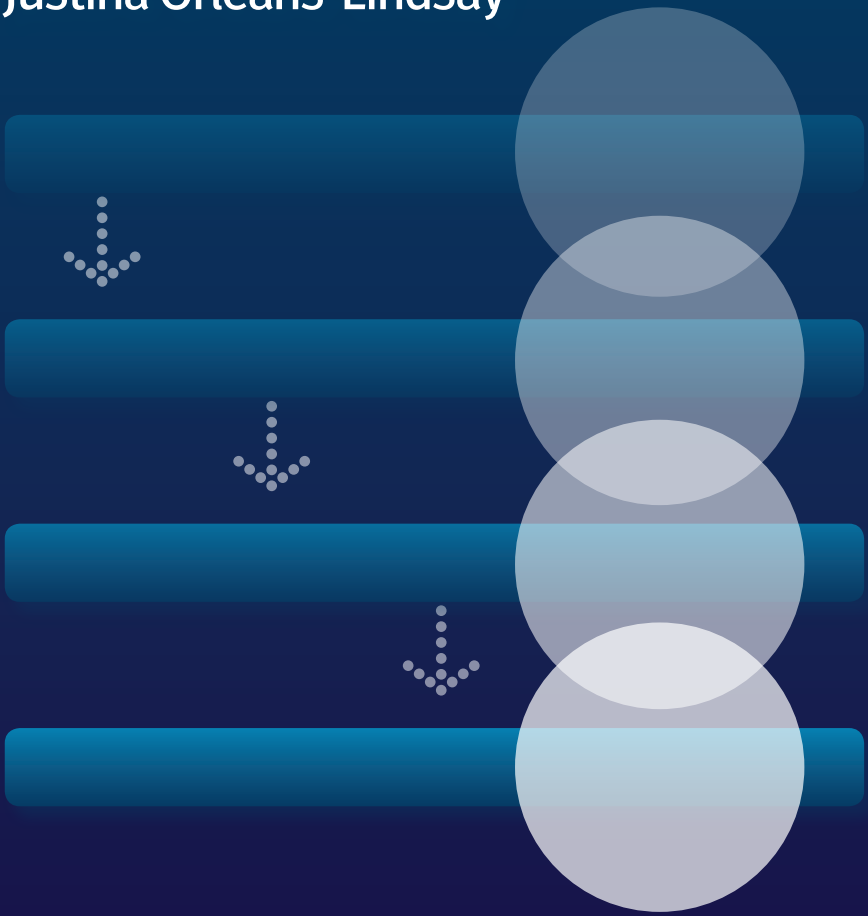
Pharmacovigilance Medical Writing

A GOOD PRACTICE GUIDE

Justina Orleans-Lindsay



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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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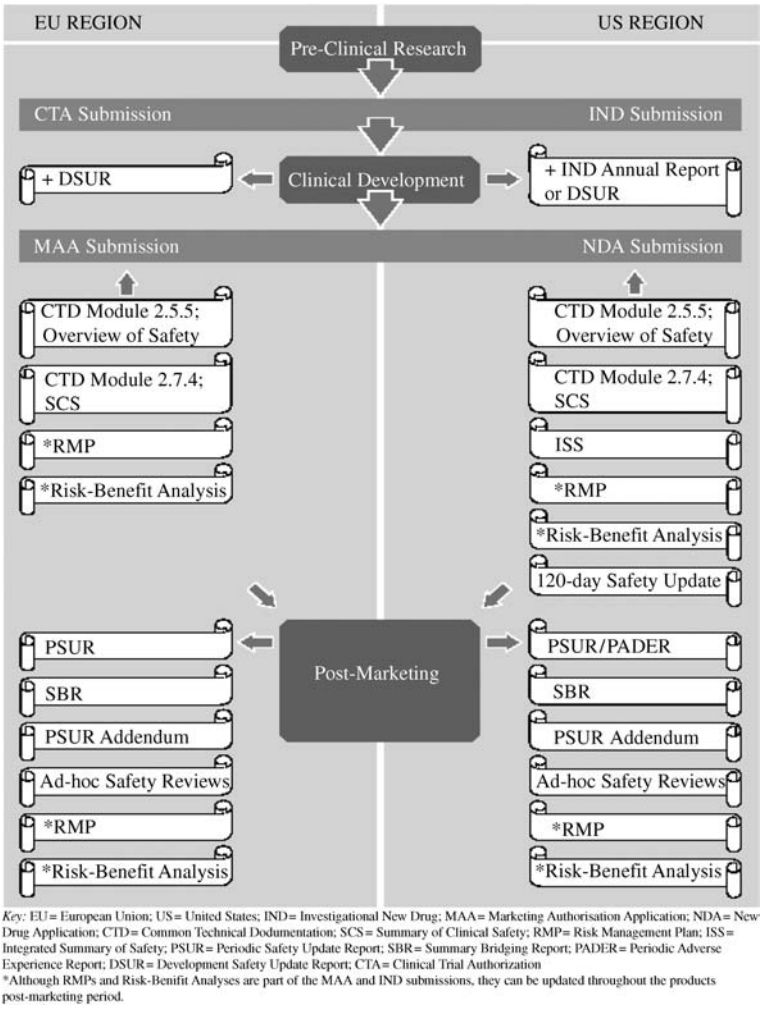

Key: EU = European Union; US = United States; IND = Investigational New Drug; MAA = Marketing Authorisation Application; NDA = New Drug Application; CTD = Common Technical Dodumentation; SCS = Summary of Clinical Safety; RMP = Risk Management Plan; ISS = Integrated Summary of Safety; PSUR = Periodic 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.