Periodic Safety Update Reports

Andrea Lohée, Pharm-AD

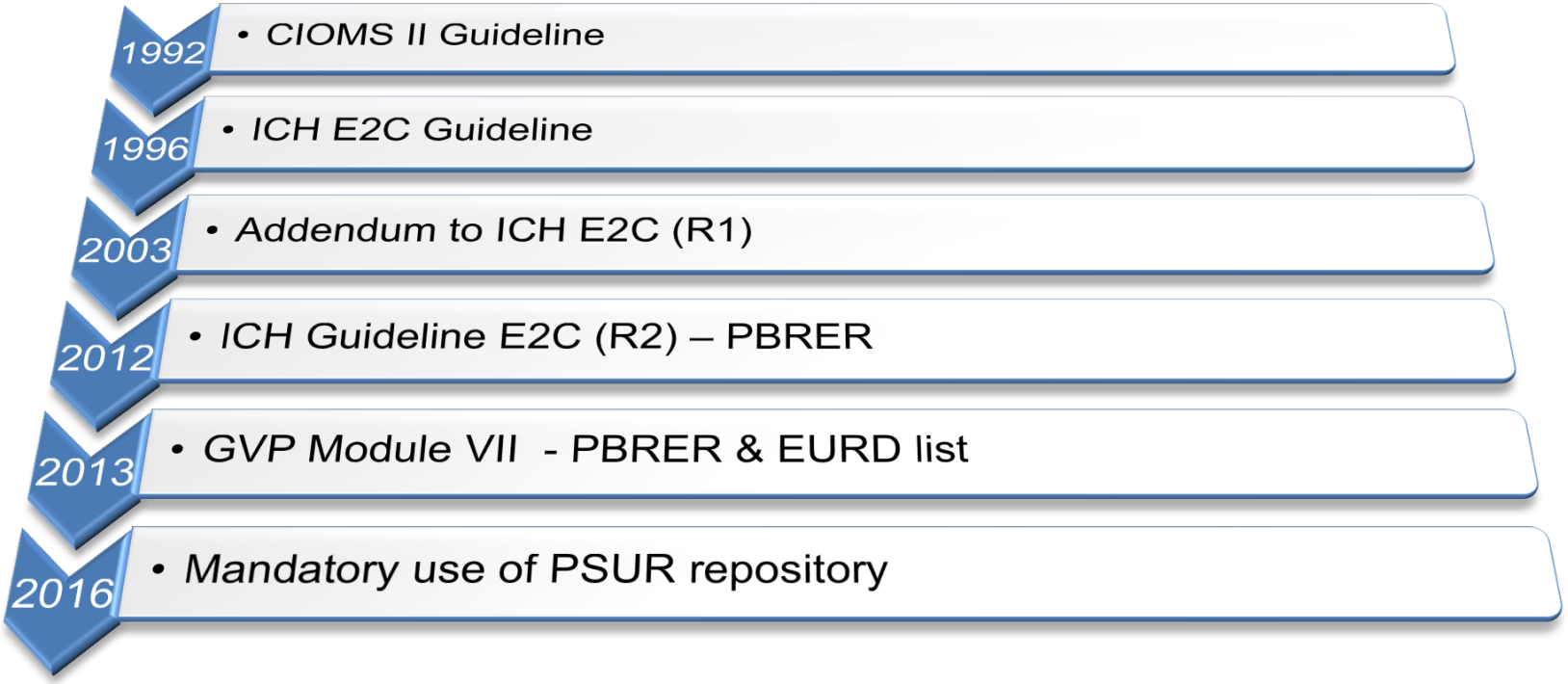
DCVMN training on PV,

May 2017

Periodic Safety Update Reports

- Evolution
- Definition
- Objective
- Frequency and timing
- EU vs USA and other non ICH countries
- Submission in the EU
- Writing the PSUR

