Industry and assessors' joint training on how to improve the content of PSURs

Introduction

PSUR Roadmap: Joint industry/assessor training
22 September 2017

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Agenda

- PSUR roadmap
- Purpose of the training
- Topics of the training
- Additional information

PSUR roadmap

- January 2016: PRAC/CMDh common understanding of optimal use of the single assessment for old substances – Workshop
- October 2016: Finalisation of PRAC/CMDh working documents on common understanding
  - Q&A for assessors
  - Explanatory note for industry on GVP VII – PSUR
- February 2017: Consultation with industry stakeholder associations on explanatory note via PhV industry platform meeting
- March 2017: Finalisation and publication of the Explanatory note to GVP Module VII and Q&A for assessors taking into account industry comments

Purpose of the training

- How to improve the content of PSURs by
  - Identifying key issues encountered by Industry and Regulators in the preparation of PSURs
  - Sharing Best Practice (advice) on ways to address these key issues to achieve a common understanding of the quality standards needed to facilitate the EU PSUR single assessment

Topics of the training

- Signals and close monitoring in the PSUR
- Safety specifications
- Product information / Reference safety information
- Use of summary tabulations

Additional information

- During the training please send your questions to PSURtraining@ema.europa.eu

- At the end of the training, please take a moment to provide your feedback on this webinar by completing a short questionnaire, available from 22 to 29 September 2017 on the EMA website

Signals and close monitoring in the PSUR

Preparing for a signal presentation / evaluation (industry's perspective)

Dr Craig Hartford

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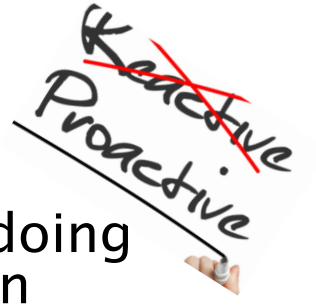
A. Proactivity is key



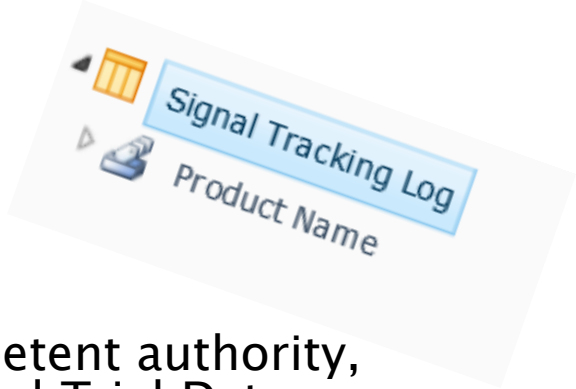
- The PSUR prep/writing period is **NOT** the time to be doing your signal detection, or worse, your signal evaluation activity.

- A successful PSUR is largely derived from a robust "interval" period running up to the PSUR
  - Reminder: "all available information" = *data the MAH might reasonably have access to and that is relevant to the characterisation of the risks.*

- A ***proactive*** SD/SE/BRM system with a dedicated product Safety Management Team conducting Signal Management and Tracking is essential and key to a successful PSUR.

B. Proactively track signal detection

(helps populate section 15)



- Signal Term
- Date Detected
- Status (ongoing or closed)
- Date Closed
- Source or trigger of signal (Inquiry from a competent authority, Spontaneous Reports, Scientific Literature, Clinical Trial Data, Routine Pv)
- Reason for evaluation and summary of key data
- Method of signal evaluation
- Action(s) taken or planned
- Linkage with Safety Management Team's close monitoring (specific topics)

C. Proactively document signal evaluations

(helps populate section 16.2, and 16.3 if new risk information)

- Evaluations should be comprehensive and systematic
  - Information received during the reporting interval should be analysed in the context of cumulative information and previous analyses
  - Evaluations should reflect all available information (sources)
  - Clear search strategy SMQ, Relevant terms
  - Justify causality in full, including index/illustrative cases
  - Include integrated summary tables, when necessary

D. Proactively document risk categorization

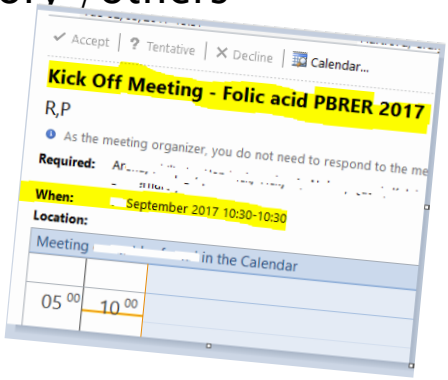
(helps populate RMP and thus PBRER section 16.4)
(helps populates sections 18/19)

- Safety Management Team's risk categorization, classification
  - Imp/not, Identified – Potential – Missing Information
  - Document at the time Risk determined, not later on

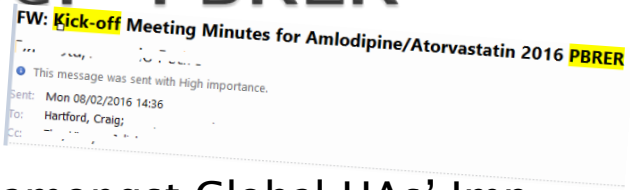
- Risk Minimization planning, including RPI proposed changes
  - underway/complete for RPI (CCDS/CCSI), and for country/region (e.g. SmPC)?

E. Proactively hold a "proper" PBRER kick-off meeting

- **Ensure the right Invitees**
  - e.g. Medical / Clinical / Statisticians / Safety / Regulatory /others
    - Previous proactivity = no surprises for Medical!
- **Activity Tips**
  - Expected contributors, timelines
  - Agree safety concerns if no RMP
    - *(Helps populate section 16.1)*
    - Document why Safety Concerns selected
  - Expect fewer Important Risks for well established mature products
  - Confirm RPI has the important risks in W&Ps, and in Adverse Effects if identified risk (ADR)
    - Especially older products!



E. Proactively hold a "proper" PBRER kick-off meeting


FW: Kick-off Meeting Minutes for Amlodipine/Atorvastatin 2016 PBRER

This message was sent with High importance.

