Czech University of Life Sciences Prague

Faculty of Economics and Management

Business Administration

Master's Thesis

Pharmacovigilance Business Model
A detailed study of the pharmaceuticals from the manufacturer to the customer

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Faculty of Economics and Management

DIPLOMA THESIS ASSIGNMENT

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Business Administration

Thesis title

Pharmacovigilance Business Model – A DETAILED STUDY OF THE PHARMACEUTICALS FROM THE MANUFACTURER TO THE CUSTOMER

Objectives of thesis

The aim of the proposal is to study this emerging business model as the pharmaceutical industry expands in size and global reach, it faces new and more complex challenges for e.g.: Covid-19. These fall heavily on PV groups which regularly keeps up with product innovation, technology advances and changing regulatory requirements while at the same time delivering on their risk management responsibilities. The broad objective of the thesis is to explore practically by work-practicing in this field and learn the innovations what gave the rise of this field of Pharmacovigilance.

- Exploration of each individual departments of Quality Assurance (QA), Pharmacovigilance (PV), Regulatory Affairs (RA), Distribution, Human Resources (HR) & Finance.
- Execution of the business.
- Roles of Legal Authorities like EMA, MHRA, CMDh & HMA involved.
- Innovations leading to the success of this business model.

Methodology

The master thesis is divided into two parts, theoretical and practical. In the theoretical part, the basic concepts related to the given topic are explained. It is an introduction to the field of Pharmacovigilance, the current dynamics of business development in Medical & Pharmaceutical sector. In the practical part, the basic characteristics of this business model are first described with the means of Qualitative research, including its influence on re-structuring and innovating the health-care industry with their legislations in regard to the European Medicines Agency.

The proposed extent of the thesis

50 -70 pages

Keywords

Pharmacovigilance (PV), Quality Assurance (QA), Regulatory Affairs (RA), European Medicines Agency (EMA), Medicines & Healthcare products Regulatory Agency (MHRA), Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh), Heads of Medicines Agencies (HMA)

Recommended information sources

Garashi HY, Steinke DT, Schafheutle EI. A Systematic Review of Pharmacovigilance Systems in Developing Countries Using the WHO Pharmacovigilance Indicators. Ther Innov Regul Sci. 2022 Sep;56(5)

Chiodin D, Cox EM, Edmund AV, Kratz E, Lockwood SH. Regulatory Affairs 101: Introduction to Investigational New Drug Applications and Clinical Trial Applications. Clin Transl Sci. 2019 Jul;12(4):334-342

Parsa N, Zibaeenezhad MJ, Trevisan M, Karimi Akhormeh A, Sayadi M. Magnitude of the Quality Assurance, Quality Control, and Testing in the Shiraz Cohort Heart Study. Biomed Res Int. 2020 Aug 11;2020

Talbot JC, Nilsson BS. Pharmacovigilance in the pharmaceutical industry. Br J Clin Pharmacol. 1998 May;45(5):427-31

Vignali V, Hines PA, Cruz AG, Ziętek B, Herold R. Health horizons: Future trends and technologies from the European Medicines Agency's horizon scanning collaborations. Front Med (Lausanne). 2022 Dec 8;9

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Declaration

I declare that I have worked on my master's thesis titled "Pharmacovigilance Business Model – A detailed study of the pharmaceuticals from the manufacturer to the customer" by myself and I have used only the sources mentioned at the end of the thesis. As the author of the master's thesis, I declare that the thesis does not break any copyrights.

In Prague on 23.11.2023 _____

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I would like to take this opportunity to thank the supervisor Mr. Wilem Heijman for consultation, advice, comments and professional guidance in processing this work. I would also like to thank the Pharmazet Group s.r.o. for allowing me to attend there the practical experience internship for the preparation of this work.

Pharmacovigilance Business Model
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Abstract

The Master thesis focuses on business model of Pharmacovigilance, which is still new to most individuals. The expertise gained during the practical internship at Pharmazet Group s.r.o. in Prague, Czech Republic, as well as published material used as references, has been used to prepare the master thesis.

Pharmaceuticals must also adhere to a number of regulations before putting their product on the market for sale, just like any other industry that produces and provides goods, eatables, and other products to the market does. The pharmaceutical industry has seen the rise of a new discipline known as pharmacovigilance in recent years. The commercial sector known as pharmacovigilance serves as the link between pharmaceutical companies and pharmacies and chemist shops.

The European Medicines Agency (EMA) oversees services and procedures that assist pharmacovigilance in the EU and coordinates the pharmacovigilance system for the European Union (EU). Pharmacovigilance, according to the EMA, is the science and actions concerned with the identification, evaluation, comprehension, and avoidance of adverse events or any other issue linked to medications. This business model consists of six different organs: Quality Assurance (QA), Pharmacovigilance (PV), Regulatory Affairs (RA), Distribution, Human Resources (HR) & Finance.

