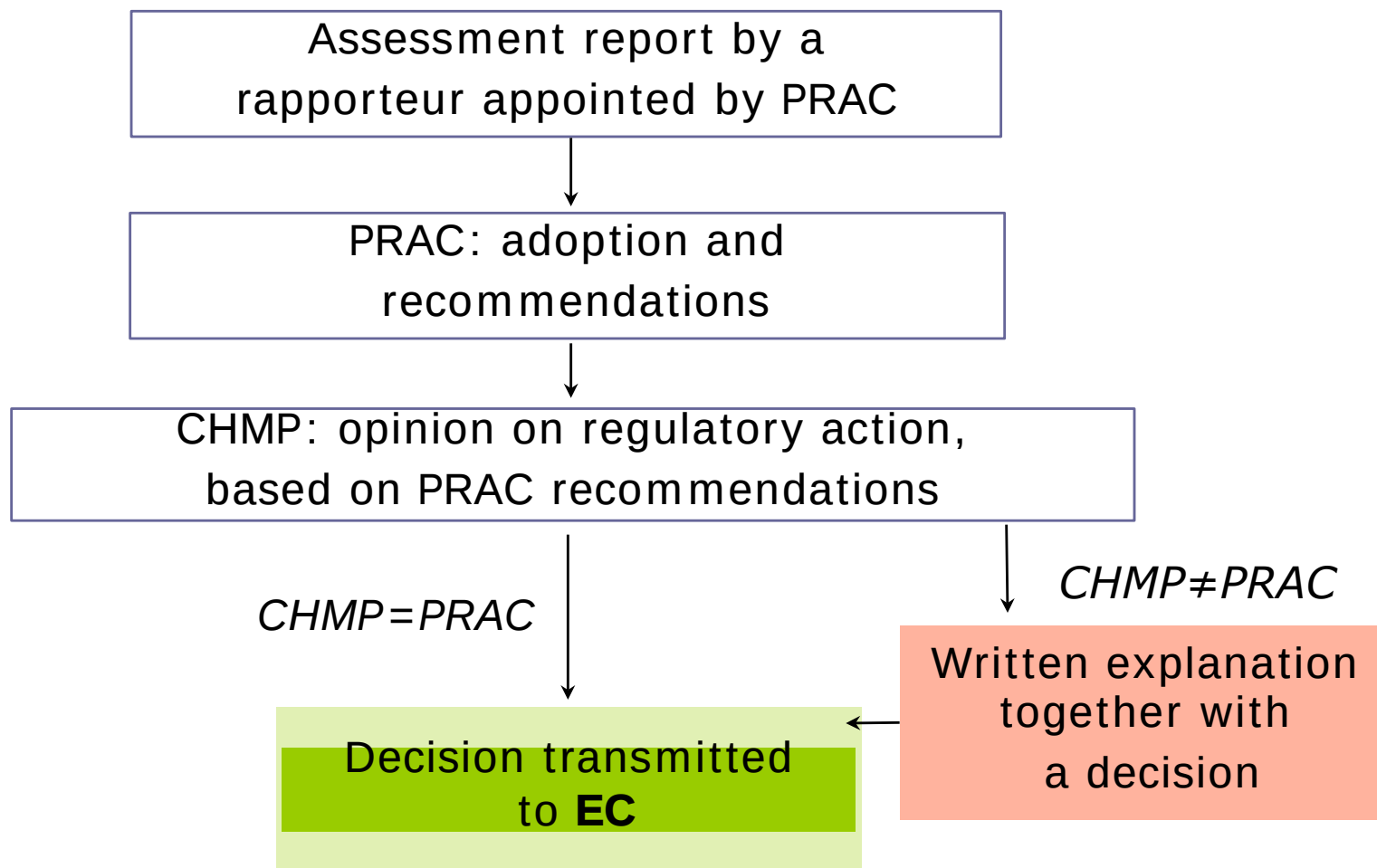
1. Post-authorisation (non-clinical trial) exposure (estimated exposure)
2. Post-authorisation use in special populations (use patterns)
3. Off-label Use of Medicinal Product (use patterns)