Sent: Mon 08/02/2016 14:36

To: Hartford, Craig;

- Use ICH E2C (R2) Q&A (13.4) to display differences amongst Global HAs' Imp Risks vs your "core" RMP/RPI
  - Or e.g. footnotes can be used to good effect
- Get ready to justify country/region PI (e.g. SmPC) vs RPI (CCSI) – occasionally due to HA differences in opinion with MAH or other HAs
  - A robust country PI tracking system with documentation helps here – continuum (linkage) between Signal Management and RPI + PI management
- Always verify the approved MAH actions as per the previous Final Assessment report (FAR).
- Additionally, verify if any additional stand-alone HA queries were received during the reporting period (such as a PRAC request to review a safety topic/Signal) or any commitments that may have been presented in the last PSUR.
  What will you document for close monitoring (specific topics)

PBRER example of the Sections FLOW for a signal

- (note; presentation is not intended as a “model example” but rather to vivify the flow of a signal’s presentation across the various PBRER sections)

Draft PBRER Screenshot of 15/16 – *15.0*

15. OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

Signal Overview

New signals detected for MEDICINALPRODUCT during the reporting interval are presented below in Table 6 along with the ongoing signals and signals closed during the reporting interval. Appendix 3 provides a summary of the safety signals that were new, ongoing, or closed during the reporting interval. See Section 16.2 for evaluation of signals that were closed during the reporting interval and Section 16.3 for evaluation of new information for previously known risks not considered to constitute a newly identified signal.

Draft PBRER Screenshot of 15/16: 15.0

Table 6. Overview of Signals

Signal	Signal Type	Source	Category
xxxx	New and Ongoing	Regulatory query[a]	Not yet determined
xxxx	New and Closed	Routine PV activities	Important Identified risk
xxxx	New and Closed	Literature review	No risk
Severe cutaneous adverse reactions**	New and Closed	Routine PV activities	Important Identified risk
xxxx	New and Closed	Routine PV activities	Important Identified risk.
xxxx	Closed	Routine PV activities	Identified risk

Draft PBRER Screenshot of 15/16: – 15's App

Appendix 3 (Referred in Section 15 Overview of Signals: New, Ongoing or Closed)
Tabular summary of safety signals that were new, ongoing or closed during the reporting interval
Product Name:_Medicinal Product
Reporting interval:

Signal Term	Date Detected	Status (ongoing, or closed)	Date Closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Severe Cutaneous Adverse Reactions	xxxx	Closed	xxxx	Non-statistical line listing	TEN, SJS and Dermatitis Exfoliative have been reported with MEDICINAL PRODUCT	Cumulative Review	Add a warning statement on SCAR to Section 4.4. Addition of SCAR Terms to SOC Skin and Subcutaneous Tissue Disorders in Section 4.8 of the CDS

Draft PBRER Screenshot of 15/16: 16.1/16.2

1. SIGNAL AND RISK EVALUATION

1.1. Summary of Safety Concerns

Table 1 summarizes the important risks and missing information for MEDICINAL PRODUCT at the beginning of the reporting interval.

Table 1. Ongoing Safety Concerns[a]

Important identified risks	xxxx
Important potential risks	xxxx
Missing information	xxxx
	xxxx

a. Severe cutaneous adverse reactions and xxxx were categorized as important identified risks per signal evaluation during this reporting interval, these two risks will be discussed under Section 1.6.2.1 and Section 16.4.1

1.2. Signal Evaluation

Severe cutaneous adverse reactions and xxxx were signals opened and closed during the reporting interval. xxxx was a signal opened during the reporting interval and still ongoing

1.2.1. Evaluation of Closed Signals

Following evaluation during the reporting interval, xxxx and Severe cutaneous adverse reactions, xxxx have been categorized as important identified risks, xxxx has been categorized as identified risks and xxxx was a signal determined to not be a risk.

Draft PBRER Screenshot of 15/16: 16.2

Table 9. Evaluation of CLOSED SIGNALS During the Reporting Interval

Signal	Evaluation
Signals Determined to Not be Risks	
Xxxx	
Risks Not Categorized as Important	
Xxxx	
Risks Categorized as Important	
Xxxx	
Severe Cutaneous Adverse Reactions	Toxic Epidermal Necrolysis (TEN) xxxx. As per routine PV activities xxxx the MAH conducted a full review of the safety database. A search of the MAH safety database through xxxx for AEs reporting the MedDRA PT TEN associated with Medicinal Product retrieved xxxx cases. xxxx of the cases were serious with the following outcome. **xxxx detailed evaluation continued…** Upon review, there is a reasonable possibility that TEN is associated with use of Medicinal Product . The MAH has added Toxic Epidermal Necrolysis (TEN) to Section 4.8, Undesirable effects, of the Medicinal Product CDS xxxx. Dermatitis Exfoliative As per routine PV activities, a cumulative search in the MAH safety database through xxxx for all xxxx cases meeting the Periodic Benefit Risk Evaluation Report (PBRER) criteria of Medicinal Product was performed by applying the following search criteria: PTs: Dermatitis exfoliative; Dermatitis exfoliative generalised; Exfoliative rash; Skin exfoliation. The cumulative search for all cases of Medicinal Product reporting the PTs listed above associated with Dermatitis exfoliative identified xxxx. The PTs of interest included in these xxxx cases were Dermatitis exfoliative (xxxx), Exfoliative rash (xxxx), and Skin exfoliation (xxxx). Of the xxxx events of Dermatitis exfoliative, xxxx were assessed as non-serious and xxxx were assessed as serious, xxxx In xxxx of these cases, no co-suspect medication was reported. The single case of Exfoliative rash, assessed as non-serious. Of the xxxx events of Skin exfoliation, xxxx were assessed as serious and xxxx were assessed as non-serious. The event outcome was not resolved in xxxx cases, resolved in xxxx cases, and unknown in xxxx cases. There were no fatal outcomes reported. A total of xxxx cases did not report any co-suspect drug. The pathogenesis of drug-induced exfoliative dermatitis is not known, although an immunologic basis has been suggested. **Xxxx detailed evaluation continued….** Upon the review of these xxxx cases and a biologically plausible allergic mechanism suggested in the published literature, the MAH concluded that an association between Dermatitis exfoliative and Medicinal Product administration xxxx _____ [[Toxic epidermal necrolysis, Stevens-Johnson syndrome (SJS), and dermatitis exfoliative may be life threatening. xxxx Given the clinical significance of these SCARs and the need for specific instructions for practitioners, the MAH is adding a warning statement on SCAR to Section 4.4, Special warnings and precautions for use of the Medicinal Product CDS. The newly added text is italicized and underlined: 4.4. Special warnings and precautions for use Hypersensitivity SCAR warning xxxx (see Section 4.8 Undesirable effects).]]