Keywords

Pharmacovigilance (PV), Quality Assurance (QA), Regulatory Affairs (RA), European Medicines Agency (EMA), Medicines & Healthcare products Regulatory Agency (MHRA), Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh), Heads of Medicines Agencies (HMA)

Obchodní model farmakovigilance
Podrobná studie léčiv z
výrobce k zákazníkovi

Abstrakt

Diplomová práce se zaměřuje na obchodní model farmakovigilance, který je pro většinu jednotlivců stále nový. Odbornost získaná během praktické stáže ve společnosti Pharmazet Group s.r.o. v Praze, Česká republika, stejně jako publikované materiály použité jako reference, byly použity k přípravě diplomové práce.

Farmaceutické přípravky musí také před uvedením svého produktu na trh k prodeji dodržovat řadu předpisů, stejně jako to dělá jakýkoli jiný průmysl, který vyrábí a dodává zboží, poživatiny a další produkty na trh. Farmaceutický průmysl zaznamenal v posledních letech vzestup nové disciplíny známé jako farmakovigilance. Komerční sektor známý jako farmakovigilance slouží jako spojovací článek mezi farmaceutickými společnostmi a lékárnami a lékárnami.

Evropská léková agentura (EMA) dohlíží na služby a postupy, které napomáhají farmakovigilanci v EU, a koordinuje farmakovigilanční systém pro Evropskou unii (EU). Farmakovigilance je podle EMA věda a činnosti týkající se identifikace, hodnocení, pochopení a vyhýbání se nežádoucím účinkům nebo jiným problémům spojeným s léky. Tento obchodní model se skládá ze šesti různých orgánů: zajištění kvality (QA), farmakovigilance (PV), regulační záležitosti (RA), distribuce, lidské zdroje (HR) a finance.

Klíčová slova

Farmakovigilance (PV), zajištění kvality (QA), regulační záležitosti (RA), Evropská léková agentura (EMA), Agentura pro regulaci léčiv a zdravotních produktů (MHRA), Koordinační skupina pro vzájemné uznávání a decentralizované postupy – lidský (CMDh), Vedoucí lékových agentur (HMA)

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1. Introduction

Pharmacovigilance (PV), which aims to minimize risks and maximize the benefits of pharmaceuticals, is a crucial tool for promoting public health. PV is described as "the science and actions pertaining to the detection, assessment, understanding and prevention of adverse effects or any other drug-related concern" by the World Health Organization (WHO).

Drug goods must go through a lot of testing and intensive examination during clinical trials in order to prove their safety and efficacy before receiving regulatory authority approval. The justification for post-marketing PV is based on the requirement to reduce the drawbacks of pre-marketing/registration clinical trials, such as their short duration, small population numbers, and exclusion of particular population groups (e.g. pregnant women and children). As a result, unanticipated or severe adverse drug reactions (ADRs), which increase morbidity, mortality, and financial loss, are frequently overlooked before regulatory approval. PV enables the post-marketing (i.e., real-world) collecting of pharmacological safety and efficacy data, lowering patient morbidity and mortality associated with drug use.

PV also lowers the financial expenses related to providing care for patients with these issues. This is accomplished by conveying the risks and advantages of medications, thereby optimizing pharmaceutical safety at different levels of the healthcare system, as well as by disseminating knowledge and information that informs regulatory actions. It is significant to remember that PV activities encompass the entirety of a drug product's lifecycle and are a progression and culmination of the analysis carried out on medications from pre-registration clinical trials. PV activities also do not just apply to post-marketing patient safety protection. By educating patients about the case of insolvency of drug goods, PV also aids drug manufacturing companies in engaging out patient outreach. This helps patients become more knowledgeable and trust the business. Insurance companies rely on PV data as a gauge of the drug commodities proven usefulness to patients when making decisions over financing because they are the group payers for pharmaceutical items.

