WHITE PAPER

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DSURs, RMPs, and PSURs

The Harmonization of Pharmacovigilance Documents

By Nicholas Churton, Manisha Chakov, Archievald Ingco, and Mary Pilkington

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Monitoring and reporting the safety information of a drug product over its lifecycle is an essential part of the drug development process and a mandatory requirement for pharmaceutical and biotech companies (the sponsor).

Aggregate safety reports include **Developmental Safety Update Reports (DSURs)** and **Periodic Safety Update Reports (PSURs)**, also called **Periodic Benefit Risk Evaluation Reports (PBRERs)**. These periodic, internationally recognized pharmacovigilance documents are submitted to regulatory authorities to help monitor risks and safety signals over the drug's development and postmarketing lifecycles. These reports are also linked to developing and maintaining the **Risk Management Plan (RMP)**, a document that is submitted at the time of application for marketing authorization in the European Union (EU; Figure 1).

The modular structure of the DSUR, PBRER/PSURs, and selected sections of the RMP have been harmonized. Thus, corresponding sections can be alike and even identical in content. This white paper will summarize key information concerning DSURs, RMPs, and PBRERs/PSURs, how they're linked, and how we can support pharmacovigilance medical writing.

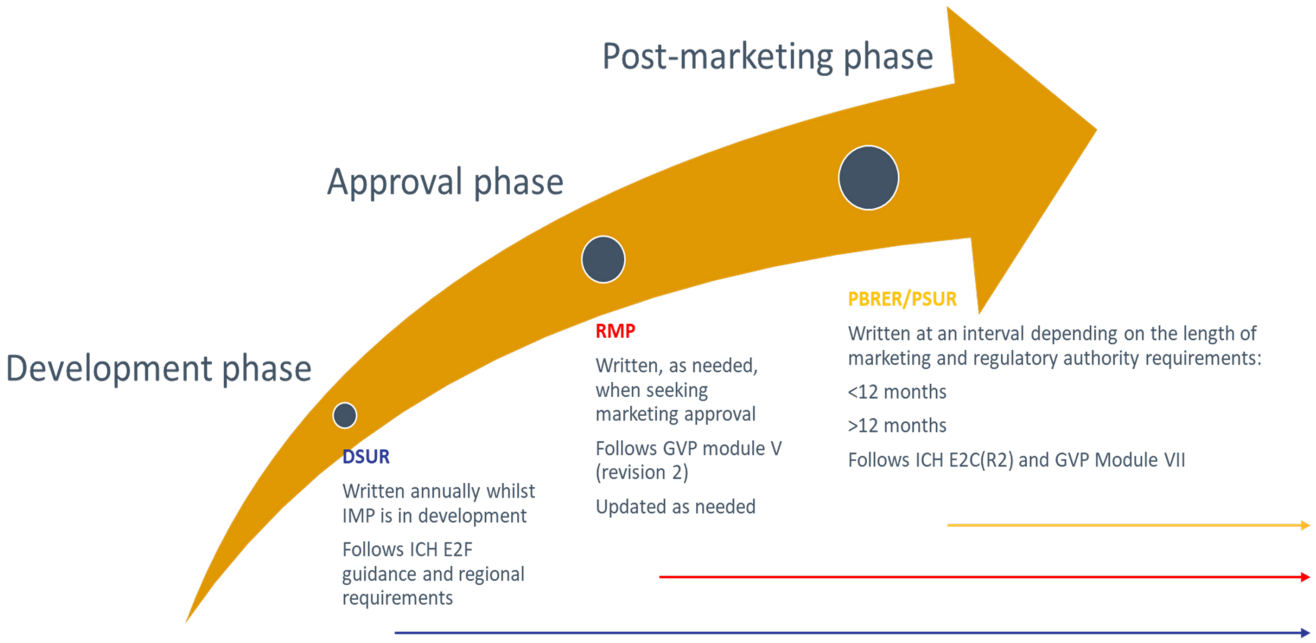

Figure 1. Aggregate Safety Reports During the Drug Development Lifecycle
Abbreviations: DSUR=Development Safety Update Report; ICH=International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IMP=Investigational medicinal product; PBRER/PSUR=Periodic Benefit- Risk Evaluation Reports/Periodic Safety Update Report; RMP=Risk Management Plan; GVP=Good Pharmacovigilance Practices.