Periodic Safety Update Reports - Evolution



Periodic Safety Update Reports - Evolution

Before 2012

- RMP for some products
- PSUR for all products

After 2012

- RMP for all products (CAP)
- PSUR for some products

Periodic Safety Update Reports - Definition

- Periodic Safety Update Reports are pharmacovigilance documents to provide an evaluation of the **risk-benefit balance** of a medicinal product for submission by a marketing autorisation holder at defined times during the post-autorisation phase
- PBRER (Periodic Benefit Risk Evaluation Report) are referred to as PSUR since implementation in Europe via GVP Module VII

Periodic Safety Update Reports – Objectives & purpose

The PSUR is a reflection of everything that happened with the product during the period of the PSUR. It contains an evaluation of new relevant information that became available to th MAH during the reporting interval and in the context of cumulative information

Periodic Safety Update Reports – Objectives & purpose

The objective of the PSUR is to:

- Present a comprehensive, concise and critical analysis of new or emerging information on the risks related to a medicinal product
- Consider whether any action regarding the MA for the medicinal product is necessary

Periodic Safety Update Reports – Frequency and timings

EU – general rules

- On request
- According to EURD list
- As specified in the MA
- Worksharing list http://hma.eu/348.html (few products)
- If not in the above:
  - At least every 6 months after MA until marketed
  - At least every 6 months for 2 yearsn after 1st EU launch
  - Once a year for the following 2 years
  - At three-yearly intervals thereafter

Periodic Safety Update Reports – Frequency and timings

- **EURD**: EU reference date list for PSUR submissions for products authorised in the EU
- Harmonisation of DLP and frequency of PSUR submissions
- Periodicity defined on a risk-based approach
- Monthly updates of EURD list ➔ MAH to review regularly for changes
- PSUR assessment reports inEU
- Electronic submission in EU

Periodic Safety Update Reports – Frequency and timings

In the EU, le legislation waives the obligation to submit PSURs routinely (unless there is a condition in the MA or requested by a CA) for the following:

Article 10(1)	Generic products
Article 10a	Well establlished use products
Aricle 14	Homeopathic medecines
Article 16	Traditional herbal medecines

Periodic Safety Update Reports – EU and non EU formats

- USA
  - Format E2B R2 accepted
  - Need a waiver to submit PSUR in place of a PADER
  - Quarterly for 2 years, then annual
  - To be submitted within 60 days of DLP
- Other countries
  - Many accept PBRER or former PSUR format
  - MAH must keep aware of local requirements in terms of format and timelines for submission

Periodic Safety Update Reports – Practical aspects

- Latest CCDS in effect at the end of the reporting interval should be used for the benefit risk section
- Level of details in certain sections should depend on the product's known or emerging important benefits and risks

Periodic Safety Update Reports – Practical aspects

- Plan ahead
  - Describe process in SOP
  - Start as early as possible (pre DLP)
  - Document what you do
  - Involve all stakeholders for provision of information and stakholders reviews
  - Ensure consistency with RMPs and DSURs
  - Ensure commitments are adressed
  - Ensure robust quality review
  - Learn from assessment reports

Periodic Safety Update Reports – Practical aspects

- 1 report for one active substance
  - Separate analysis (route, indication, population etc) where appropriate
  - Separate PSURs may be prepared for fixed dose combinations
  - Same product with multiple MA → joint PSUR preferable

Periodic Safety Update Reports – Practical aspects

- Include all relevant safety information (clinical, pre-clinical, non-clinical)
- Interval and cumulative data
- Focus on adverse drug reactions
- Focus on summary information, scientific safety assessment and integrated benefit-risk evaluation

Periodic Safety Update Reports – Practical aspects

- Sources of information
  - Direct case reports (spontaneous, HA, partners, solicited, etc)
  - Published literature
  - Epidemiological databases

Periodic Safety Update Reports – Practical aspects

NO DATA DUMP!

