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Benefit-risk evaluation and Pharmacovigilance Planning: *Changes to PSURs, RMPs and Signal Management*

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Presentation Outline

1. Changes to PSURs

- Format and Content
- Submission requirements
- Outcomes and transparency.

2. Changes to RMPs

- Format and Content
- Submission requirements
- Transparency

3. Signal Management



Scope of the PSUR



Scope of the PSUR

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**;
- a) 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**.
- a) 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**.



Impact of Article 107b

Interval safety data → Benefit-risk evaluation

Reorientation of its objective:

1. To provide a tool for post marketing evaluation of the risks and benefits of a medicinal product based on the available data at a defined time point in the lifecycle of the product.
2. Based on the assessment of the PSUR, to consider whether any action concerning the marketing authorisation for the medicinal product is necessary

→ **Legally binding outcome.**



Why the change in scope?

- Global recognition that the benefit-risk profile may change throughout the product lifecycle as pharmacovigilance data emerge.
 - Stakeholder expectations.
 - Developments in regulatory science
 - Technological developments (e.g. electronic reporting of ICSRs).
- > PSUR should provide a regulatory framework for periodic review of the benefit-risk profile.

Goal: Strengthened Public Health Protection



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1997

Format and Content



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).
- Takes account of ongoing work on international harmonisation specifically the revision of the **ICH E2C (R2) Guideline.**



Format and Content

- **Modular** structure
- **No** routine requirement for **line listings**
- **Data presentation** sections — exposure and analysis of use patterns, summary tabulations, CT findings, findings from non-interventional studies etc.
- Risk **evaluation** sections including signals and effectiveness of risk minimisation
- Benefit **evaluation** sections
- **Integrated benefit-risk analysis**



Estimated exposure and Use Patterns*

3.5.1 Cumulative Subject Exposure in Clinical Trials

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

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

* Draft proposal



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Signal and Risk Evaluation*

3.16.1 Summary of safety concerns

3.16.2 Signal evaluation

3.16.3 Evaluation of Risks and New Information

3.16.4 Characterisation of Risks

* Draft structure



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Benefit Evaluation*

1. Important Baseline Efficacy and Effectiveness Information
2. Newly Identified information on Efficacy and Effectiveness
3. Characterisation of Benefits

When there is significant change to the risk profile, or new evidence that suggests benefit is significantly less than originally demonstrated, this section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness.

Benefit Risk Analysis Evaluation

- A benefit-risk profile is specific to an indication and population.
- For products approved in more than one indication, benefit-risk profiles should be evaluated and presented for each indication individually.
- If there are important differences in the benefit-risk profiles among populations within an indication, benefit-risk evaluation should be presented by population, if possible.



Actions

- Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the MAH should assess the need for changes to the product information.
- In addition, the conclusion should include preliminary proposal(s) to optimise or further evaluate the benefit-risk balance, for further discussion with regulatory authorities. This may include proposals for additional risk minimisation activities.
- **Core Safety Profile will be replaced by key particulars for risk minimisation including changes to product information.**



Requirements for PSUR submissions and Union Reference Date (URD) List



PSUR submissions

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).



URD List - Legal basis

Article 107c (paragraphs 4 and 7) of Directive 2010/84/EU,
and Article 26(g) of Regulation (EU) 1235/2010

The Agency “shall make public a list of Union reference dates and frequency of submission of periodic safety update reports by means of the European medicines web-portal”



Interpretation

- URD list will include a comprehensive list of active substances and combinations of active substances for which Periodic Safety Update Reports (PSURs) shall be submitted as determined by the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group (CG) after consultation of the Pharmacovigilance Risk Assessment Committee (PRAC).
- The submission frequency defined on the list will **overrule**
 - 1) any condition laid down in the Marketing Authorisation (MA) of the products concerned.
 - 2) the standard submission frequency in accordance with Article 107c, paragraph 2 of Directive 2010/84/EU .