Draft PBRER Screenshot of 15/16: 16.3

16.3. Evaluation of Risks and New Information

Evaluation of ***new information*** for previously recognized important identified and potential risks, other risks (not categorized as important), special situations, and special patient populations for Medicinal Product is provided below in Sections

Table 11.Evaluation of Important Identified Risks

Topic **Search Criteria**	**Evaluation** ***Clinical Trial (CT) Data – Total No. of Cases in the Reporting Interval= xxxx*** ***Post-Marketing (PM) Data – Total No. of Cases in the Reporting Interval= xxxx***
Important Identified Risk: ***xxxx*** *Search: SMQ= xxx*	
CT Data	xxxx
PM Data	xxxx
Literature	xxxx.
Risk Assessment of New Information	The interval data during the reporting period provide new information that has an impact on the characterisation…

Draft PBRER Screenshot of 15/16: 16.4

Table 15. CHARACTERISATION of Important Risks

Important Identified Risk: Severe Cutaneous Adverse Reactions

Search: SMQ= Severe cutaneous adverse reactions (narrow and broad)

Characterisation	*Include per PBRER Guidance the Medicinal Product's SCAR data pertaining to:* • *frequency;* • *numbers of cases (numerator) and precision of estimate, taking into account the source of the data;* • *extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;* • *estimate of relative risk and precision of estimate;* • *estimate of absolute risk and precision of estimate;* • *impact on the individual patient (effects on symptoms, quality or quantity of life);* • *public health impact;* • *patient characteristics relevant to risk (e.g. patient factors (age, pregnancy/lactation, hepatic/renal impairment, relevant co-morbidity, disease severity, genetic polymorphism);* • *dose, route of administration;* • *duration of treatment, risk period;* • *preventability (i.e. predictability, ability to monitor for a "sentinel" adverse reaction or laboratory marker);* • *reversibility;* • *potential mechanism; and* • *strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.*
Cumulative Case Characterisation	Post-marketing sources: - Number of cases: xxxx (reporting xxxx relevant AEs) -The most frequently reported relevant PTs (≥ 10 occurrences): xxxx - Gender: female (xxxx), male (xxxx), unknown (xxxx) - Age Range: xxxx - Seriousness: Serious (xxxx), Non-serious (xxxx) Clinical trials: - Number of cases: xxxx (xxxx of which involved Medicinal Product and xxxx involved other study drug) ….Severe cutaneous adverse reactions (SCARs) include erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP).xxxx Although their incidence is low, SJS and TEN can result in disability or death, with a mortality rate of 10%-40% . Xxxx Reliable epidemiological data of EM and related disorders are scarce xxxx **Characterisation continued…**

How to address requests for close monitoring (industry's perspective)

Val Simmons MB BS FFPM
EU QPPV
Eli Lilly and Co, UK

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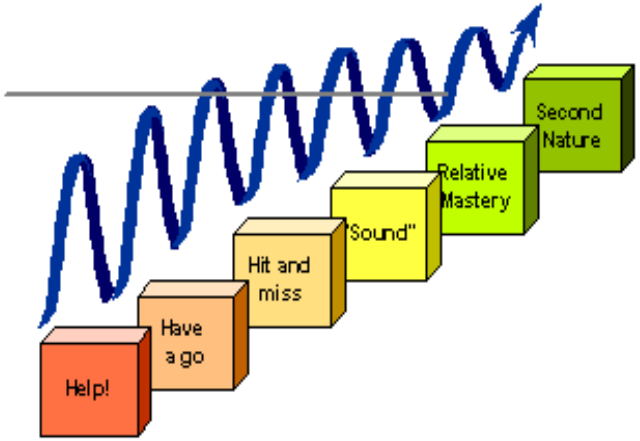
Monitoring in the PSUR/PBRER
A Dilemma for ICH E2C(R2)

- Main objective of a PBRER is to present a comprehensive, concise, and critical analysis **of new or emerging information on the risks of the medicinal product**, and on its benefit (approved indications) to enable an appraisal of the benefit-risk profile.
- Scope of the PSUR (information included/evaluated):
  - Significant efficacy and safety findings from multiple sources
  - Signals
  - Potential and identified risks (Important and Other)
  - (Important) missing Information
  - New information on previously recognised risks and update on missing information
- No provision for "monitoring" in Step 2 guideline
  - GVP Module VII published in July 2012
  - Added at Step 4 (Nov 2012)

A possible root cause at the time???

Section 15
Subsection on Handling Regulatory Requests

- Handling regulatory authority requests
  - New concepts, format and content introduced for PBRER but regulatory requests and expectations appeared to want to re-create the “old PSUR”
  - Sub- section created to accommodate requests for a specific topic to be *monitored and reported in future periodic reports*
    - **NB: Topic not considered to be a signal**
    - **Source of major confusion**
- Further clarity provided by IWG ICH E2C(R2) Q&A
  - Focussed on what goes where.....



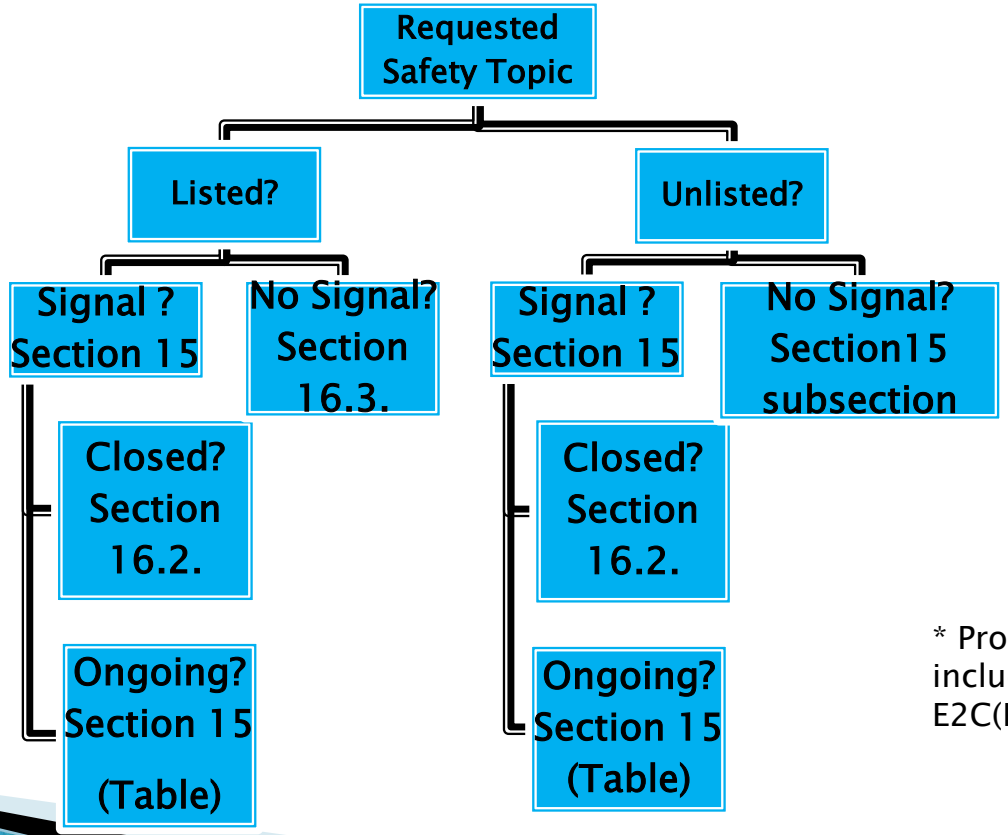
Handling Topics Requested for Continued Monitoring

When a regulatory authority has requested that a specific topic be monitored and reported in a PBRER, where in the PBRER should the MAH summarise the results of the analysis?