DEVELOPMENTAL SAFETY UPDATE REPORTS

In 2011, the DSUR was introduced in the EU with the release of the ICH E2F guidance.[1] Clinical trial sponsors must submit an annual DSUR starting from the Development International Birth Date (date of first approval/authorization for conducting an interventional clinical trial in any country) to the data lock point (the last day of the 1-year reporting period).

The format of the DSUR meets the national and regional requirements of the EU and the US. Thus, it can replace

the preceding **EU Annual Safety Report** and the **US Investigational New Drug (IND) Annual Safety Report**. A DSUR must be submitted annually until all clinical studies have ended or while an IND remains active (when submitting to the United States Food and Drug Administration; FDA).

The purpose of a DSUR is to present a comprehensive evaluation of safety information of the sponsor's investigational drug. This information can be collected from clinical, non-clinical, and scientific literature as well as post-marketing sources, when applicable.

DSURs help to:

1. *Support the ongoing assessment of risks to trial subjects,*
2. *Inform regulators and other interested parties of the evolving safety profile of an investigational drug, and*
3. *Describe any actions needed to address any safety concerns.*

DSURs also provide an annual re-evaluation of important identified and potential risks based on the current knowledge.[1]

DSURs must be submitted to regulatory authorities within 60 calendar days of the data lock point.[1] To comply with national or regional requirements, additional region-specific appendices should be added to the DSUR as required. Examples include the UK/Canada,[2] China,[3] US,[1] and EU.[4]

RISK MANAGEMENT PLANS

The RMP is a mandatory part of the EU marketing application. The RMP was introduced in the EU in 2012 with the release of the Guideline on Good Pharmacovigilance Practices (GVP) Module V – Risk management systems. This module adopted a new template in 2017 (Revision 2).[5] This revision also clarified what RMPs should focus on regarding important identified or potential risks and missing information to create RMPs that are proportionate to the risks.

RMPs consist of detailed product information, epidemiology of the indication, non-clinical and clinical experience, safety specification, pharmacovigilance plan, risk minimization plan, and a lay (plain language) summary.

Despite being an EU mandate, several non EU countries also accept the RMP format. Over time, insights from postmarking safety data can cause differences in the risks depending on the region. Furthermore, RMPs may need to discuss more relevant epidemiological data for the targeted regions. Such updates can be included as addenda to the RMP.

PERIODIC SAFETY UPDATE REPORTS

The PSUR was introduced in the EU in 2012, following the release of the Guideline on GVP Module VII (Revision 1) for PSURs.[6] Subsequently, the ICH guideline E2C (R2) of 2013,[7] defined the recommended PBRER format and content. The ICH-E2C (R2) Implementation Working Group supplemented this guidance with Questions and Answers (Q&A)[8] and explanatory notes to the PSUR guidance GVP Module VII.[9]

The purpose of a PBRER/PSUR is to present a periodic evaluation of the product's benefit-risk profile in approved indications based on the analysis of new or emerging information obtained during the reporting interval. As with the DSUR, this new information may come from clinical, non-clinical, spontaneous, and solicited post-marketing case reports, and scientific literature sources. The PBRER/PSUR provides an evaluation of important identified and potential risks and missing information by analyzing both the cumulative and interval safety findings.

The frequency for submitting a PBRER/PSUR can depend on several factors including how long the product has been on the market and can range from 6 months to 3 years. The need for a PBRER submission is published in the European Union Reference Date list.[10] Market authorization holder(s) (MAHs) must comply with these reporting requirements. The reporting period may differ when submitting across multiple countries with differing reporting requirements. Per 21 Code of Federal Regulations 314.80 and 600.80, the US FDA recommends periodic submission of a **Periodic Adverse Drug Experience Report (PADER)**. However, the MAH can submit a PBRER/PSUR in place of a PADER once a waiver has been obtained per 314.90(b) and 600.90(b).[11]

PBRERs/PSURs must be submitted to the regulatory authorities within 70 days or 90 days of the data lock point for PBRERs/PSURs with a reporting period of <12 months or >12 months, respectively. As with the DSUR, additional region-specific appendices should be added to the PBRER/PSURs to comply with national or regional requirements. Examples include the US[11] and the EU[6].

HOW ARE THE DSUR, RMP, AND PBRER/PSUR LINKED?

Harmonization of the modular structure of the DSUR, PBRER/PSUR, and selected sections of the RMP means that corresponding sections can be alike and even identical (Table 1). However, it is important to ensure that the interval data in the DSUR and PBRER/PSUR align. For example, an annual DSUR may not be appropriate for a PBRER/PSUR with a 6-month, 2-year, or 3-year cycle, and vice versa.

