Developing Countries Vaccine Manufacturers Network

Vaccine Safety Monitoring
DCVMN Regional Training Workshop
Sao Paulo 27 - 30 May 2019

PSUR – Periodic Safety Update Report:

Scheduling and Preparation

Content and Format

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Aggregate Reporting Requirements
Periodic reporting to regulatory authorities

- Pre-licensure from clinical trials: ICH E2F Development Safety Update Report DSUR

  DSURs to replace existing annual reporting requirements

- Post-licensure from authorized products: ICH E2C (R2) Periodic Benefit-Risk Evaluation Report PBRER
  - EU: GVP Module VII Periodic Safety Update Report PSUR
  - US: Guidance for Industry: Providing Post-marketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report) 2014:
    - FDA grants waivers to allow applicants to substitute PBRER for PADER / PAER and existing PSUR (ICH E2C R1) waivers
  - National requirements: .....

Periodic Safety Update Report PSUR -
Periodic Benefit Risk Evaluation Report PBRER

ICH E2C (R2) Periodic Benefit Risk Evaluation Report (PBRER)

- is intended to be a common standard for periodic benefit – risk evaluation on marketed products among the ICH regions.
- introduced new concepts linked to the evolution of the traditional Periodic Safety Update Report PSUR from an interval safety report to a cumulative benefit-risk report.
- Changed the focus from individual case safety reports to aggregate data evaluation.

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

ICH HARMONISED TRIPARTITE GUIDELINE

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER)

E2C(R2)

Current *Step 4* version
dated 17 December 2012

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

HMA Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 December 2013
EMA/816292/2011 Rev 1*

Guideline on good pharmacovigilance practices (GVP)
Module VII – Periodic safety update report (Rev 1)

Date for coming into effect of first version	2 July 2012
Draft Revision 1* finalised by the Agency in collaboration with Member States	21 March 2013
Draft Revision 1 agreed by ERMS FG	27 March 2013
Draft Revision 1 adopted by Executive Director	19 April 2013
Release for consultation	25 April 2013
End of consultation (deadline for comments)	25 June 2013
Revised draft Revision 1 finalised by the Agency in collaboration with Member States	23 October 2013
Revised draft Revision 1 agreed by ERMS FG	11 November 2013
Revised draft Revision 1 adopted by Executive Director as final	9 December 2013
Date for coming into effect of Revision 1* (for PSURs with data lock point after 12 December 2013)	13 December 2013

Objective of a PSUR /PBRER

- Presentation of a comprehensive and critical analysis of new or emerging information on the risks and new evidence of benefit (appraisal of overall benefit risk)
- Evaluation of new relevant information becoming available during the reporting interval, in the context of cumulative information.
- Examination if new information is in accord with previous knowledge of the benefit risk profile
- Summary of relevant new safety information that may impact the benefit risk profile
- Summary of any important new efficacy / effectiveness information
- Integrated Benefit / Risk Evaluation where new important safety information has emerged.

The Evaluation of the benefit-risk assessment to be undertaken in the context of ongoing pharmacovigilance and risk management:

- GVP Module VII Post-authorization studies
- GVP Module V Risk management systems

Periodicity / Submission

PSUR must be prepared at the following intervals:

- Immediately upon request
- Every 6 months from authorization until vaccine is placed on the market
- Every 6 months for the first 2 years on the market
- Annually for the next 2 years
- Thereafter every 3 years