Changes to decision-making process

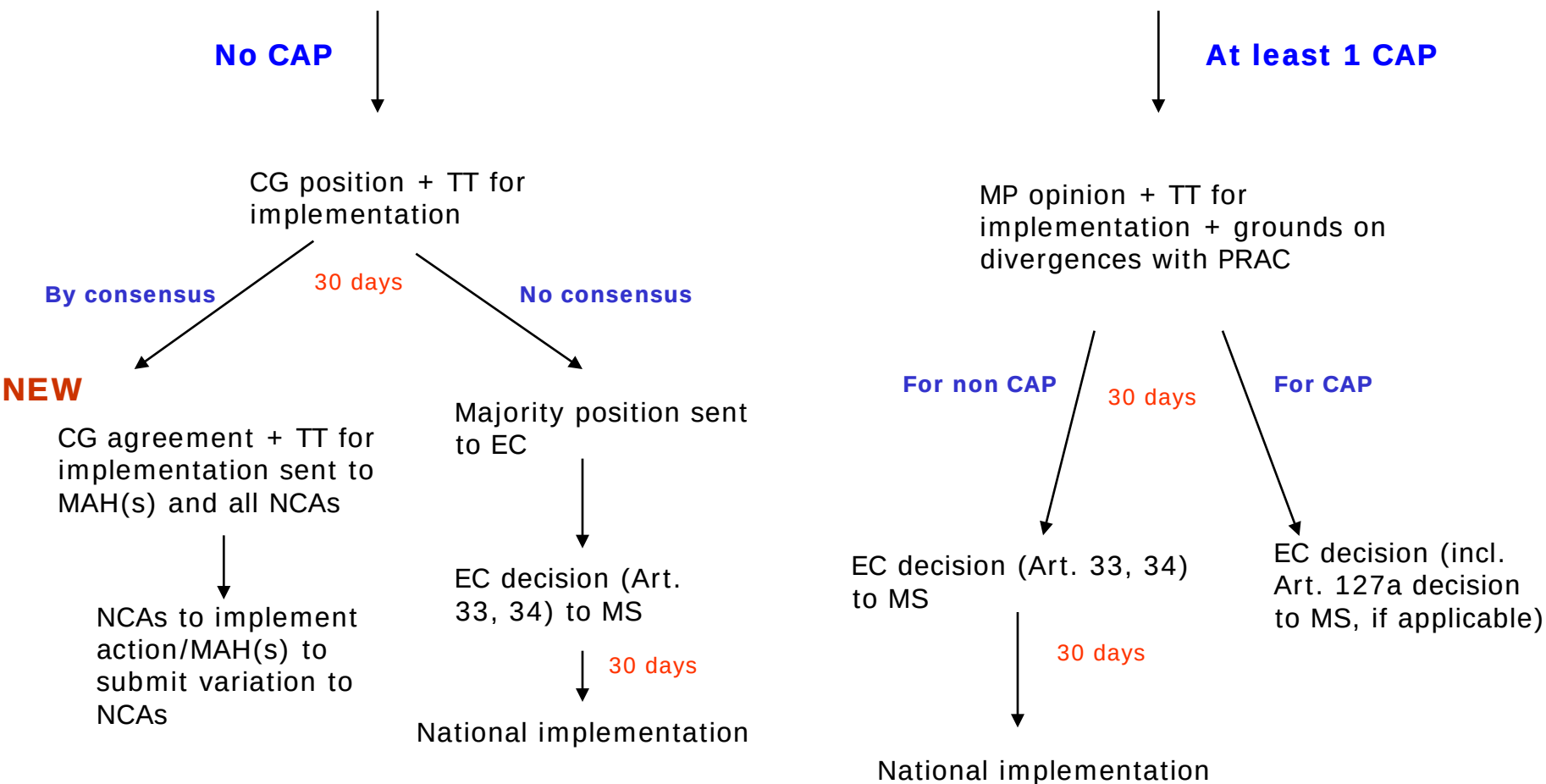


centrally authorised medicine





Single EU assessment – binding outcomes



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



Single EU assessment - Implementation

- An annex to the opinion/position will include
 - the new safety warnings and
 - key risk minimisation recommendationsto 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.



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.



Implementation of changes for PSURs

New format and content:

- Implementing Measure comes into force in July (legal transitional period to be defined in the Implementing measure).
- Draft GVP module published Feb 2012, final GVP PSUR module by July.

Submission requirements

- Draft URD list published April 2012, final list to be adopted Autumn 2012 – in the meantime, transitional guidance to be provided in a Q&A.

Assessment procedure

- PRAC involvement for CAPs from July 2012.
- Single EU assessment postponed until after 2012, from autumn 2012, URD list will be used to manage submissions to NCAs but initiation of formal single EU assessment procedure is postponed.



Questions?



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 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.



Application of the URD list

Provisions laid down in accordance with Article 107b(3)(b) will be applied by specifying on the URD list, the substances for which PSURs for generic, WEU, THMP and homeopathic medicinal products are required.

Rationale:

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

Public consultation on the draft URD list launched April 4th 2012



PSUR/RMP interface

3.16.1 Summary of safety concerns – important identified risks, important potential risks and important missing information at the start of the reporting period.

3.16.4 Characterisation of Risks – Output from the integrated assessment of prior and new information -> important identified risks, important potential risks, important missing information.

3.16.5 Effectiveness of risk minimisation



Summary Tabulations (1) - SAEs

Table 6 – Cumulative Tabulations of Serious Adverse Events from Clinical Trials

<u>System Organ Class</u> Preferred Term	[medicinal product]	Blinded	Active comparator	Placebo
<u>Investigations</u>	n	n	n	n
Alanine aminotransferase increased	n	n	n	n
Aspartate aminotransferase increased	n	n	n	n
<u>Nervous System Disorders</u>	n	n	n	n
Syncope	n	n	n	n
Headache	n	n	n	n



Summary tabulations (2) – Postmarketing

Table 7 - Numbers of Adverse Drug Reactions by Term from Post-marketing Sources*

		Spontaneous, including regulatory authority and literature				Non-interventional post-marketing study				Total
		serious		non-serious		serious		non-serious**		
		interval	cumulative	interval	cumulative	interval	cumulative	interval	cumulative	cumulative, all
SOC 1										
	MedDRA PT									
	MedDRA PT									
	MedDRA PT									
SOC 2										
	MedDRA PT									
	MedDRA PT									
	MedDRA PT									
	MedDRA PT									

*Non-interventional studies and spontaneous ICSRs (i.e., reports from healthcare professionals, consumers, regulatory authorities, and scientific literature)

** Non-serious ADRs from non-interventional Post-Authorisation Safety Studies (PASS) only should be tabulated here. See Glossary.