If the MAH determines that the specific topic constitutes a signal, the MAH should include it in the signal tabulation, evaluate it as such, and handle it in accordance with the usual approach for summarising signals within the PBRER.

If the MAH does not consider the specific topic to constitute a signal, the MAH should summarise its analysis on the requested monitoring topic in section 15 of the PBRER.

Topics Requested for Continued Monitoring Listed or Unlisted ADR*?



* Proposal not included in ICH E2C(R2) guideline

Continued Monitoring in the PSUR/PBRER Remains a Dilemma for MAHs

- Highly variable rationale for request
  - No reason provided
  - Based on "signal of disproportionality" in Eudravigilance
  - Based on numbers of cases in the summary tabulations
    - Even for very old products (where " N" is <10, exposure in multiple millions and confounding is acknowledged by Assessor)
  - Common rationale:
    - Event is serious
    - Potential for a risk "cannot be ruled out" or "excluded"
- Appears to disproportionately involve older products
  - May often involve known important risks
  - Repeated requests to monitor a topic in every PSUR

Continued Monitoring in the PSUR/PBRER What Does " Monitoring" Actually Mean?

- Variously described in Assessment Reports
  - Monitor the topic/cases
  - Conduct a cumulative review
  - Very detailed request on expected analysis
    - Including provision of narratives/detailed description of cases
- Frequently no guidance is provided
  - Unclear what is needed
    - Simple statement that the matter has been monitored?
      - No new data or signals?
    - Cumulative review?
    - Interval review?
    - What level of detail?

Continued Monitoring in the PSUR/PBRER Not an Unusual Request

In the previous PSUR the MAH was requested to close monitoring the following ADR: blood dyscrasias particularly thrombocytopenias, myocardial infarction, QT prolongation, retinal detachment, pancreatitis, hepatic disorders (focus on hepatic failure), pneumonia, glucose metabolism disorders, rhabdomyolysis, fractures, cerebrovascular disorders, renal failure, serious skin reactions and bleedings.

N=12

What would help MAHs

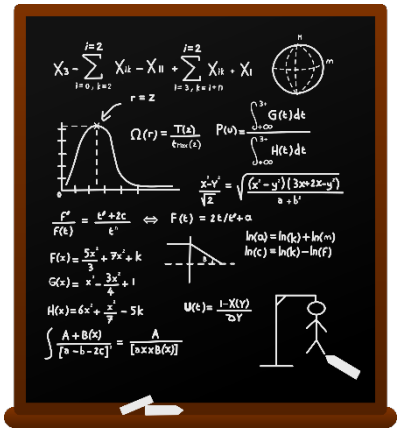
- Remember that the R2 PBRER is not the “old PSUR”
- ..... or a compliance monitoring tool
  - Data indicate that there is either a signal or there is not
    - If data indicate a signal, use existing procedures
    - If there is concern that an MAH has inadequate procedures for signal management, use other procedures to address
- Scientific rationale/trigger for request
  - e.g. literature paper or perceived increase in reporting
- Clear objectives for monitoring
  - What is it expected to achieve?
  - Will more detailed analyses of spontaneous data really answer the question???
    (especially for mature products with extensive experience)
- Guidance on the analyses expected
  - Ensure that these are likely to meet the objectives

Advice to MAHs

- Adopt a risk proportionate approach
  - Assess on a case by case basis
  - Apply medical judgement and common sense....
- Examine the root cause for the request
  - Allows a more tailored approach to meet concerns
- Could this have been predicted?
  - Ensure that any striking increase in numbers in the summary tabulations are addressed
    - Context of increase in exposure
    - Context of other reasons e.g. legal class action, disproportionate increase in exposure

Advice to MAHs

- Provide sufficient detail to allow Assessor to understand how conclusions were reached
- Topics of continued monitoring that have been addressed by a separate procedure prior to next PSUR
  - More likely when PSUR/PBRERs are on a 3 or 5 year cycle
  - Unnecessary to include in the next PSUR (as originally requested)
    - Refer to original request
    - Include procedure where it has been resolved (including outcome of PRAC/CMDH decision)



Advice to MAHs

- Do not leave conclusion open ended on future action
  - Propose future action and rationale
    e.g. if monitoring remains negative after multiple reviews propose that topic becomes subject to routine surveillance .
- If the request has been made too close to submission of the next PSUR propose a reasonable alternative e.g.
  - Include in next PSUR/PBRER (six month cycle)
  - Earlier notification if warranted by ongoing surveillance
- If in doubt, ask to speak directly to Assessor
  - Understand concerns
  - Clarify expectations

Monitoring in the PSUR/PBRER
Personal Impression

The number of requests for monitoring seems to be decreasing

What do assessors expect to receive in a PSUR? (regulatory authorities' perspective)

Ulla Wändel Liminga
Scientific Director
PRAC Member, Sweden

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LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

High level overview of signals

Section 16.2 Signal Evaluation

- New, Ongoing and Closed signals during reporting interval
- Tabular format – GVP Module VII Appendix 2
  - Helpful for what to address in detailed analysis of each topic

Overview – Tabular format

Signal term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Stroke	MMM/YYYY	Ongoing	MMM/YYYY	meta-analysis (published trials)	Statistically significant increase in frequency	Review meta -analysis and available data	Pending
SJS	MMM/YYYY	Closed	MMM/YYYY	Spontaneous case reports	Rash already an identified risk SJS not reported in pre authorisation CTs. 4 reports within 6 months of authorisation; plausible time to onset and no possible alternative causes.	Targeted follow up of reports with site visit to one hospital. Full review of cases by MAH dermatologis t and literature searches	RSI updated with a warning and precaution DHPC sent Effectiveness survey planned 6 months post DHPC. RMP updated