PSUR requirements

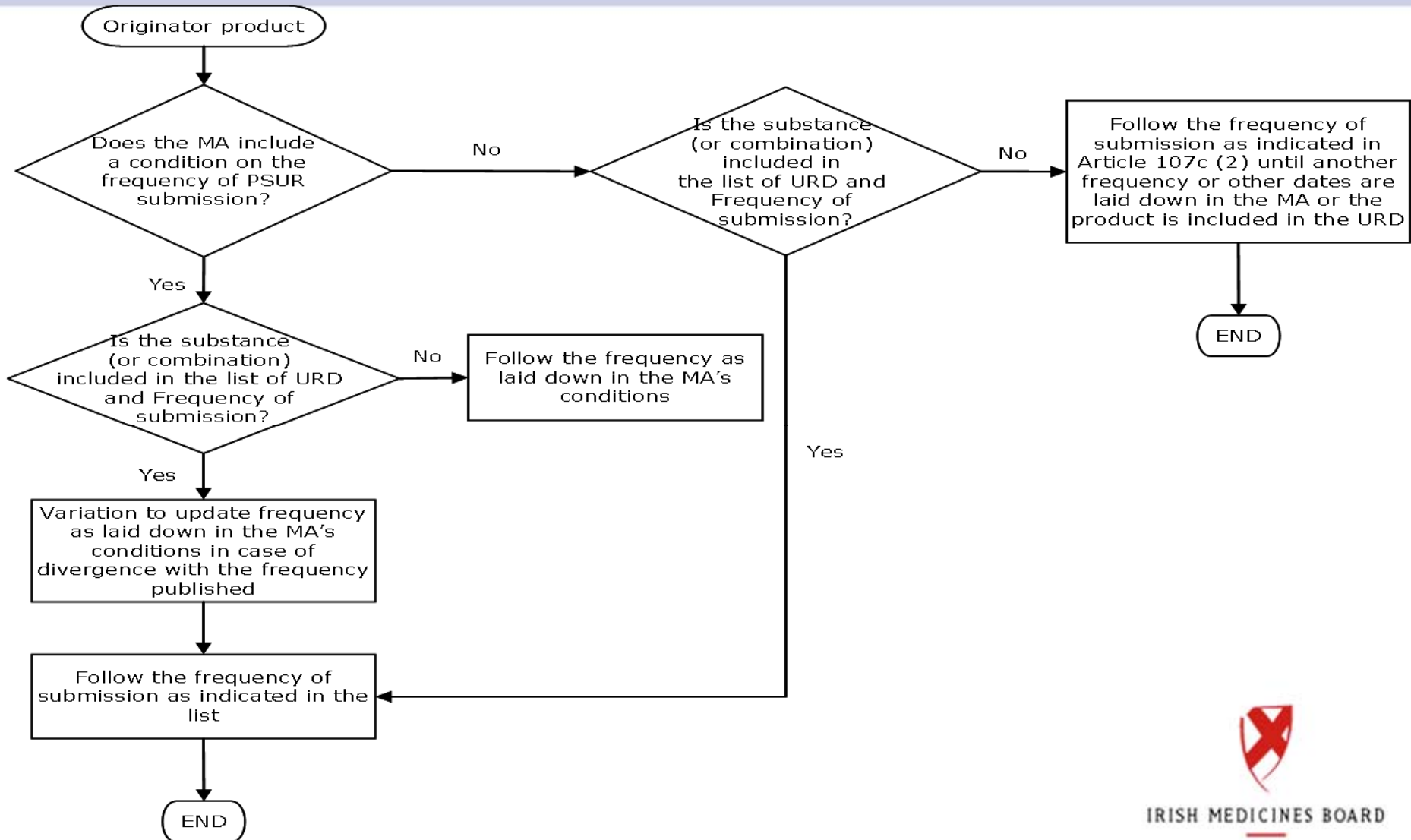
PSURs for medicinal products for which MAs were granted before July 2012 should be:

- ✓ submitted in accordance with Article 107c paragraph 2 of Directive 2010/84/EU and Article 28 (2) of Regulation (EU) 1235/2010, i.e. *“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”*,

unless otherwise detailed
- ✓ As a condition of the MA **or**,
- ✓ On the List of Union Reference Dates (URD) and frequency of submission.
- ❖ PSURs also need to be submitted immediately upon request from a Competent Authority.