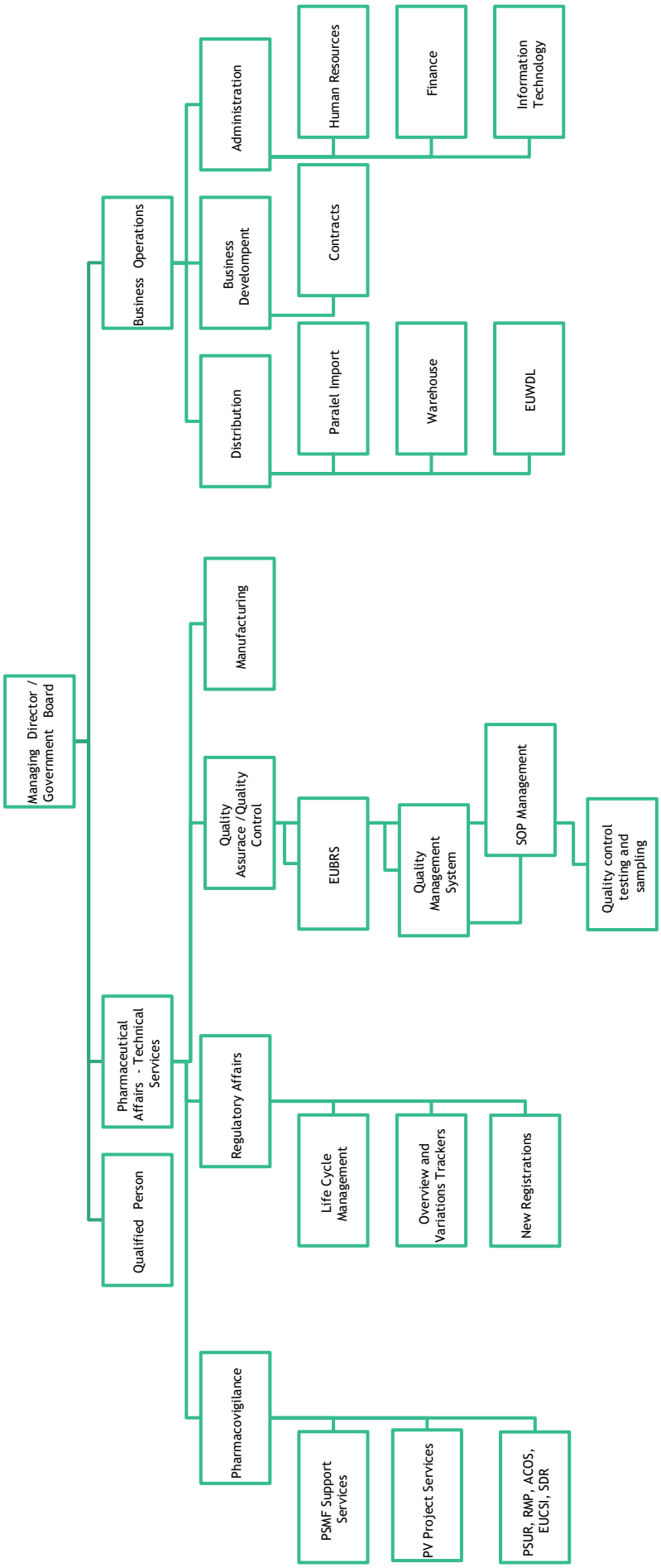
Local elements including healthcare spending, disease categories and incidence, and state of politics affect how PV systems differ in emerging economies. Every nation must establish its PV system because these variations can affect how medications are used and the types of side effects that patients experience. Following the thalidomide catastrophe in the 1960s, the majority of industrialized nations began their PV efforts by installing PV systems and enlisting in the WHO Programme for International Drug Monitoring (PIDM). Emerging

economies were reluctant to join the PIDM through till 1990s or thereafter, however since then, an increasing number of emerging economies have accepted PV and joined the WHO PIDM.

National medicines regulatory agencies (NMRAs), as well as national and global lawmaking organizations, have released a substantial number of law and regulation over the last few years in order to give nations a legitimate basis and effective guidelines and procedures for national PV systems. The European Medicines Agency (EMA) implemented Guidelines on Good Pharmacovigilance Practices (GVP) in 2012 with the objective of simplifying the execution of PV in the European Union (EU). The EMA's GVP recommendations are frequently used as a guide when setting up national PV systems in emerging nations that seek to align their brand-new and advancing PV frameworks with world norms.

Pharmacovigilance involves more than just informing regulatory authorities of cases, as safety signals are validated, the outcomes of post marketing surveillance and theory testing should yield critical info that may be shared with healthcare practitioners by upgrading the Summary of product characteristics and Patient Information Leaflet. One aspect of the European regulations is that organizations holding marketing authorizations, or corporations, are required to have an adequately qualified person in charge of pharmacovigilance. Their duties involve the creation and upkeep of a system that makes sure all ADRs reported to company personnel are gathered and compiled so they can be made available at a centralized point within the community, the creation of numerous reports, and responding to inquiries from the authorities for the provision of additional information.

The optimal organizational structure for Pharmocovigilance is further discussed in the appendix, followed by a breakdown of each department's duties.


Managing Director / Government Board
Business Operations
Administration
Human Resources
Finance
Information Technology
Business Development
Contracts
Distribution
Paralel Import
Warehouse
EUWDL
Pharmaceutical Affairs - Technical Services
Manufacturing
Quality Assurace /Quality Control
EUBRS
Quality Management System
SOP Management
Quality control testing and sampling
Regulatory Affairs
Life Cycle Management
Overview and Variations Trackers
New Registrations
Qualified Person
Pharmacovigilance
PSMF Support Services
PV Project Services
PSUR, RMP, ACOS, EUCSI, SDR

In this appendix, we would understand all individual and significant components of Pharmaceutical Affairs – Technical Services; without which the further supply chain of distributing and delivering medicines to customer cannot be initiated.

a. Pharmacovigilance

Pharmacovigilance is the practice of monitoring and evaluating the safety and effectiveness of pharmaceutical goods, including drugs, vaccines, and medical devices, after they have been approved and made widely available to the consumer. It is the science and endeavors associated to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.