Signal evaluation – 16.2

- MAH present evaluation for each signal incl. conclusion and proposal for way forward
- Evidence for or against possible causal relationship described & discussed
- MAH to provide analyses to support conclusion:
  - signal refuted
  - signal became identified risk
  - signal became potential risk

} MAH should discuss how /if B/R affected; as well as RMP

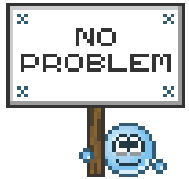
Signal evaluation – 16.2

- If signal cannot be refuted or confirmed ADR
  - Follow-up in next PSUR or different procedure depending on urgency
  - If evaluation in next PSUR also inconclusive, need to continue assessment decided case by case
    - medical importance of signal, extent of exposure, likely impact on B/R, overall weight of evidence
  - If follow up in next PSUR – put interval data in cumulative context

Evaluation include (minimum)

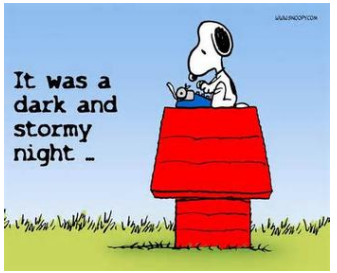
- Clearly presented; sufficient information & interpretation to enable assessor to understand rationale for MAH's conclusions & actions
- **Description** of signal incl. source / trigger
- **Background** relevant for analysis
- **Methods** including data sources, search criteria
- **Results**
  - Summary & critical analysis of key data for evaluation including case overview (where appropriate & integral)
  - Based on robust cumulative review & analysis
- **Conclusion**
  - Need for further evaluation or not
  - Activities taken or planned

Refuted signal



- MAH provide clear rationale together w. data supporting conclusion (e.g. cumulative review and analysis) against causal relationship
- If agreed by PRAC
  - No need for additional 'precautionary' follow
  - Closed – Routine PhV will apply ahead

Case narratives



- PSUR focus on summary information, scientific safety assessment & integrated benefit/risk evaluation
- Line listings or case narratives neither systematically included by MAH nor requested by LMS
  - unless integral to scientific analysis of signal or safety concern
- Sometimes detailed description of key / illustrative cases including summary of case narratives relevant
  - searches in safety databases/literature should include all relevant terms related to signal
  - search strategy & terms clearly specified – selection requires medical & scientific judgement

Close monitoring

- PRAC may request topic be closely monitored & reported in PSUR; with justification
- If MAH, based on analysis, concludes
  - negative – describe in Section 15
  - topic becomes signal – add to signal tabulation & discuss in Section 16.2
- MAH may propose discontinue specific monitoring in future PSURs if analyses refute topic
  - PRAC may disagree – reasons clearly explained along with recommendations for evaluation in future PSUR
- Once topic sufficiently monitored & no safety signal identified – Routine PhV appropriate

NCA/PRAC Questions re. signals evaluation

- Cumulative review requested in previous PSUR not submitted
- Signal refuted without appropriate explanation
- Insufficient analysis, description, explanation e.g.
  - fatal cases mentioned w/o further detail
  - superficial detail of important cases
    - preferably summarised in tabular format if more than handful
  - insufficient analyses
  - cumulative review lacking
  - literature inadequately addressed
  - Numbers do not match

NCA/PRAC Questions re. signals evaluation

- No follow up of possibly important cases / literature information
- Cases inadequately dismissed
  - Strict case definition /adjudication applied; disregard relevant cases because detail lacking
  - Medical assessment lacking
  - Unlikely confounder e.g.
    - 'Blaim' concomitant medication despite event not labelled
- Overall discussion incomplete e.g.
  - no mechanistic discussion

Summary of common understanding

- **Signal presentation / evaluation**
  - PSUR prep/writing period not time to be doing signal detection /evaluation
  - Proactively track/evaluate signals/risks as part of signals & risk management system
- **Close monitoring**
  - Request judiciously (where an evaluation is likely to answer the question)
  - Provide rationale/trigger for request
  - Provide sufficient detail; Assessor needs to see how conclusion was reached
- **Expectations of PSUR**
  - Provide clear, scientifically, medically based assessments, draw conclusions & propose way forward
    - Explain how and why conclusion was reached
    - Provide sufficient detail of facts behind these conclusion

Safety specifications

How is the inclusion of safety concerns substantiated (Industry's perspective)

Klaudija Marijanović Barać

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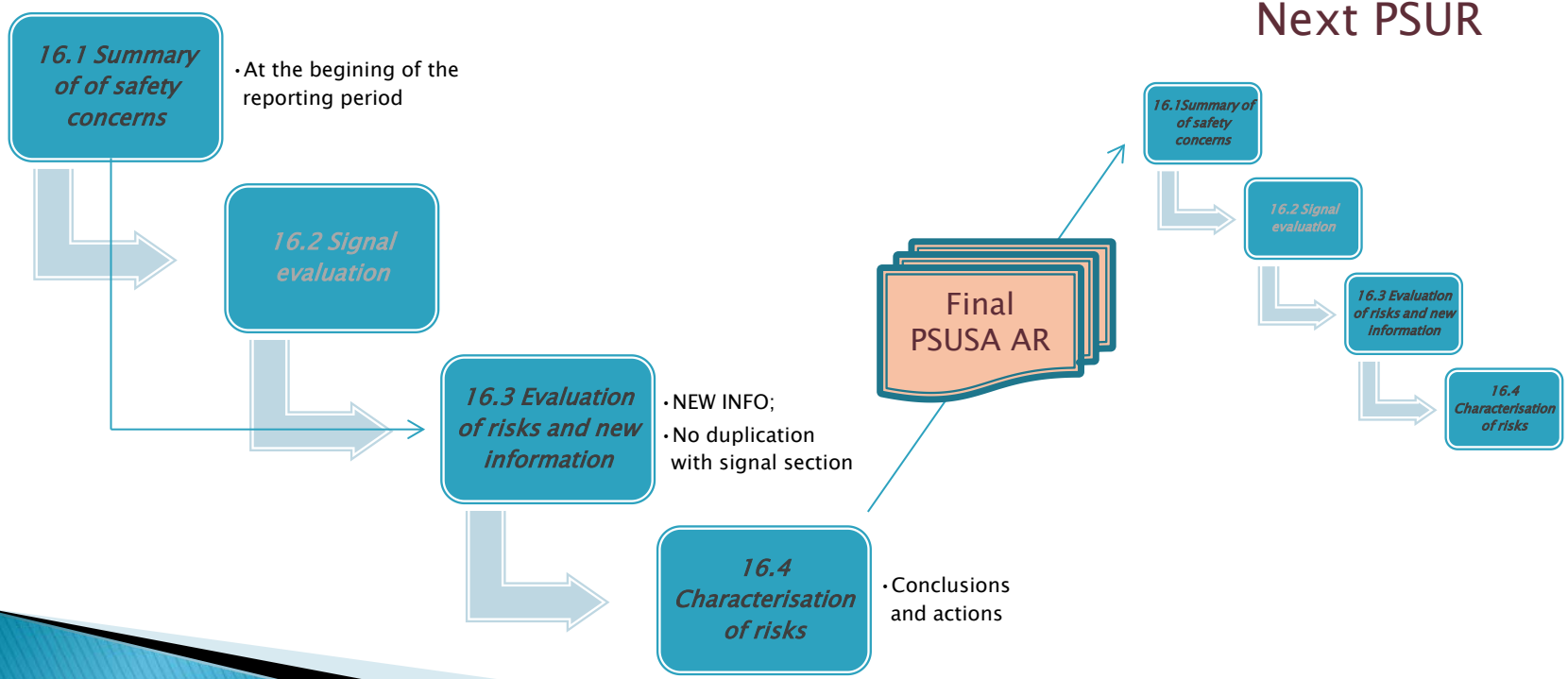
Safety spec. requirements