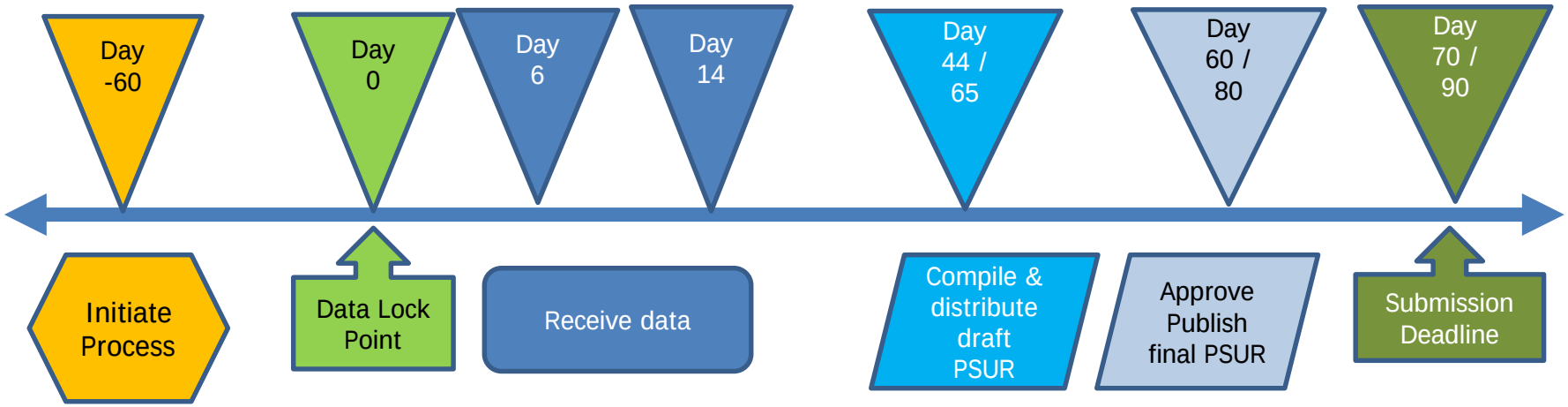
Exception in the EU: Frequency and dates are laid down as a condition of the MA or determined in the list of European Union Reference Dates (EURD List) .

Submission of PSUR:

- By day 70 after data lock point (DLP) for intervals up to 12 months
- By day 90 after DLP for intervals > 12 months

BUT: Various differences in periodicity / submission schedules and regional content requirements according to national legislation or as agreed with NA at the time of authorization.

PSUR Preparation Planning



Format - ICH E2C PBRER /	GVP Module VII PSUR
Part I Title page	9. Information from other clinical trials and sources
Part II Executive Summary	10. Non-clinical data
Part III Table of contents	11. Literature
1. Introduction	12. Other periodic reports
2. Worldwide marketing approval status	13. Lack of efficacy in controlled clinical trials
3. Actions taken in the reporting interval for safety reasons	14. Late-breaking information
4. Changes to the reference safety information	15. Overview on signals: New, ongoing or closed
5. Estimated exposure and use patterns 5.1. Cumulative subject exposure in clinical trials 5.2. Cumulative and interval patient exposure from marketing experience	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. Characterization of risks 16.5. Effectiveness of risk minimization (if applicable)
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	17. Benefit evaluation 17.1. Important baseline efficacy / effectiveness information 17.2. Newly identified information on efficacy / effectiveness 17.3. Characterization of benefits
7. Summaries of significant findings from clinical trials during the reporting period 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	18. Integrated benefit-risk analysis for authorized indications 18.1. benefit-risk context – medical need and important alternatives 18.2. Benefit-risk analysis evaluation
8. Findings from non-interventional studies	19. Conclusions and actions
	20. Appendices to the periodic safety update report