PSUR Submission Requirements



Generics, well established use, homeopathic and THMPs

As per Article 107b (3) of Directive 2010/84/EU, 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;
- 2) Requested by a Competent Authority on the basis of the grounds defined in legislation.
- 3) The active substance is included on the List of URDs and the requirement for submission of a PSUR according to the harmonised frequency is indicated on the list in accordance with Competent Authority consultation.



Substances included on the list

- List of substances extracted from the EVMPD*
 - Substances included on the Work Sharing list
 - Substances included on the Synchronisation list
 - List of Centrally Authorised Products (CAPs)
-
- List will aim to be comprehensive.
 - Concept of risk proportionality inherent to submission requirements

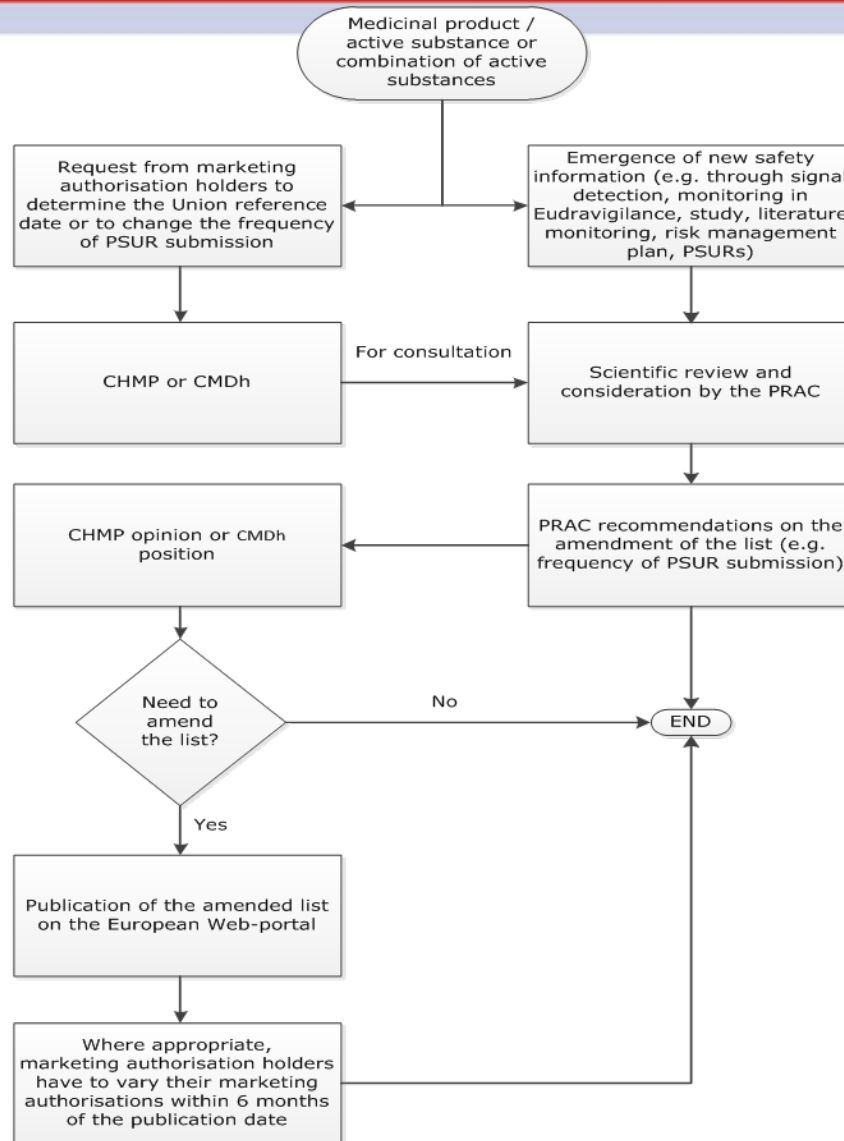
* List of URD to be cross referred and updated in line with the “*list of all medicinal products for human use authorised in the Union*” that the Agency is to set up as per the Article 57(b) of Regulation (EU) No 1235/2010, and to the “*list of medicinal products that are subject to additional monitoring*” as defined in Article 23 of Regulation (EU) No 1235/2010.