The fundamental aim of pharmacovigilance is to guarantee that patients receive reliable and effecient therapy, by noticing and preventing adverse drug reactions, identifying and evaluating potential safety signals, and conveying risks and benefits to healthcare professionals and patients.

Pharmacovigilance involves a range of activities, including collecting and analyzing data on adverse events, developing risk management plans, implementing safety measures, and conducting post-marketing surveillance studies. The information obtained through pharmacovigilance activities is used to inform regulatory decision-making, and to improve patient safety and the overall quality of healthcare.

Significant tasks carried out under pharmacovigilance are PSMF support service, PV project services, PSUR, RMP, ACO, EUCSI, SDR

b. Pharmacovigilance System Master File (PSMF)

Pharmacovigilance System Master File (PSMF) is a comprehensive document that provides a detailed description of the pharmacovigilance system of a pharmaceutical company. It is an important regulatory requirement in many countries, including the European Union, where it is required for all marketing authorization holders in pharmaceuticals.

The PSMF includes information on the organizational structure, roles and responsibilities, processes, and procedures of the pharmacovigilance system. It also outlines

the tools and techniques used for collecting, analyzing, and reporting adverse drug reactions (ADRs) and other drug-related problems. The purpose of the PSMF is to demonstrate that the pharmaceutical has a robust and effective pharmacovigilance system in place to ensure patient safety.

The PSMF is a living document that is regularly updated to reflect changes in the pharmacovigilance system. It is typically reviewed and approved by regulatory authorities during marketing authorization applications or as part of routine inspections.

The PSMF is an important tool for ensuring the continuous improvement of pharmacovigilance systems and enhancing the safety of medicinal products.

c. Pharmacovigilance (PV) project services

Pharmacovigilance (PV) project services refer to the variety of services offered by businesses or organizations to support the organization, management, and planning of pharmacovigilance activities for pharmaceuticals. Pharmacovigilance consultancies, contract research organizations (CROs), or other PV-focused businesses may offer these services..

Some examples of PV project services include:

1. Signal detection and management: This entails identifying potential safety hazards by analyzing data on adverse events and developing and putting into practice suitable risk management measures..
2. Risk management planning: This entails the creation of risk management plans (RMPs) for pharmaceuticals, which aim to reduce the risks connected with using the medication.
3. Post-marketing surveillance: This entails the monitoring of adverse events and other safety-related data after the product has been marketed, in order to identify potential safety issues that may not have been discovered during clinical trials.
4. PV training and support: This entails the provision of training and support to healthcare professionals, patients, and other stakeholders to ensure the proper reporting and management of adverse events.
5. Regulatory compliance: This entails ensuring that pharmacovigilance activities are conducted in compliance with regulatory requirements and guidelines.

Overall, by offering knowledge and assistance for the organizing, carrying out, and managing of pharmacovigilance activities, PV project services play a significant part in guaranteeing the safety and efficacy of pharmaceuticals.

d. PSUR stands for Periodic Safety Update Report

PSUR stands for Periodic Safety Update Report, which is a regulatory document that provides an overview of the safety profile of a medicinal product. PSURs are required to be submitted to regulatory authorities at specified intervals, typically every 6 months or annually, depending on the product and regulatory requirements.

A PSUR's main goal is to give a thorough analysis of the safety information for a medical product, including adverse reactions, suspected adverse responses, and other safety-related data. A review of the product's risks and advantages should also be included in the report, along with any updates to the product information, such as the product labeling or package insert.

All pharmaceutical products with marketing authorization, including those that have been on the market for a long time as well as brand-new medications, must have PSURs. They are a crucial instrument for keeping track on the safety of pharmaceuticals and making sure that any new safety problems are discovered and dealt with effectively.

Regulatory agencies establish the format and content of PSURs, and these elements may change based on the product and the legal requirements of the nation or region in which the product is promoted. Regulatory authorities must examine and approve PSURs, which are normally created by the marketing authorization holder (pharmaceutical) or a designated representative, such as a contract research organization (CRO).

e. An addendum to a clinical overview (ACO)

An addendum to a clinical overview (ACO) is a supplement that offers updates or extra information to the initial clinical summary of a medication. Clinical overviews, which offer a thorough description of the clinical data supporting the product's safety and efficacy, are an essential part of the regulatory submission package for medical products.

If further studies are carried out that were not covered in the first clinical overview or if new data become available after the initial submission, addenda can be required. The

addendum may also be used to respond to queries or issues expressed by regulatory bodies throughout the review procedure.

The exact information being provided or updated will determine the format and content of an addendum to a clinical summary. The addendum might, for instance, provide new information on the pharmacology or pharmacokinetics of the product or updated efficacy or safety data.

The addendum to a clinical overview is similarly subject to evaluation and approval by regulatory authorities as the initial clinical overview. In order to speed up the review procedure and support a positive regulatory conclusion for the product, it is crucial to make sure the addendum is comprehensive, correct, and presented in a clear and straightforward manner.

f. European Union Core Safety Information (EUCSI)

The European Union Core Safety Information (EUCSI) is a standardized set of safety information that is required by the European Medicines Agency (EMA) for all medicinal products marketed in the European Union. The EUCSI includes a range of safety-related data, including adverse reactions, clinical trial data, and risk management plans.