NEW in PBRER

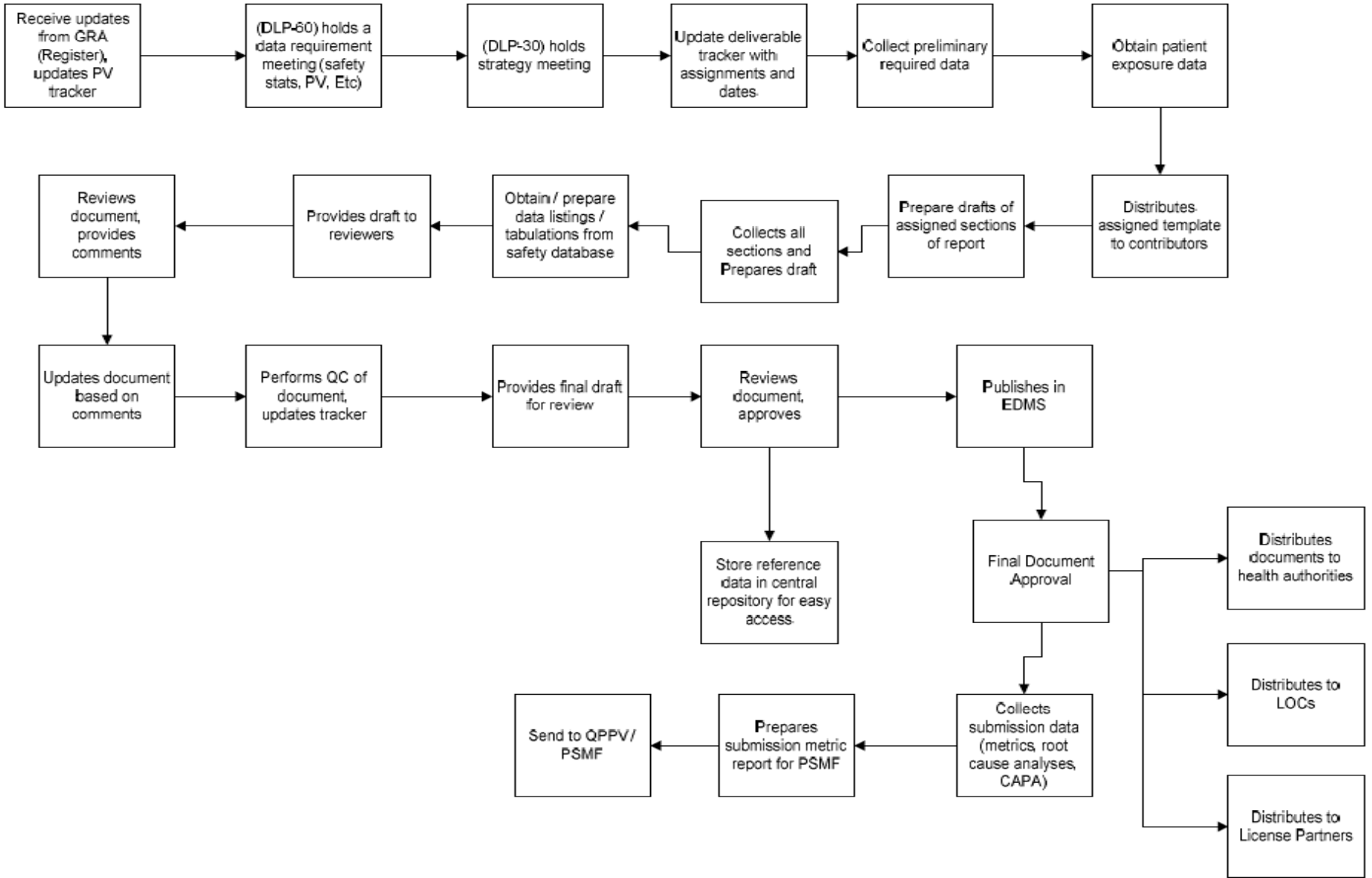
GVP Module VII: Periodic Safety Update Report - Vaccines

In addition, the following data must be provided in PSURs for vaccines:

- Consideration to any potential impact on safety of changes in the manufacturing process
- Batch and age-related adverse reactions must be evaluated
- Analysis of adverse reactions for different doses and across different vaccination schedules
- Reports on vaccine failure , lack of efficacy / effectiveness
- Vaccination errors
- Vaccination-anxiety-related reactions such as syncope
- Literature data relevant to similar vaccine / vaccine components (e.g., stabilizers, preservatives, adjuvants)
- Integrated benefit–risk analysis using all available data:
  - Prevention of target disease
  - Severity of symptoms
  - Hospitalisation
  - Complications
  - Effect of target disease on offspring in case of vaccination of pregnant women