16. SIGNAL AND RISK EVALUATION



16.1 Summary of safety concerns

- Summary information at the beginning of the reporting interval
- Present risks by indication, formulation, or route of administration

Table 1: Examples how to choose list of safety concerns

Products with EU RMP/RMP	Products without EU RMP (GVP V Rev 2)
Copy list of safety concerns from RMP	List of safety concerns could be very brief (should not be listing of all ADRs)
Several approved RMPs in the EU by one MAH – combine all	EMA public summary, CMDh list, previous PSUR/PSUSA AR
Additional safety concerns requested by non-EU regulators (explanatory note)	A justification for each inclusion should be provided – GVP V Rev 2 definitions

16.3 Evaluation of risks & new info.

- Critical appraisal of **NEW INFORMATION** relevant to previously recognized risks
- No need for detailed discussion of the information arising during the period
- covered by the PSUR that merely confirms the established safety profile

data could confirm those risks

- Level of detail should be proportional to the available evidence on the risk, its medical significance and public health relevance
- Method(s) of evaluation, including data sources, search criteria, and analytical approaches + results, discussion, conclusion ⟶ 16.4

New information can be organised as follows:
1. New information on important potential risks.
2. New information on important identified risks.
3. New information on other potential risks not categorised as important.
4. New information on other identified risks not categorised as important.
5. Update on missing information.

16.4 Characterisation of risks

- Characterise important risks based on cumulative data (i.e. not restricted to the reporting interval), and describe missing information
- Update characterisation of important potential and identified risks or state that *„Safety concerns remain unchanged."*
- Based on previous PSUR sections, provide justification for:
  - Proposal for new important risk to be added
  - Proposal for important risk or missing information to be re-classified or removed

16.4 Characterisation of risks

Examples from assessment reports:

1. *Copy risk characterization from RMP section SVII?*
   - *GVP VII vs GVP V; branded vs generics*
   - *Avoid data dump*
2. *Branded vs generic products:* Data provided proportional to the available evidence - *Risk overview based on the data presented in PSUR and cumulative data (non-clinical/clinical data, SPC, CCSI, literature)*
3. *Statement: „Safety concerns remain unchanged" – provide enough info for evaluation and how company came to the conclusion*
4. *Topic is repeatedly requested to be closely monitored in AR - consider whether the topic should be added as an important risk in the RMP or handled through routine pharmacovigilance.*

Request to review the safety specification (regulatory authorities' perspective)

Menno van der Elst

Background

Q & A for assessors:

2.3. Dealing with inconsistencies of safety specification/RMP

2.3.1. Can/should the PSUSAs be used as a tool for harmonisation of the safety specification?

- PSUR is not a tool for harmonisation of the safety specification per se (note: CMDh initiative ongoing)
- If a new important risk is identified, LMS can recommend that all MAHs include that particular risk in the safety spec
- This does not entail that the whole safety specification should be amended or harmonised
- Independent of a safety issue being included in the safety specification, MAHs are obliged to review and discuss all issues identified during the interval period

Review of the safety specification

- GVP VII for PSURs and GVP V Rev 2 for RMPs
- Q & A: If a new important risk is identified, the MAH is expected to propose update. Alternatively, LMS can recommend inclusion in the safety spec.
- Consider safety spec in the stage in a medicinal product's lifecycle (characterisation of risks, knowledge gaps filled, extent of exposure)
- Safety specification is expected to change/ as knowledge regarding a medicinal product's safety profile increases over time
- Assessors can expect MAHs to explain how conclusions are reached ('safety concerns unchanged' not particularly helpful)
- Assessors can accept some disharmony as long as key risks are included
- Beyond PSUSA: MAHs continue to be encouraged to strive for consistent safety specs, and the efforts of both CMDh and individual Member States are instrumental

Review of the safety specification, what do we expect?

- ***Active review of the safety specification***

- *Not only focussed on reducing the list of safety concerns: for example, emerging resistance for an antibiotic might need to be included as important risk.*

- *Some important potential risks might no longer be considered important risks as further data is gathered, but …*
  - *‘ no case reports received’ not enough justification – critical appraisal of cumulative experience expected: #pts exposed, characteristics of population*
  - *explain what has changed since time of inclusion of risk in safety spec.*

Review of the safety specification, what do we expect?

- *For some important potential risk a causal relationship might have been established:*
  - *Change to important identified risk could be appropriate as further characterisation (e.g. risk factors, at risk population, outcome) might be desirable.*
  - *If the risk is no longer considered important, this should be justified*

- *New study data can be support a proposal to remove an important potential risk:*
  - *aspects to be considered are the ability to investigate the outcome in this study, size of the study, population (incl/excl criteria vs real life)*
  - *Cave: while e.g. a CVOT may rule out risk of MI, at the same time it could point towards the increased risk of another CV outcome*

Summary of common understanding

- Aim of PSUSA is a comprehensive, concise and critical analysis of the benefit/risk balance of the medicinal product taking into account new or emerging information, in the context of the cumulative information on the risks and benefits
- Amount of data/evidence to be provided:
  - Extent of evaluation included in this sub-section should be proportional to degree risks are characterised, new evidence, and stage in product's life cycle
  - Provide enough information for assessor to evaluate data/risks, explain how conclusions are reached
- Not harmonization of list of safety concerns (other procedures more suitable)
- Clear actions in final AR:
  - Risk/issue to address in the next PSUR and update of the RMP
  - Relevance to certain or all MAHs
  - PSUSA outcomes need to be implemented by MAHs not participating in the PSUSA