To further harmonize the structure of the PBRER/PSUR to the DSUR, the reporting period of the DSUR can be aligned based on the PBRER/PSUR International Birth Date (the date of the first marketing authorization for the active substance granted to any company in any country in the world[7] so that the reporting periods of the DSUR and the PBRER/PSUR can be synchronized.[8]

Table 1 - Harmonized Sections of the DSUR, PBRER/PSUR, and RMP

DSUR	PBRER/PSUR	RMP
Section 2: Worldwide Marketing Approval Status	Section 2: Worldwide Marketing Approval Status	-
Section 3: Actions Taken in the Reporting Period for Safety Reasons	Section 3: Actions Taken in the Reporting Period for Safety Reasons	-
Section 4: Changes to Reference Safety Information	Section 4: Changes to Reference Safety Information	-
Section 6.1: Cumulative Subject Exposure in the Development Program	Section 5.1: Cumulative Subject Exposure in Clinical Trials	Part II: Module SIII - Clinical Trial Exposure
Section 6.2: Patient Exposure from Marketing Experience	Section 5.2: Cumulative and Interval Patient Exposure from Marketing Experience	Part II: Module SV - Post authorization Experience
Section 7.1 Reference Information	Section 6.1 Reference Information	-
Section 7.3: Cumulative Summary Tabulations of Serious Adverse Events	Section 6.2: Cumulative Summary Tabulations of Serious Adverse Events From Clinical Trials	-
Section 8: Significant Findings from Clinical Trials During The Reporting Period	Section 7: Summaries of Significant Findings from Clinical Trials During the Reporting Period	-
Section 8.1 Completed Clinical Trials	Section 7.1 Completed Clinical Trials	-
Section 8.2 Ongoing Clinical Trials	Section 7.2 Ongoing Clinical Trials	-
Section 8.3 Long-term Follow up	Section 7.3 Long-term Follow up	-
Section 8.4 Other Therapeutic Use of Investigational Drug	Section 7.4 Other Therapeutic Use of Investigational Drug	-
Section 8.5 New Safety Data Related to Combination Therapies	Section 7.5 New Safety Data Related to Combination Therapies	-
Section 9: Safety Findings from Non interventional Studies	Section 8: Safety Findings from Non interventional Studies	-
Section 10: Other Clinical Trial/Study Safety Information	Section 9.1: Other Clinical Trials	-
Section 11: Safety Findings From Marketing Experience	Section 5.2: Other post-approval use Section 9.2: Medication Errors Section 15: Overview of Signals: New, Ongoing, or Closed	-
Section 12: Nonclinical Data	Section 10: Nonclinical Data	-
Section 13: Literature	Section 11: Literature	-
Section 14: Other DSURs		
Section 15: Lack of Efficacy	Section 13: Lack of Efficacy In Controlled Clinical Trials	-
Section 17: Late Breaking information	Section 14: Late Breaking information	-

Section 18.1 Evaluation of the Risks	Section 16.2: Signal Evaluation Section 16.3: Evaluation of Risks and New Information Section 16.4: Characterization of Risks	-
Section 18.2 Benefit-Risk Considerations	Section 18.2 Benefit-Risk Analysis Evaluation	-
Section 19: Summary of Important Risks	Section 16.1: Summary of Safety Concerns	Part II: Module SVIII - Summary of the Safety Concerns
-	Section 16.4: Characterization of Risks	Part II: Module SVII - Identified and Potential Risks
-	Section 16.5: Effectiveness of Risk Minimization	Part V: Risk Minimisation Measures (Including Evaluation of The Effectiveness of Risk Minimisation Activities)
Section 20: Conclusions	Section 19: Conclusions	

OUR PHARMACOVIGILANCE MEDICAL WRITERS CAN HELP YOU

Submitting DSURs and PBRERs/PSURs follows strict timelines (60 days or 70/90 days, respectively). Failure to submit on time can lead to warning letters, fines and penalties, and reputational damage.

Compiling these documents can involve stakeholders from various departments. Managing the collection of sources and authoring the reports to meet the strict regulatory deadlines can be challenging. Certara regulatory writers are experts in developing these complex pharmacovigilance documents. Harnessing their expertise is a great asset to any biopharmaceutical company.

Learn more about how our Pharmacovigilance experts can help you assure patient safety!
https://www.certara.com/regulatory-science/safety-and-pharmacovigilance/

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