PSUR Process Flowchart

Example

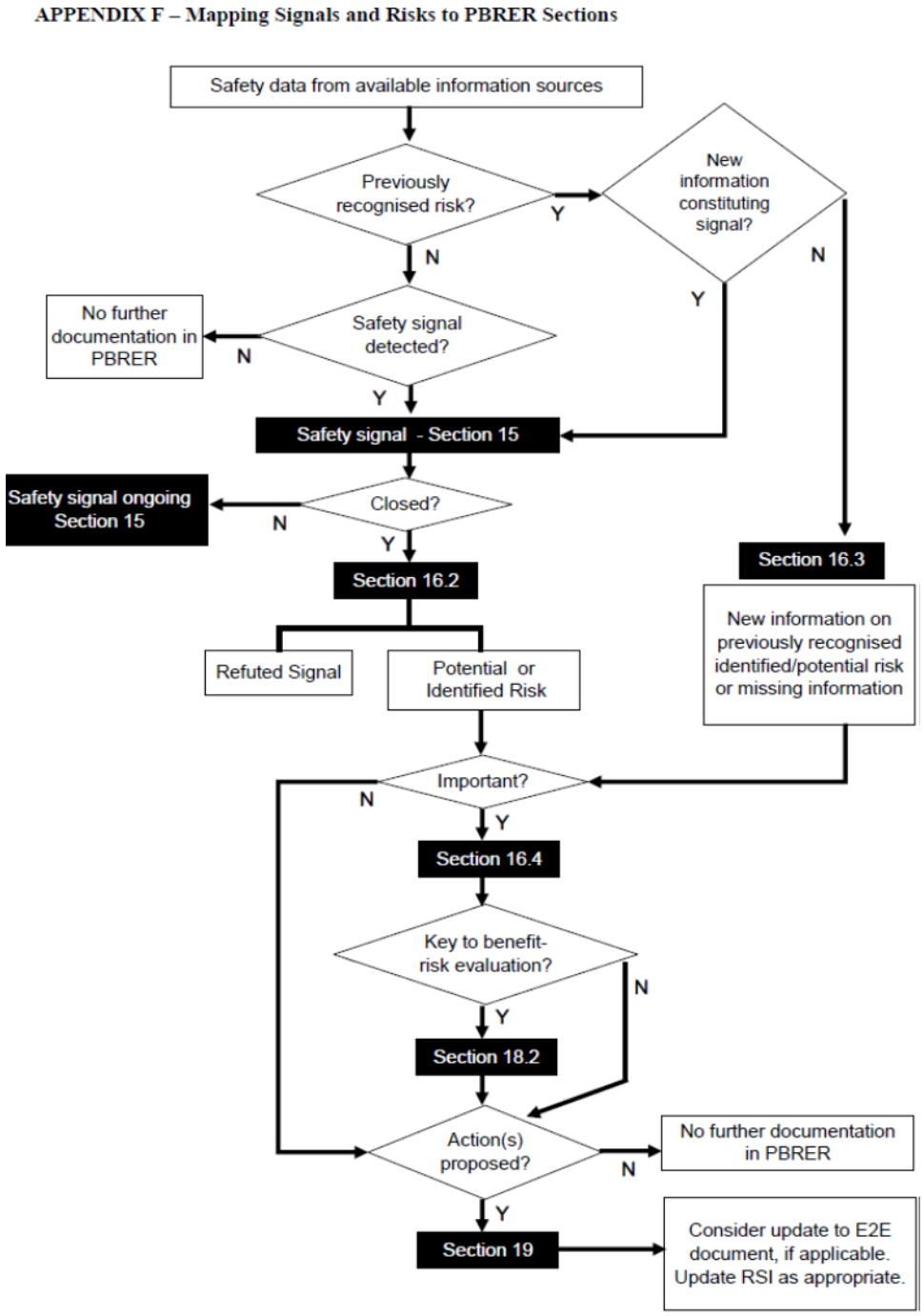


Evaluation of the Benefit-Risk Balance within PBRERs / PSURs

ICH E2C (R2): Appendix C – Example of a Tabular Summary of Safety Signals, ongoing or closed during Reporting Interval

Signal term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation & summary of key data	Method of signal evaluation	Action(s) taken or planned
Stroke	month/ year	ongoing	month/year	meta-analysis (published trials)	statistically significant increase in frequency	review meta-analysis and available data	pending
SJS	month/ year	closed	month/year	spontaneous case reports & one case report in Phase IV trial	Rash already an identified risk SJS not reported in pre authorisation CTs. 4 apparently unconfounded reports within 6 months of approval; plausible time to onset.	targeted follow up of reports with site visit to one hospital. Full review of cases by MAH dermatologist and literature searches	RSI updated with a Warning and Precaution DHPC sent to oncologists Effectiveness survey planned 6 months post DHPC. RMP updated.

ICH E2C (R2)
Periodic Benefit-Risk Evaluation Report (PBRER)



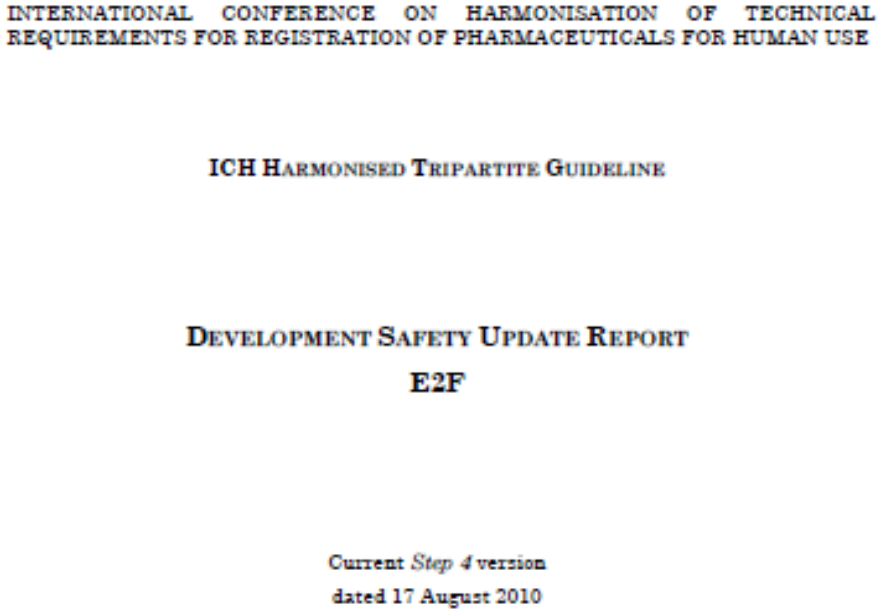
Preparation of PSUR: Consistency with RMP