Regardless of the particular regulatory requirements or procedures that may apply to the product, the EUCSI aims to ensure that a uniform set of safety information is accessible for all pharmaceuticals marketed in the European Union. The EUCSI is designed to make it easier for regulatory agencies and other stakeholders to share safety information, as well as to make sure that the safety of pharmaceuticals is monitored and maintained in a systematic and open way.

The EUCSI is typically prepared and maintained by the marketing authorization holder (pharmaceutical) or a designated representative, such as a contract research organization (CRO). The EUCSI is subject to review and approval by regulatory authorities, and any updates or changes to the EUCSI must be submitted for review and approval on an ongoing basis as new safety information becomes available.

Overall, the EUCSI is a crucial instrument for guaranteeing the security of pharmaceuticals throughout the European Union, and it aids in making sure that patients and healthcare professionals have access to reliable and consistent data regarding the dangers and advantages of the goods they use.

g. Regulatory affairs

The field of regulatory affairs in the life sciences sector is concerned with the creation, application, and observance of rules and regulations pertaining to the creation, approval, and marketing of medicines, medical devices, biologics, and other healthcare goods.

Regulatory affairs specialists work to verify that healthcare goods are high-quality, safe, and effective as well as that they adhere to all applicable laws and regulations in the nations or regions in which they are marketed. To make sure that all relevant regulatory requirements are completed at every stage of the product development and approval process, they collaborate closely with product development teams, clinical research organizations, and regulatory agencies.

The preparation and submission of regulatory submissions, such as New Drug Applications (NDAs) or 510(k) submissions, to regulatory authorities for clearance is the responsibility of regulatory affairs experts. Also, they keep an eye out for modifications to laws and rules and make sure that items are updated to comply with any new needs.

Professionals in regulatory affairs may also be in charge of overseeing interactions with regulatory bodies, responding to informational or data requests, and organizing the creation and filing of regulatory reports like safety reports or monthly updates.

Altogether, regulatory affairs is a crucial job function in the life sciences sector that ensures the development, approval, and marketing of healthcare goods in a safe, efficient, and legal manner.

h. Life cycle management (LCM)

The process of managing a product over its full life cycle, from original development to marketing and final discontinuation, is known as life cycle management (LCM). LCM refers especially to the management of a drug product throughout its life cycle when referring to the pharmaceutical business.

LCM is a crucial component of pharmaceutical development since it enables businesses to enhance and lengthen the lifecycle of their products. This is especially crucial in a market where businesses are continuously looking for ways to enhance their goods and beat off rivals.

LCM covers a wide range of operations, including as the creation of novel pharmacological indications, formulations, or delivery systems, as well as the alteration of current production procedures to increase productivity or lower costs. Additionally, it requires implementing risk management techniques to handle any potential safety concerns that may surface as well as continual monitoring of the safety and effectiveness of medications.

The development of companion diagnostics, the identification of new target patient populations, and the discovery of new product prospects through market research and competitive analysis may all be further parts of LCM.

Therefore, life cycle management is a crucial step for pharmaceutical firms because it helps them optimize the value of their goods and maintain competitiveness in a market that is continuously changing. Companies can maintain a drug product's relevance, efficacy, and safety for patients while also satisfying the requirements of healthcare providers, payers, and regulatory authorities by carefully managing a drug product throughout its entire life cycle.

In the context of regulatory affairs, **new registration** refers to the procedure for getting regulatory approval for a novel medical device or pharmaceutical product in a particular nation or region. A regulatory dossier or application must normally be submitted to the appropriate regulatory agencies, such as the US Food and Drug Administration (FDA) or the European Medicines Agency, as part of the process of new registration (EMA).

Detailed information regarding the product, such as results from preclinical and clinical trials, manufacturing and quality control data, labeling and packaging specifics, and any other pertinent data requested by the regulatory authorities, is often included in the regulatory dossier or application. Interactions with the regulatory bodies during the application process could include responding to information requests or attending regulatory review sessions.

Depending on the type of product and its intended use, the country or region in which it is being marketed, and the conditions for new registration may change. But, in general, the procedure for new registration can be difficult and time-consuming, and it necessitates a complete comprehension of the legal criteria and regulations in the pertinent nations or regions.

A new product's commercial success depends on a successful new registration since it enables businesses to market their products to consumers and healthcare providers and to make money from sales. Professionals in regulatory affairs are crucial to the new registration process since it is up to them to make sure that all regulatory requirements are completed and that the product is swiftly and effectively approved for marketing.

i. Quality Assurance

Quality assurance (QA) is a process-focused strategy for ensuring that goods or services fulfill predetermined standards for quality. QA refers especially to the steps taken to assure that medications and medical equipment are secure, efficient, and of the highest caliber in the context of the pharmaceutical sector.