Product information / Reference safety information

QPPV oversight of the product information (industry's perspective)

Michael Richardson
QPPV & Head of GPVE International
Bristol-Myers Squibb Company

PSUR Roadmap: Joint industry/assessor training
22 September 2017

PSUR and RSI – GVP VII

- **VII.B.5.4. PSUR section "Changes to reference safety information"**
- This PSUR section should list any significant changes made to the reference safety information within the reporting interval.
- Specific information relevant to these changes should be provided in the appropriate sections of the PSUR

PSUR GVP VII B 4 Reference Information

- Having one reference source of information that can be applied across the three ICH regions would facilitate a practical, efficient, and consistent approach to the benefit-risk evaluation and make the PBRER a unique report accepted in all countries and regions.
- Risk minimisation activities evaluated in the PSUR include updates to the product information.
- The reference product information for the PSUR should include “core safety” and all “authorised indications” components.
- Additional indications in specific regions should be added to the RSI or handled in a regional appendix or appropriate MAH

PSUR GVP Mod VII and Explanatory Note

- The reference product information should be provided in English.
- Where appropriate, a brief description of ongoing procedures (e.g. variations) to update the PI is a requirement of the EU regional appendix and should be included in section "proposed PI" of GVP Module VII section VII.C.5.1.
- Variations to update the PI expected to be included would normally be those where changes are made to safety relevant information in the PI.

PSUR GVP Mod VII and Explanatory Note

reference product information

- can be provided in any format as per the ICH-E2C (R2) guidelines
- the QPPV must have the full oversight of the authorised PI
- this document is the key routine risk minimisation tool in pharmacovigilance

changes to the reference safety information (RSI)

- It is essential that any discussions and considerations with regards to proposed
- in the PSUR are always also put into the context of the PIs that are authorised in the EU.

PSUR GVP Mod VII and Explanatory Note

- Known ADR and the communication of it (CI or W&P) is in or will be in the RSI this will also be in the PI.
- As this is EU specific it will be in the Regional appendix
- If Assessor identifies an issue they feel is not adequately covered by RSI/PI additional data/Review may be requested during PSUR assessment

PSUR GVP Mod VII and Explanatory Note

Based on the evaluation

- MAH to draw conclusions from the cumulative safety data and the benefit/risk balance analysis
- consider the need for changes and/or actions
- Include any implications for the approved PI for the medicinal product(s) for which the PSUR has been submitted

Based on relevant safety information

- from the cumulative analysis during the PBRER reporting period or at the time of the PBRER development
- for impacts on benefit/risk, implications and details of the conclusions may be presented in the PBRER

PSUR and CCDS

- The following possible options can be considered by the marketing authorisation holders when selecting the most appropriate reference product information for a PSUR:
  - CCDS
  - Other (SmPC)
- The marketing authorisation holder should continuously evaluate whether any revision of the reference product information are required.

Product Information/Reference Safety Information and QPPV oversight

As per ICH E2C (R2), an objective of a PBRER is to evaluate whether information obtained during the reporting interval is in accord with previous knowledge on the product's benefit and risk profile, and to indicate whether changes should be made to the reference product information

QPPV is made aware of any important and urgent safety concerns or emerging safety issue then participates in the review and discussion of the safety issue, as applicable

After the immediate action taken has been completed (if needed) and dependent on the safety issue, a possible outcome would be to update the Product Information (PI) / Reference Safety Information (RSI)

Following the duty to warn intent, proactive communications to healthcare providers would be presented in the PI/RSI

QPPV has oversight of the PI/RSI updates if there is a significant change in the medical benefit-risk balance, impact on public health, and/or addition of important medical safety information

The role of the RSI and/or the PI (regulatory authorities' perspective)

Menno van der Elst

Role of RSI and PI

- RSI is key document for preparation of PSUR
- MAHs should assess the need for changes to the reference product information
- However, PSUSA recommendations concern the EU product information
- In PSUR EU regional appx, “Proposed product information”, MAH should provide track change version of proposed SmPCs and PLs, if MAH considers changes needed

Role of PI

- Assessors will make recommendations regarding the EU product information (and not the CCDS)
- While PSUSA procedure may not be the appropriate tool for harmonisation of the existing product information across products, all MAHs are expected to keep their PI in line with latest scientific knowledge

Role of PI

- PSUSA will recommend PI wording to be applied across all products covered by the PSUSA – positive side effect: increased consistency
- PI proposal not differentiated per product or MAH – even if some wording already included for certain products – implementation aspect.
- Indication and/or formulation differences of medicines should be taken into account if applicable

Summary of common understanding

- RSI to be provided in English
- RSI can be CCDS or (EU)SmPC
- Reference product information for the PSUR should include “core safety” and all “authorised indications” components
- While MAH may conclude on RSI changes needed based on the PSUR data, PSUSA will conclude on changes to PI
- Proposed EU-PI changes need to be submitted in EU regional appendix

Use of summary tabulations

How are they created (industry's perspective)

Dr David J Lewis
Senior Adviser Pharmacovigilance
Novartis Global Drug Development

PSUR Roadmap: Joint industry/assessor training
22 September 2017

NOVARTIS

Situation: Summary Tabulations produced by MAHs

- Summary tabulations are mandatory per ICH & EMA guidelines
- Clear counts help all reviewers, not least the Assessor!
- Content is defined, MAHs use various methods to generate data
  - Out of the box (pre-configured) vendor solutions – example later
  - Ad hoc searches
    - Based on formal user requirements
    - Multiple approaches, each requiring formal validation

Requirements for summary tabulations MAHs

Summary tabulations focus on adverse (drug) reactions

- ICH E2C (R2) @page 31, Table 7

Table 7 – Numbers of Adverse Drug Reactions by Term from Post-Marketing Sources

	Spontaneous, including regulatory authority and literature			Non-interventional post-marketing study and reports from other solicited sources*
	Serious	**Non-serious**	**Total Spontaneous**	**Serious**

- EMA/CHMP/ICH/544553/1998 @page 39,

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

	Spontaneous, including regulatory authority and literature			Non-interventional post-marketing study and reports from other solicited sources*
	Serious	Non-serious	Total Spontaneous	Serious

Requirements for summary tabulations: Spontaneous reports

Explanatory text on inclusion of adverse (drug) reactions & all spontaneous AEs

- ICH E2C (R2)

3.6.3 Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

Section 6.3 of the PBRER should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the DLP of the current PBRER. As described in ICH Guideline E2D, for marketed medicinal products, spontaneously reported* adverse events usually imply at least a suspicion of causality by the reporter, and should be considered to be adverse reactions for regulatory reporting purposes. The tabulation should include:

- Serious and non-serious adverse drug reactions from spontaneous ICSRs, including reports from healthcare professionals, consumers, scientific literature, and regulatory authorities;
- Serious adverse reactions from non-interventional studies; and
- Solicited reports* of serious adverse reactions.