RMP section	PSUR section
Part II, module SV – "Post-authorisation experience", section "Regulatory and marketing authorisation holder action for safety reason"	Section 3 – "Actions taken in the reporting interval for safety reasons"
Part II, module SV – "Post-authorisation experience", section "Non-study post-authorisation exposure"	Sub-section 5.2 – "Cumulative and interval patient exposure from marketing experience"
Part II, Module SVII – "Identified and potential risks"	Sub-section 16.4 – "Characterisation of risks"
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 16.1 – "Summary of safety concerns"
Part V – "Risk minimisation measures", section "Evaluation of the effectiveness of risk minimisation activities"	Sub-section 16.5 – "Effectiveness of risk minimisation (if applicable)"

Development Periodic Safety Update Report DSUR

ICH E2F Development Safety Update Report (DSUR)

- Harmonization of format, content and scheduling of annual reports through ICH regions
- Harmonizes with ICH E2A and E2C
- Single DSUR for Investigational Product with complete picture of the evolving safety profile
- Comprehensive thoughtful and structured annual review
- New concept with “Summary of Important Risks” highlighting issues to monitor for Industry and Regulators



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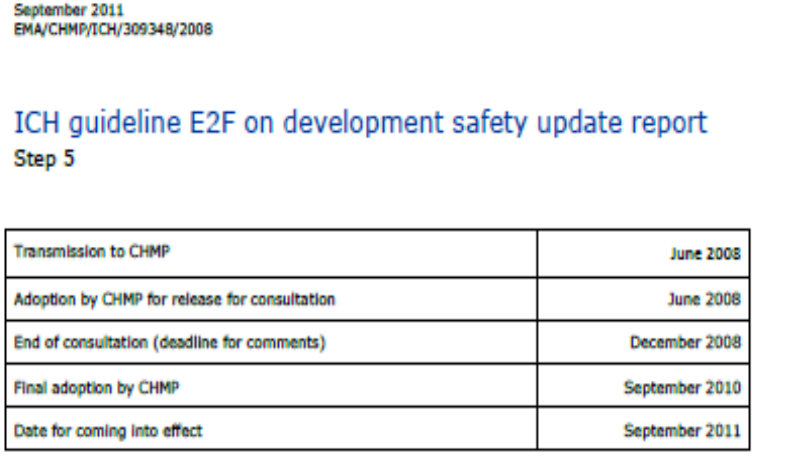
ICH HARMONISED TRIPARTITE GUIDELINE

DEVELOPMENT SAFETY UPDATE REPORT

E2F

Current *Step 4* version

dated 17 August 2010



EUROPEAN MEDICINES AGENCY

SCIENCE MEDICINES HEALTH

September 2011

EMA/CHMP/ICH/309348/2008

ICH guideline E2F on development safety update report

Step 5

Transmission to CHMP	June 2008
Adoption by CHMP for release for consultation	June 2008
End of consultation (deadline for comments)	December 2008
Final adoption by CHMP	September 2010
Date for coming into effect	September 2011

Objective of DSUR

- Presentation of the annual review and evaluation of safety information
- Information reported during the current review period and analysis based on previous knowledge of safety
- Description of new issue that may impact the overall clinical program or specific clinical trials
- Summarization of current understanding and management of known or potential safety risks to exposed trial participants
- Examine changes in the product's safety profile
- Update on the status of the clinical development program

Scope of DSUR

- A single DSUR includes safety data from all clinical trials conducted with the investigational product
  - The sponsor is responsible for DSURs
  - In case of multiple sponsors for a development program formal agreements re the DSUR responsibility must be in place
- Focus on clinical trials of investigational product (drugs, vaccines, biologicals)
- Focus on findings that impact safety and welfare of clical trial subjects (e.g., non-clinical studies, observational studies)
- Focus on investigational product, providing information on comparators where relevant to the safety of trial participants
- Provision of concise information to assure regulators that sponsors are adequately monitoring and evaluating the safety profile of the investigational product.