The purpose of quality assurance is to avoid mistakes or flaws in the design, production, and distribution of products. Implementing standardized processes and procedures for each phase of the product life cycle, from development to post-market monitoring, is a key component of quality assurance. Activities including risk analyses, document control, supplier management, and quality control testing are included in this.

In order to ensure that goods are both safe and effective for patients as well as compliant with the legal and regulatory requirements of the nations or areas where they are marketed, quality assurance (QA) is a crucial part of pharmaceutical research and manufacture. Observing Good Manufacturing Practices (GMP) and other legal regulations is part of this.

QA is often managed by a specialized team that is tasked with creating and executing quality rules and procedures, keeping track of how well they are being followed, and conducting audits and inspections to verify that the right methods are being used.

Therefore, quality assurance plays a critical role in the pharmaceutical sector, as it helps to ensure that products are of highest caliber, safe, and effective for patients, while also meeting the regulatory and quality standards of the markets in which they are sold.

EU batch release refers to the procedure of releasing a batch of pharmaceuticals for sale or distribution in the European Union in the context of quality assurance (EU). An essential step in the pharmaceutical manufacturing process is EU batch release, which guarantees that the finished product satisfies the necessary quality requirements and is secure for patient use.

The Quality Control (QC) and Quality Assurance (QA) departments of the manufacturer normally oversee the EU batch release procedure. They are in charge of making sure the product adheres to the parameters given in the marketing authorization and other regulatory requirements.

The EU batch release procedure includes several processes, such as **sampling and testing** the batch to make sure it adheres to the necessary quality standards, reviewing the batch paperwork, and assuring that production and quality control procedures have been followed. The QA division must approve the batch's release before it may be given to wholesalers, pharmacies, and other authorized distributors for patient purchase.

The EU's Good Manufacturing Practice (GMP) standards, which specify the criteria for producing, testing, and releasing pharmaceuticals, control the batch release procedure. Each EU member state's regulatory agencies are in charge of upholding these rules and making sure that goods are only put on the market when they have attained the necessary levels of quality.

Ultimately, the EU batch release procedure is essential to the production and distribution of pharmaceuticals since it guarantees that the finished goods are of the highest caliber and that patients can use them safely and effectively.

j. Quality Management System (QMS)

A Quality Management System (QMS) is a collection of rules, processes, procedures, and records that specify and regulate how a company makes sure that its goods and services satisfy the needs and expectations of its clients. The goal of a QMS is to create a systematic approach to quality that guarantees consistency, effectiveness, and ongoing output improvement for an organization.

Typically, a QMS has the following elements:

1. Quality policy: A declaration of a company's dedication to quality that serves as a foundation for the formulation of quality objectives and targets.
2. Quality objectives: Measurable targets that support the quality policy and drive continuous improvement.

3. Quality manual: A document that outlines the quality management system, including the policies, processes, procedures, and responsibilities of each individual in the organization.
4. Procedures and work instructions: Detailed instructions that describe the steps required to perform specific tasks and processes, and ensure that they are performed consistently and in accordance with the quality policy and objectives.
5. Records: Documentation of the quality management system, including records of quality checks, inspections, audits, and corrective actions.
6. Management review: A regular review of the quality management system by top management to ensure its effectiveness and identify opportunities for improvement.

Many advantages, such as increased productivity, higher levels of customer satisfaction, and improved regulatory compliance, can result from the incorporation of a QMS. It also enables businesses to spot quality problems early on and fix them, lowering the chance of product recalls, safety mishaps, and legal trouble.

k. SOP management

The process of developing, putting into practice, and upholding Standard Operating Procedures (SOPs) inside an organization is referred to as SOP management. SOPs are detailed written instructions that describe how to carry out particular tasks or processes in a predictable and controlled way. SOPs are a crucial part of quality management systems and are employed to guarantee adherence to legal standards, boost productivity, and lower the chance of mistakes and non-conformities.

The following actions are necessary for effective SOP management:

1. Development: SOPs should be created with the help of key stakeholders, including subject matter experts, quality staff, and end users, using an organized way. SOPs should be prepared in plain, simple language with the right amount of detail.
2. Approval: Before being put into use, SOPs should be reviewed and approved by the appropriate personnel. By doing this, it is made sure that the SOPs are correct, useful, and in line with company policies and practices.

3. Implementation: Relevant staff members should be informed about SOPs, and training should be offered to guarantee that staff members comprehend and can correctly carry out the procedures.
4. Maintenance: SOP changes should be handled by following a controlled change management procedure that involves authorized staff for evaluation and approval. SOPs should be reviewed and updated on a regular basis to make sure they are still accurate and useful.
5. Archiving: To ensure that SOPs are accessible and available for reference as needed, they should be archived and maintained in a regulated way.