Development of the URD list

- Frequency of submissions will be determined based on a risk based approach. EU network consultation on the development of the list is ongoing.
- As no *routine* PSURs for generics, WEU, homeopathics and THMPs are foreseen, the list will aim to clearly indicate the situations where MAHs of generics, WEU, homeopathics and THMPs are required to submit PSURs.
- URD list will be agreed by the CHMP and CG after PRAC consultation.
- List will be dynamic – regular review and amendment , responsive to the emergence of relevant new information.
- **Public Consultation on the draft list is envisaged.**



Adoption and Maintenance of the list



PSUR Submissions

At the end of the transitional period and following audit, EMA Management Board will announce functional repository.

Subsequently, stepwise implementation of associated deliverables has been proposed:

- 1) Phase 1 - Centralised electronic submissions.
- 2) Phase 2 – Implementation of Electronic format.

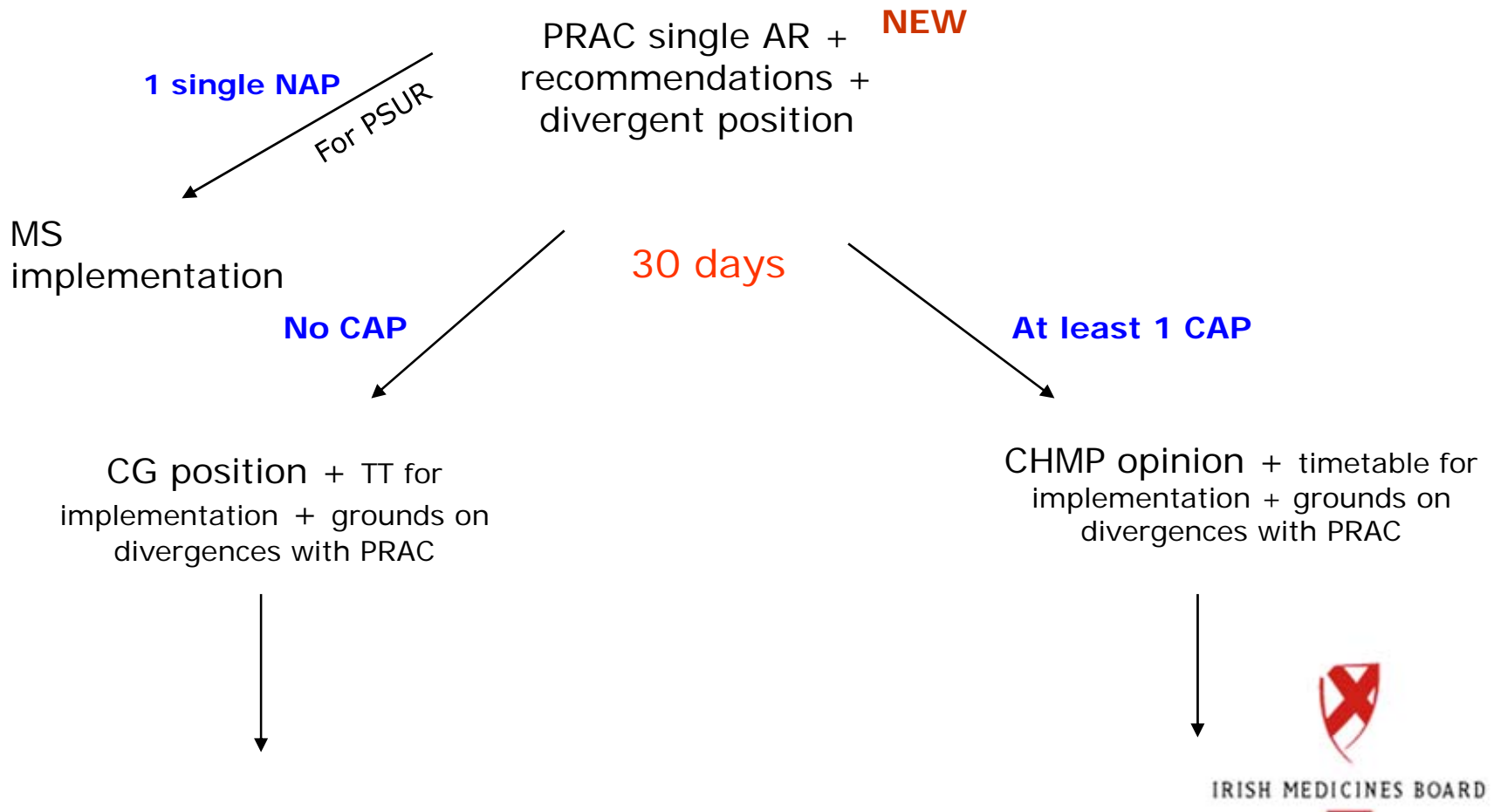
Updates will be provided as proposals are matured.