Periodicity / Submission of DSUR

- Annual report with data lock point DLP based on the Development International Birth Date (DIBD)
  - DIBD: Date of first approval (or authorization) for conducting an interventional clinical trial in any country worldwide
- When clinical trials continue after receiving market approval, both DSUR and PSUR are needed separately
  - DSUR DIBD can coincide with PSUR IBD

Submission of DSUR:

- Regulatory Authorities: within 60 days from the DIBD
- Ethics Committee (EC) / Institutional Review Board (IRB), if required: Executive Summary plus Line Listings of SA(D)Rs
- Final DSUR in a Territory is notified with a cover letter
  - Sponsor must indicate whether clinical trials are continuing elsewhere

Content of a DSUR

Part I Title page	9. Safety findings from non-interventional studies
Part II Executive Summary	10. Other clinical trial / study safety information
Part III Table of contents	11. Safety findings from marketing experience
1. Introduction	12. Non-clinical data
2. Worldwide marketing approval status	13. Literature
3. Actions taken in the reporting interval for safety reasons	14. Other DSURs
4. Changes to the reference safety information	15. Lack of efficacy
5. Inventory of Clinical Trials, Ongoing and Completed	16. Region-specific information
6. Estimated cumulative exposure 6.1. Cumulative subject exposure in the Development Program 6.2. Patient exposure from marketing experience	17. Late-breaking information
7. Data in Line Listings and Summary Tabulations 7.1. Reference Information 7.2. Line Listings of serious adverse reactions during reporting period 7.3. Cumulative summary Tabulations of serious events	18. Overall Safety Assessment 18.1. Evaluation of the risks 18.2. Benefit-risk considerations
8. Significant findings from Clinical Trials during the Reporting Period 8.1. Completed clinical trials 8.2. Ongoing clinical trials 8.3. Long-term follow-up 8.4. Other therapeutic use of investigational product 8.5. New safety data related to combination therapies	19. Summary of important risks
	20. Conclusions
	Appendices to the DSUR

Region-specific Information

- Section to be used to comply with national / regional requirements
  - Can be provided in Appendices
- National / regional requirements may require:
  - Cumulative summary tabulations of serious reactions
  - List of subjects who died during reporting period
  - List of subjects who dropped of due to adverse event
  - Significant protocol modifications
  - Significant manufacturing changes
  - General investigation plan for the coming year
  - US: log of outstanding business with respect to US IND

Preparation of DSUR: Consistency with PSUR

Potential shared module with ICH E2C PSUR
2. Worldwide marketing approval status
3. Actions taken in the reporting interval for safety reasons
5.1. Cumulative subject exposure in clinical trials
6.2. Cumulative summary tabulations of serious adverse events from clinical trials
7. Summaries of significant findings from clinical trials during the reporting period 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
8. Findings from non-interventional studies
9. Information from other clinical trials and sources
10. Non-clinical data
11. Literature
13. Lack of efficacy in controlled clinical trials
14. Late-breaking information (if report covers the same period and submitted at same time)
19. Conclusions and actions

Some Section numbers differ between DSUR and PSUR

Common PSUR inspection findings

- Non-submission
  - Complete non-submission of PSUR
  - Submission, but time frame not correct
- Poor quality reports
  - Incorrect format of the document
  - New safety signals not or poorly assessed
  - Medication errors not highlighted
  - Absence of use of standardized medical terminology (MedDRA)
  - Published literature not properly reviewed
- Omission of required information
  - Update of Regulatory or MAH Actions taken for Safety Reasons
  - Changes to Reference Safety Information
  - Subject exposure poorly calculated, explanation of calculation missing
- Previous requests from Regulatory Agencies not addressed
  - E.g. close monitoring of specific safety issues

PSUR versus RMP

The two primary post-authorization PV documents

RMP	PSUR / PBRER
Main focus: **Pre- and postauthorisation risk-benefit management and planning**	Main focus: **Integrated post-authorisation risk-benefit assessment**
Risk minimisation plan	Ensuring benefit-risk balance remains favourable
PASS / PAES: data collection	Signal detection and evaluation
Risk minimisation measures	Establishing and documenting the „core safety profile“
Ensuring effectiveness of measures	Ensuring up-to-date product information

Tools to be used differently, depending upon where the product is in its life-cycle.