In order to guarantee that an organization's procedures are reliable, legal, and effective, effective SOP management is essential. Also, it aids in lowering the possibility of mistakes, deviations, and non-conformities, which can have detrimental effects on product quality, safety, and regulatory compliance.

l. Quality control testing and sampling

To guarantee that the safety and efficacy of medications are maintained throughout their lifecycle, pharmacovigilance also includes key operations like quality control testing and sampling. The following are some examples of quality control testing and sampling in pharmacovigilance:

- Adverse Event Reporting: Pharmaceutical businesses are in charge of gathering, assessing, and reporting adverse events (AEs) to regulatory agencies. AEs are reported by healthcare professionals and patients to pharmaceutical corporations. To guarantee that adverse events (AEs) are reported accurately, thoroughly, and on time, quality control testing and sampling are required.
- Signal Detection: Using statistical and analytical techniques, signal detection seeks to pinpoint any potential drug safety issues. Verifying the accuracy and completeness of the data used in signal detection, making sure the signal detection algorithms are functioning properly, and checking the results to make sure they are accurate are all part of the quality control testing and sampling process in signal detection.

- Pharmacovigilance Inspections: To make sure that pharmaceutical businesses are adhering to pharmacovigilance requirements, regulatory bodies carry out pharmacovigilance inspections. Verifying the accuracy and comprehensiveness of the pharmacovigilance data and documentation delivered to regulatory authorities is done through quality control testing and sampling during pharmacovigilance inspections.
- Quality Control Checks: In order to ensure that the data and information used in pharmacovigilance are correct and comprehensive, quality control checks must be performed. Data verification, quality checks of pharmacovigilance documentation, and compliance checks of pharmacovigilance processes are all included in quality control testing and sampling in pharmacovigilance checks.

In pharmacovigilance, efficient quality control testing and sampling serve to guarantee that medications are safe and effective, lower the likelihood of adverse events, and improve patient safety. Also, it aids in pinpointing areas where pharmacovigilance procedures need modification, resulting in ongoing development and better goods.

3. Pharmacovigilance - Business Model

The practice of monitoring, identifying, evaluating, and preventing side effects or any other drug-related issues connected with the use of pharmaceutical products is known as pharmacovigilance. To ensure that the advantages of medicines outweigh their hazards and to increase patient safety is the ultimate goal of pharmacovigilance.

There are a number of pharmacovigilance business models, and the following are some of its salient features:

Service Provider Model: Providing pharmacovigilance services to pharmaceutical firms, contract research organizations (CROs), and regulatory bodies is the most typical pharmacovigilance business model. Adverse event reporting, signal detection, risk management, and regulatory compliance are some of these services. The amount of pharmaceuticals, patients, or events that a company monitors can determine how much it charges, or it can set a fixed rate for each project or contract.

In-house Model: To manage all facets of medication safety monitoring, several pharmaceutical corporations opt to maintain an internal pharmacovigilance staff. Long-term cost-effectiveness and increased process control are both possible with this paradigm. Nonetheless, a large investment in manpower and infrastructure is needed.

Hybrid Model: Some businesses employ a hybrid approach, using an internal team for core pharmacovigilance functions and contracting out some less important duties to a service provider. More flexibility and cost effectiveness are made possible by this paradigm.

Outsourcing Model: Some businesses hire a third-party service provider to handle all pharmacovigilance tasks. Small to mid-sized pharmaceutical companies that lack the resources or knowledge to perform pharmacovigilance internally frequently utilize this model. The service provider is capable of managing all aspects of medication safety monitoring, including risk assessment and reporting of adverse events.

Collaborative Model: To carry out pharmacovigilance efforts, some pharmaceutical corporations team up with academic institutions, patient advocacy organizations, and regulatory bodies. This methodology can help to increase patient engagement, transparency, and drug safety outcomes.

There are several ways to guarantee patient safety, and the pharmacovigilance business model is complex.

a. Modes of Revenue

Here are a few typical ways that pharmacovigilance companies make money:

Fees for Services: Pharmaceutical corporations, contract research organizations (CROs), and regulatory authorities often pay pharmacovigilance businesses for the services they offer. These fees can be fixed for each project or contract, or they can be depending on the quantity of medications, patients, or events being tracked.

Licensing Fees: Several pharmacovigilance companies create their own tools and software for monitoring the safety of pharmaceuticals. For their clients to use these products, they might charge license fees.

Outsourcing: Some pharmaceutical firms contract with a third-party service provider to handle all pharmacovigilance tasks. Businesses engaged in pharmacovigilance can make money by offering all necessary services for drug safety monitoring.

Collaborative Agreements: Businesses engaged in pharmacovigilance work together with academic institutions, patient advocacy organizations, and regulatory bodies to carry out these operations. Under these circumstances, they can get payment for their services in the form of grants, funding, or other cooperative arrangements.

Consulting Services: In order to help their clients establish and implement drug safety policies, adhere to regulatory standards, and deal with challenging pharmacovigilance situations, several pharmacovigilance organizations offer consulting services.

This shows, companies involved in pharmacovigilance make money by offering a variety of services pertaining to managing and monitoring medication safety. Depending on the size, breadth, and emphasis of the firm, the specific revenue model may change.

b. Well-known PV companies

Pharmacovigilance businesses might be small, specialized businesses or massive, worldwide corporations. Listed below are a few well-known pharmacovigilance firms:

IQVIA: A major supplier of pharmacovigilance services, commercial solutions, and clinical research on a global scale.