Decision Making Process for Single EU Assessments



Decision-making process for single PSUR



Legally Binding Outcome

No CAP

At least 1 CAP

CG position + TT for implementation

CHMP opinion + TT for implementation + grounds on divergences with PRAC

By consensus

30 days

No consensus

For non CAP

30 days

For CAP

NEW

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

Majority position sent to EC

EC decision (Art. 33, 34) to MS

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

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

EC decision (Art. 33, 34) to MS

30 days

National implementation

National implementation

'Follow-up' variation

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



Outcomes - impact

Future situation:

- Within 30 days of receipt, the CMD(h) should consider the PRAC assessment report and recommendation and reach a position, by consensus or by majority vote, on the maintenance, variation, suspension, revocation of the marketing authorisation(s) concerned.
- **Agreed position binding**



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.



2. Changes to Risk Management Plans



Legal basis for Risk Management System

- **Risk Management System:**
 - ‘ a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions’.
- **Risk Management Plan:**
 - ‘ a detailed description of the risk management system. ‘



RMPs –key principles

- ✓ Information on safety is limited at the time of authorisation
- ✓ Planning pharmacovigilance activities will be improved if it is based on product specific issues
- ✓ The purpose of risk identification and characterisation is to allow for risk minimisation or mitigation wherever possible
- ✓ Risks need to be understood in the context of benefit



RMP Format and Content



RMP Format and Content

- Article 108 b of Directive 2010/84/EU
- EC Implementing Measure will describe the technical detail of the format and content of electronic Periodic Safety Update Reports and **Risk Management Plans**
- ICH E2C (R2) introduces ‘modular’ concept – public consultation on draft 2 planned for early 2012.
- GVP modules on PSURs and RMPs – due for publication by February 2012 – concept of common modules likely to be reflected.



Evolution of risk management principles

- ICH E2E
- Guideline on Risk Management Systems for Medicinal Products for Human Use (EMA Guideline November 2005)
- Now with 'due regard to therapeutic effect'
- Development of a more flexible modular format to support risk proportionality and taking account of the global context for risk management.





European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 14 November 2005
Doc. Ref. EMEA/CHMP/96268/2005

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON RISK MANAGEMENT SYSTEMS FOR MEDICINAL
PRODUCTS FOR HUMAN USE**



Safety Specification – basis for pharmacovigilance planning and risk minimisation

- Important identified risks of a drug
- Important potential risks of a drug
- Important missing information

The safety specification is the basis for the Pharmacovigilance plan and the evaluation of the need for risk minimisation



Pharmacovigilance Planning

- PASS and PAES integrated into RMPs
- Moving up the hierarchy of evidence and embracing a plurality of evidence with increased focus on pharmacoepidemiology.
- new and improved methodologies