- EMA/CHMP/ICH/544553/1998 includes identical text on page 20, Section 3.6.3

Inspection question related to transferred products (new MAH fulfilling PV obligations)

"Please explain why the counts in MAH2 summary tabulations are lower than those in the previous PSUR submitted by MAH1."

July 2017, UK

Lower counts in summary tabulations in consecutive PSURs

Cumulative post-marketing cases

- Table details number of AEs/SAEs by individual PT per product for MAH1 and MAH2 PSURs
- Last column is the total number of events (all events with no exclusions) included in MAH2 listings
- All PV data are considered in our safety evaluation

MedDRA level & System Organ Class (SOC) name or preferred term (PT)	Report	App 2B / 2.2	Grand total Spont/Lit/PMS
SOC Infections and infestations	PSUR 3 (MAH1)	604	
	PSUR 4 (MAH2)	541	1000
PT Pneumonia	PSUR 3 (MAH1)	138	
	PSUR 4 (MAH2)	109	167
PT Sepsis	PSUR 3 (MAH1)	64	
	PSUR 4 (MAH2)	55	77
SOC Neoplasms benign, malignant & unspecified	PSUR 3 (MAH1)	422	
	PSUR 4 (MAH2)	346	494
PT Myelodysplastic syndrome	PSUR 3 (MAH1)	48	
	PSUR 4 (MAH2)	35	54

Differences in summary counts in consecutive PSURs

Inclusion of not suspected and non-serious AEs from NIS, PMS & other solicited ICSRs

- MAH1-authored PSUR 3 states:
  "Cumulative totals are derived from all adverse reactions for [product], irrespective of source, ***relationship to drug*** *and formulation/indication/route of administration..."*
- ***Not suspected*** events (from PMS reports) included in the summary tabulation in Appendix 2B
- In addition, Section 6.3 in PSUR 3 states that:
  "Seriousness is based on whether or not the ***case*** *[ICSR] in which the event resides* ***is serious****..."*
- Hence, non-serious events (from PMS reports) were included, if the ICSR was considered serious;
- Known bug in a vendor system - present in the standard PSUR summary tabulation software
- Raised with the vendor >12 months ago; no solution provided to date...

Summary tabulation: zero count (null return)

Cumulative post-marketing cases

Table details number of AEs/SAEs by individual PT per product for MAH1 and MAH2 PSURs
Last column is the total number of events (all events with no exclusions) included in MAH2 listings
All PV data are considered in our safety evaluation

MedDRA level	Report	App 2B / 2.2	Spont/Lit/PMS
SOC Infections & infestations	PSUR 4	251	
	PSUR 5	232	569
PT Erysipelas	PSUR 4	8	
	PSUR 5	3	14
PT Lower respiratory tract infection	PSUR 4	13	
	PSUR 5	4	18
PT Urinary Tract Infection	PSUR 4	25	
	PSUR 5	22	64
SOC Ear and labyrinth disorders	PSUR 4	15	
	PSUR 5	12	36
PT Hearing Impaired	PSUR 4	3	
	PSUR 5	0	6

Appendix 2.2 / 2B differences in counts

Change in MedDRA mapping impacting counts for PT 'Hearing impaired'

- PBRER 4 (MAH1) MedDRA PT 'Hearing impaired' cumulative count = 3
- Term did not appear in PBRER 5 written by Novartis (i.e. count = 0)
- **Explanation**: MedDRA mapping change occurred in the period!
- PT 'Hearing impaired' in MedDRA v18.1; May 2016 MedDRA v19.0 released & implemented
- PT 'Hearing impaired' moved to LLT and re-mapped under PT 'Hypoacusis'
- 'Hearing impaired' not in App 2.2 PSUR 5 (Novartis) **but** total count = 6 for PT 'Hypoacusis'
- **QED**

Discussion: Multiple sources of errors

Differences between the counts in PBRER Appendices 2B vs 2.2

- Different counts between 2 MAHs relate to the inclusion criteria:
  - NIS, PMS & other non-interventional solicited sources
  - MAH2 tables include (only) serious, suspected adverse (drug) reactions
- Focus on serious, suspected events in MAH2 PBRERs has produced lower counts for certain PTs, despite the cumulative total counts increasing (in fact most counts increased)
- Re-mapping MedDRA term ‘Hearing loss’ (PT to LLT) resulted in a null
- **BUT** count was 6 for PT ‘Hypoacusis’
- Comprehensive safety evaluation (inclusive of <u>all</u> ICSRs and <u>all</u> terms) essential per PBRER

MAH summary tabulations: Conclusions

- Summary tabulations are challenging
  - Important to ensure that your (MAH) method is validated
    - Does your QPPV (or designate) understand exactly how the counts are generated?
    - Is the QPPV (or designate) able to explain the process clearly a verify the numbers?
    - Have you implemented a quality check (e.g. cumulative counts must not decrease)?
  - Provide points of clarification for the Assessor
    - Make it obvious – no shame in being transparent
    - Clear – what has changed and why
    - Precise – where the figures differ and how
  - Are your counts correct & contiguous with other PSURs in sequence?

Place in the assessment of PSURs (regulatory authorities' perspective)

Menno van der Elst

Role of summary tabulations

- A high quality PSUR, especially presentation of signals & risks, is a prerequisite
- Then, summary tabulations provide a broad overview of the PSUR data
- While not intended for signal detection as they lack necessary detail for causality assessment and other tools more suitable for signal detection, striking figures cannot be ignored

Role of summary tabulations

- MAHs are advised to provide some background information on aspects that stand out (e.g. striking increase in certain SOCs or PTs)
- This may prevent assessor's questions in the assessment report

Summary of common understanding

- Importance of validated method for creating summary tabulations
- Understand how exactly the counts are generated
- Sanity check – do the counts match expectations?
- Explain to the Assessor:
  - Figures that stand out;
  - Unexpected or discrepant changes;
  - Counts that are incontiguous with previous PSURs…

Next steps

- PSUR roadmap next step: Revision of GVP Module VII
- Upcoming training and meetings in 2017:
  - Eudravigilance webinars
  - Industry stakeholders platform meetings
  - QPPV meeting
  - EU NTC assessors training

- Please take a moment to provide your feedback on this webinar by completing a short questionnaire, available from 22 to 29 September 2017 on the EMA website