

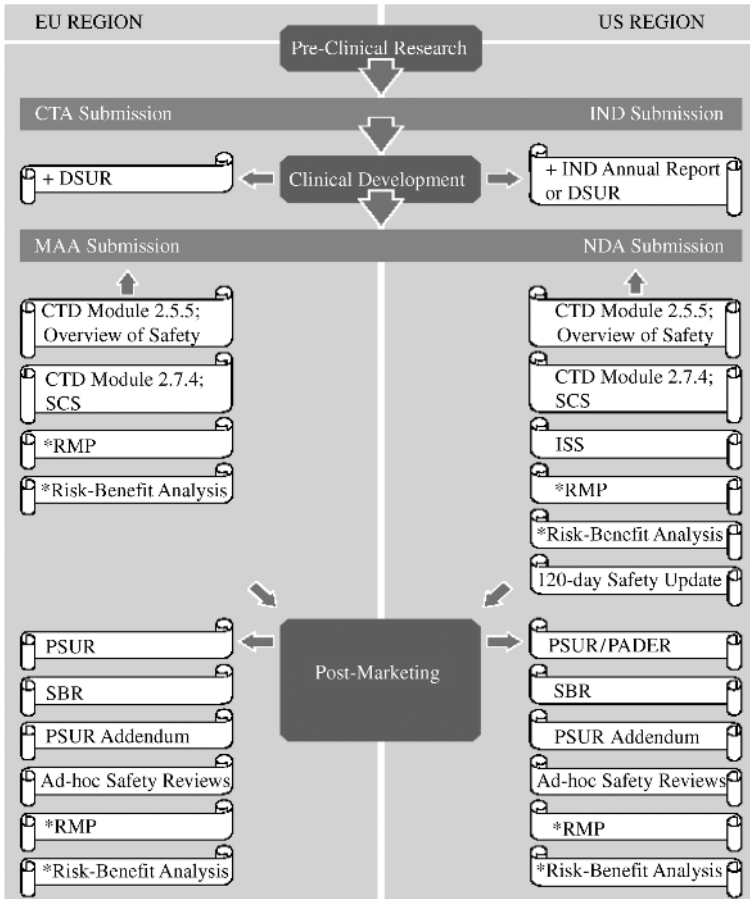
Chapter 1 **Pharmacovigilance medical writing – an overview across the drug development process**

A misconception considers that pharmacovigilance medical writing is concerned solely (or primarily) with the preparation of Periodic Safety Update Reports (PSURs) in the post-marketing phase of a product's life cycle. In truth, pharmacovigilance medical writing impacts on the clinical development and post-marketing phases, as well as making a significant contribution to the mandated submission documents required before the regulating authorities can grant marketing authorization/approval.

To fully appreciate the significance of pharmacovigilance medical writing within the drug development process, it is useful to take a step back and review each stage of the process and the accompanying pharmacovigilance or safety documentation. To this end, a summary outline of the key stages of the clinical development process and associated pharmacovigilance documents is presented in Figure 1.1.

In the first instance, the clinical development phase is associated with annual submissions of the Development Safety Update Report (DSUR) in the European Union (EU) and the Investigational New Drug (IND) Annual Report in the United States (US), with submission of the DSUR also being acceptable in the US. These documents represent a mechanism, through which the safety of subjects participating in clinical studies can be monitored by the sponsoring company and the regulatory authorities, as well as ethics committees and institutional review boards.

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Key: EU = European Union; US = United States; IND = Investigational New Drug; MAA = Marketing Authorisation Application; NDA = New Drug Application; CTD = Common Technical Documentation; SCS = Summary of Clinical Safety; RMP = Risk Management Plan; ISS = Integrated Summary of Safety; PSUR = Periodic Safety Update Report; SBR = Summary Bridging Report; PADER = Periodic Adverse Experience Report; DSUR = Development Safety Update Report; CTA = Clinical Trial Authorization

¹Although RMPs and Risk-Benefit Analyses are part of the MAA and IND submissions, they can be updated throughout the products post-marketing period.

Figure 1.1 Pharmacovigilance medical writing across the drug development process.

At the time of marketing authorization applications, pharmacovigilance documents represent a significant proportion of documents contained in the submitted dossiers, including:

- Common Technical Documentation (CTD) Module 2.5.5 – Overview of Safety;
- CTD Module 2.7.4 – Summary of Clinical Safety;

- Integrated Summary of Safety (ISS);
- 120-Day Safety Update Report;
- Risk Management Plan (RMP);
- Benefit-Risk Evaluation Report.

The CTD modules (i.e. CTD Modules 2.5.5 and 2.7.4) and the ISS represent integrated analyses of all safety data collected in the clinical development of the given medicinal product, and form the basis for the product's labeling and totality of safety information that is made available to prescribers and other healthcare professionals once the product has received marketing authorization (i.e. licensed for use).

The RMP is required at the time of application for marketing authorization of most medicinal products in the EU. This document describes the safety information yet to be determined for the given medicinal product and specifies the measures that will be taken by the company to address these gaps in the product's safety profile. In addition, the RMP outlines the processes that will be taken by the company to minimize the product's known safety issues and how these efforts will be evaluated and monitored for effectiveness.

The Benefit-Risk Evaluation Report assesses the benefit derived from use of the medicinal product against the risks for a particular patient population and treated indication, to determine whether the product has a favorable benefit-risk profile (i.e. that the benefits outweigh or justify the potential risks).

After successful application for marketing authorization, a number of other pharmacovigilance documents come into effect, including:

- PSURs (or Periodic Adverse Experience Reports [PADERS] for the US region);
- PSUR Addendums;
- Summary Bridging Reports (SBR);
- RMPs and Benefit-Risk Evaluation Reports;
- Ad-hoc safety reviews.

The PSUR, PADER, and associated documents (i.e. the PSUR Addendum and SBR) are mandated for submission at periodic intervals after marketing authorization, and are intended as a means through which the Marketing Authorization Holder (MAH), that is the company granted permission to market the medicinal product, can continue to review and update the regulating authorities of the product's safety profile, so that any changes (and potential risks) can be quickly identified and addressed.

Although RMPs and Benefit-Risk Evaluation Reports are an integral part of the documents submitted for marketing authorizations, these documents will continue to be amended and updated throughout the product's post-marketing life. A number of scenarios exist that require updating of RMPs and Benefit-Risk Evaluation Reports, including:

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- license renewals;
- identification of a new safety concerns;
- registration of new and clinically dissimilar indications;
- registration of treatment in a special treatment population (e.g. paediatrics and the elderly).

To afford greater utility, a separate chapter within this practitioner's manual is devoted to each phase of the drug development process that is impacted by pharmacovigilance medical writing, with a discussion of all associated pharmacovigilance or safety documents.

For ease of use and reference, the review of each pharmacovigilance document in this practitioner's manual is set out according to the following sections:

- review of regulatory requirements that underpin the preparation of each document;
- the scheduling/submission frequency for each document;
- the required data and data sources;
- the interdisciplinary team involved in the preparation and review of each document;
- an example timeline for document preparation and finalization;
- a generic model document.

The format of templates for these documents will clearly vary among different companies; however, the generic model presented for each document should provide a resource that can be modified based on therapeutic area and data requirements.