Lifecycle benefit-risk management



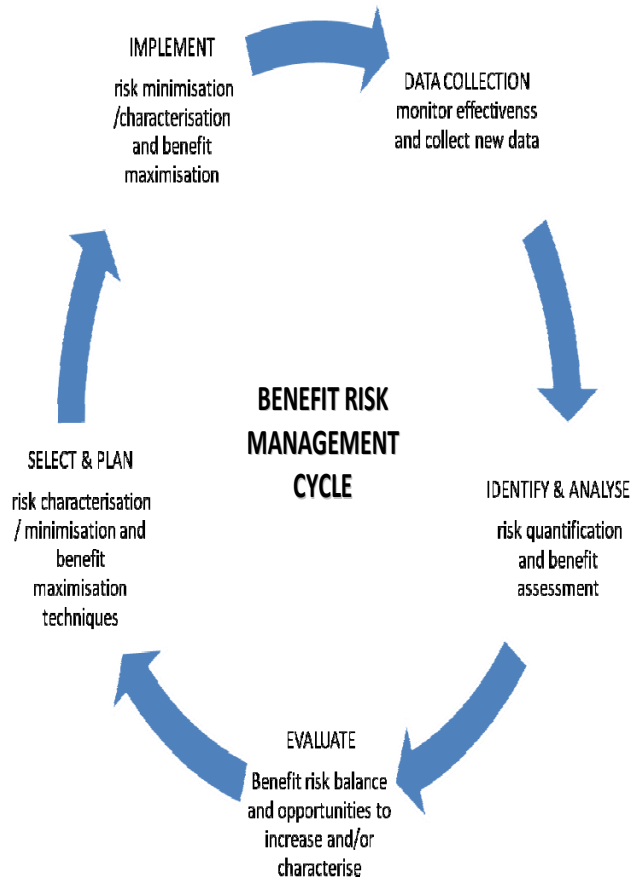
Risk Minimisation Activities

- Public health interventions intended to prevent the occurrence of Adverse Drug Reactions (ADRs) associated with the exposure to a medicine or to reduce their severity should they occur.
- Legal obligation to monitor the effectiveness of RMAs included in RMPs.
- Separate Module under development (second wave of modules).





Risk Management within the EU



- Substance specific
- Risk proportionate
- Key elements, including final milestones, as part of the conditions and requirements of the MA
- From risk management toward B-R management approach



Part I Product 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 – SVII Clinical part of the Safety Specification

Module SIII-SV Limitations of the Human Safety Database

Module SIII: Clinical trial exposure

Module SIV: Populations not studied in clinical trials

Module SV: Post authorisation experience

Module SVI: Identified and potential risks

Module SVIa: Identified and potential risks (ATMPs)

Module SVII: Additional EU requirements for the Safety Specification

Module SVIII: Summary of the Safety Concerns

Part III Pharmacovigilance Plan

Part IV Plans for studies on effectiveness and long term efficacy

Part V Risk Minimisation Plan(s)

Part VI Summary of Activities in the EU-BRMP

Part VII Annexes

What is new?

- Modular structure and increased flexibility.
- Plans for studies on efficacy and effectiveness
- Formal requirement for monitoring the effectiveness of risk minimisation.



Submission Requirements

- RMP describing the RMS required for all new MAA
- Operation of a RMS may be imposed in PM phase if there are concerns about the risks affecting the R-B balance
- MAH shall operate a RMS for each medicinal product as part of the PhV system



Requirements in specific situations

- In general, all parts of an EU-RMP should be submitted.
- However, in line with the concept of proportionality, certain parts or modules may be omitted *unless requested otherwise by the competent authority*.
- For example, an abbreviated RMP is envisaged for generics where only certain modules would be required.

The requirements will be made clear in the GVP Module on RMPs (due for public consultation by February 2012).



Impact of legislative changes

- RMP required for all applications.
- Risk Proportionate
- Focus is on Planning – prospective.
- PASS and PAES need to be integrated elements.
- Summary of the Risk Management Plan will be made public.
- Need to monitor the effectiveness of RMAs.



Interface between the PSUR and RMP



PSUR and RMP

- PSUR = Evaluation
- RMP = Planning
- There is some overlap; a modular structure will maximise the functionality of common elements.
- ICH E2C R2 concept paper introduces the idea of a modular approach to PV documentation.



Some areas of overlap

Safety Specification

1. PSUR **Exposure** and **Use Patterns**

(+Actions taken in the reporting period for safety reason) ~ RMP Post Authorisation experience.