Data to be presented in summary tabulations – no narratives

Periodic Safety Update Reports – Practical aspects

- Sections 1-4: ‘set the scene’
- Sections 5-14: present data (no analysis)
- Sections 15-18: analysis (don’t repeat data)
- Section 19: conclusion

Periodic Safety Update Reports – Practical aspects

- Introduction
  - IBD, reporting interval, sequential number of report
  - Medicinal product details
  - Brief description of the approved indication(s) and population(s)
  - Explanations (e.g data not included, multiple reports, etc)

Periodic Safety Update Reports – Practical aspects

- Market autorisation status
  - Cumulative
  - Brief overview
  - Cumulative table of authorisations per date

Periodic Safety Update Reports – Practical aspects

- <u>Actions taken for safety reasons</u>
  - During the reporting period related to investigational of marketing experience
    - Actions impacting the conduct of a trial
    - Action with impact on B/R balance
  - By whom (MAH, sponsor of CT, DMC/EC, PRAC
  - Reason for each action
  - Include relevant information
  - Summarise relevant updates to previous actions

Periodic Safety Update Reports – Practical aspects

- Reference Safety Information
  - Document that determines whether an AE is listed or unlisted (Core safety information or SmPC)
  - Append RSI in affect at the end of the PSUR period
  - Discuss whether revision of the RSI was needed in the period
  - Highlight differences (if any) between CSI and SmPC

Periodic Safety Update Reports – Practical aspects

Patient exposure

- Clinical trials

  - Cumulative since DIBD for all completed & ongoing studies
  - Subgroups by age/sex, race, etc if available
  - Different tables for different routes, indications, formulations, etc
  - Separate data on special populations if relevant
  - Exposure by active substance/placebo/blinded data

Periodic Safety Update Reports – Practical aspects

- Post-marketing data
  - Cumulative and interval data
  - Number of patients exposed and method to calculate
  - Split by gender, age, indication, dose, formulation, special population when relevant, different disease, etc
  - Patterns of use e.g off label, misure, abuse, etc

Periodic Safety Update Reports – Practical aspects

Data in summary tabulations

- Clinical studies

  - Cumulative tabulations of SAEs (from DIBD to DLP)
  - Narrative (background to appendices)
  - In appendix:
    - Tabulations by SOC and PT
    - Columns by IMP, comparator, placebo and blind
    - By trial or indication
    - Only serious events from serious cases
    - May exclude certain events like study endpoints, anticipated events in populations

Periodic Safety Update Reports – Practical aspects

- Post-marketing data

  - Cumulative and interval data from all sources by SOC and PT
  - For non-interventional studies limit to ADRs
  - Serious and non-serious events in one table
  - Additional tabulations by indication, route of administration etc if relevant

Periodic Safety Update Reports – Practical aspects

Significant findings from CTs

- List of trials ongoing/completed in the interval
- Brief summary of clinically important emerging efficacy/safety findings

Other information

- Summarise relevant safety information and information with potential impact on B/R assessment

Periodic Safety Update Reports – Practical aspects

- Discuss findings from sections 16 – 18
  - Findings from non-interventional studies
  - Information for other clinical trials (meta-analysis, IIS, etc)
  - non-clinical data
  - Literature (new & significant findings drug class actions)
  - Other periodic reports
  - Lack of efficacy in controlled trials
  - Late breaking information

Periodic Safety Update Reports – Practical aspects

Sections 15 – 18

- Overview of signals (new, ongoing, closed)
- Signal an risk evaluation
  - Summary of safety concerns
  - Signal evaluation
  - Evalution of risks and new information
  - Characterisation of risks
  - Effectiveness of risk minimisation measures
  - Benefit evaluation
  - Integrated B/R analysis for approved indications

Periodic Safety Update Reports – Practical aspects

Conclusions and actions

- Implication of new information
- Implications of changes to B/R
- Assess need for changes for RSI
- Assess need for new risk minimisation activities

Periodic Safety Update Reports – Practical aspects

Appendices

- Reference safety information
- Cumulative summary tabulations
  - SAEs from CTs
  - Cumulative & interval data from PMS sources
- Tabular summary of safety signals
- List of MAH sponsored studies
- List of the sources of information used
- Regional appendices

Periodic Safety Update Reports – Practical aspects

Excecutive summary

- Introduction and reporting interval
- Medicinal product information
- Estimated cumulative exposure in CTs
- Estimated interval and cumulative post-marketing exposure
- Number of countries where drug is authorised
- Actions taken and proposed actions for safety reasons
- conclusions