2. Important Safety Issues/Characterisation of risks ~ **Important identified and potential risks**

and

3. Evaluation of the **effectiveness of risk minimisation**



Common Modules

- PSUR and RMP are complementary PV documents but may be evaluated as stand alone documents.
- Some common content with different perspectives – exposure, evaluation and characterization of risks, effectiveness of risk minimization.
- PSUR evaluation may inform risk minimization or pharmacovigilance planning.
- In the absence of an electronic format, all sections/modules will be included but there may be defined common sections/modules.



Signal Management



Legal Obligation for Signal Detection

Directive 2010/84/EU, Art 107h

(...) national competent agencies in collaboration with the Agency, shall take the following measures:

- (c) monitor the data in the EudraVigilance database to determine whether there are new risks or whether risks have changed and whether those risks impact on the risk-benefit balance



Implementing Measures (minimum requirements)

- principle of worksharing at the level of the active substance, i.e. a lead Member State nominated by the PRAC for each active substance
- frequency of data monitoring in EudraVigilance to be proportionate to potential risks, identified risks and missing information
- “common triggers for signal detection” (EC’s view in IM published for consultation)
- steps in signal management: signal detection, validation, prioritisation, evaluation + decision-making (PRAC)



GVP Module - Concept of signal management

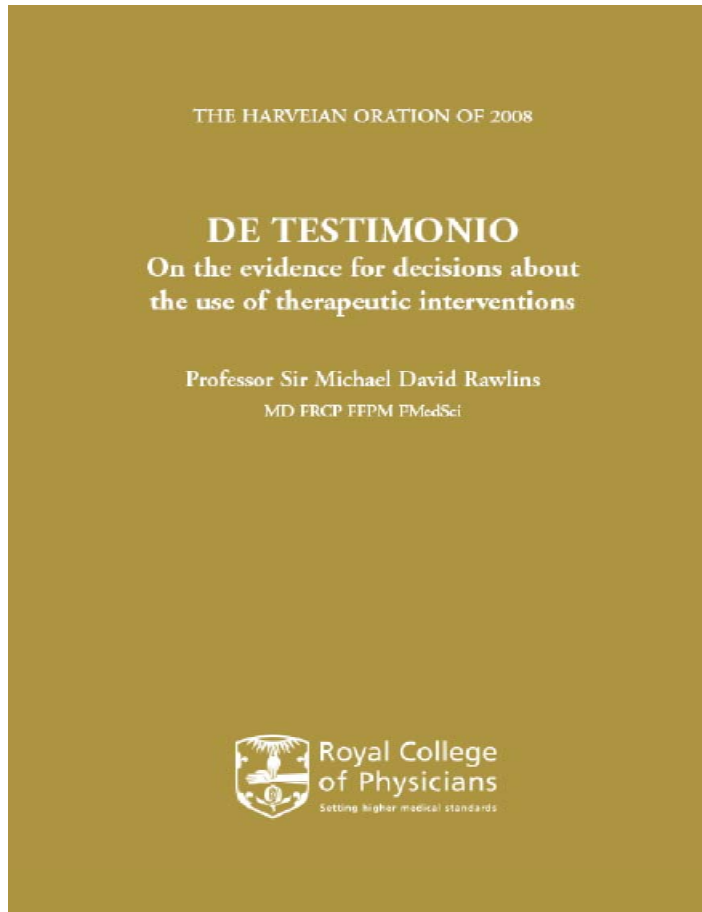
- *Data sources for signal management*
- *Steps of the signal management process*
 - *signal detection*
 - *signal validation*
 - *signal prioritisation*
 - *signal evaluation*
 - *recommendation for action*
 - *exchange of information*
- *Quality requirements*
 - *Tracking*
 - *Quality systems and documentation*
 - *Training*



Conclusions



A 'plurality of evidence'



*“Hierarchies of evidence
should be replaced by
embracing a diversity of
approaches.....
....Scientific judgement
conditioned by the totality
of the available evidence”*



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Future vision for benefit-risk management

- Bringing together all available evidence on effectiveness and harms in clinical use
- Clearly identifying limitations of evidence and uncertainty
- Better justified regulatory decisions
- Better public understanding of benefit risk



Questions?



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