PPD: A worldwide contract research company (CRO) offering regulatory, medication safety, and clinical trial management services.

ICON plc: A world-wide supplier of pharmacovigilance services and services related to medication research and commercialization.

WCG Clinical: A provider of pharmacovigilance services as well as clinical trial management and drug safety services.

PAREXEL International Corporation: A multinational biopharmaceutical services provider that offers pharmacovigilance, clinical trial administration, and drug development services.

Syneos Health: A multinational biopharmaceutical services firm that offers services in medication development, clinical trial administration, and pharmacovigilance.

Covance: A worldwide contract research organization (CRO) that offers pharmacovigilance services as well as services for medication development and safety.

PRA Health Sciences: A worldwide contract research company (CRO) that offers pharmacovigilance, clinical research, and drug development services.

Drug Safety Navigator: A company that offers consultancy services for pharmacovigilance and medication safety.

SGS: A multifaceted organization that offers testing, inspection, and certification services worldwide, including pharmacovigilance services.

It is significant to note that this list is not complete and that there are other additional pharmacovigilance businesses operating on a global scale.

Pharmazet's financial situation cannot be seen in public streams because it is a small corporation. But, remembering the illustration of other businesses like IQVIA.

Clinical research, business solutions, and healthcare services, including pharmacovigilance services, are all offered globally by IQVIA. IQVIA is mandated to declare its financial performance annually in its annual report and quarterly in its earnings release as a publicly traded corporation.

The company produced total revenue of $12.5 billion in 2020, according to IQVIA's 2021 financial figures, and its pharmacovigilance and drug safety division is a sizable portion of its overall business portfolio. Unfortunately, IQVIA doesn't publicly state how much money is actually made from its pharmacovigilance services.

It is crucial to remember that a pharmacovigilance company's revenue might change depending on a number of variables, including its size, the range of services it offers, the locations of its clients, and the demand for its services.

c. Pharmacovigilance Market

The Pharmacovigilance Market in Europe is expected to increase at a CAGR of 13.9% from its projected value of USD 1.53 billion in 2022 to USD 2.93 billion by 2027. (Source: https://www.marketdataforecast.com/market-reports/europe-pharmacovigilence-market)

The estimated size of the global pharmacovigilance market in 2022 was USD 9.07 billion, and it is anticipated to expand to over USD 16.23 billion by 2030, with a projected CAGR of 7.5% from 2021 to 2030. (Source: https://www.precedenceresearch.com/pharmacovigilance-market)

4. Procedures and tasks

The following module provides an illustration of the typical pharmacovigilance practises and tasks, which provides a comprehensive overview of the pharmacovigilance system of a pharmaceutical company. Understanding the tasks and procedures employed in the ideal pharmacovigilance organisation would be made easier by doing this.

Directive 2010/84/EU established the mandate that holders of marketing authorizations must keep and make a Pharmacovigilance System Master File available upon request.

This document includes an overview and information on the key elements of the pharmaceuticals and pharmacovigilance system as outlined in Directive 2001/83/EC and Regulation (EC) No. 726/2004. It also complies with the requirements and structure outlined in Module II of GVP and the Commission Implementing Regulation (EU) No. 520/2012. (The Implementing Regulation is referred to as "the IR"). The guidance provided in this GVP Module supports the particular requirements stated in the Commission Implementing Regulation in further detail.

The information in this module reflects the global accessibility of safety data for drugs with EU authorization. It provides evidence for and documentation of the pharmacovigilance system's adherence to the regulations.

a. Role of Qualified Person Responsible For Pharmacovigilance

This is a list of the qualified person responsible for pharmacovigilance's duties and job description. The Qualified Person Responsible For Pharmacovigilance in her absence performs the same duties as the Deputy Qualified Person Responsible For Pharmacovigilance. The Qualified Person Responsible For Pharmacovigilance's Work Description is Included in (the document which includes the individual CV of Qualified Person Responsible For Pharmacovigilance & Deputy of Qualified Person Responsible For Pharmacovigilance).

- Overseeing the company's pharmacovigilance system and the EU pharmacovigilance team.
- Informing the European Medicines Agency (EMA) and the Competent Authorities of the Member States of the name of the Qualified Person Responsible for

Pharmacovigilance and Deputy Qualified Person Responsible for Pharmacovigilance (when necessary) and keeping a log of the information for both of these individuals.

- The Qualified Person Responsible For Pharmacovigilance serves as a single point of contact for the European Medicines Agency and the competent authorities around-the-clock and also serves as a point of contact for pharmacovigilance inspections.
- Ongoing supervision of the business's pharmacovigilance operations by the appointment of a duly qualified deputy competent person responsible for pharmacovigilance and/or through a formal after-hours arrangement
- Keep a record of the qualifications of the qualified person responsible for pharmaceutical oversight and the deputy qualified person responsible for pharmaceutical oversight for backup purposes.
- Possessing a general understanding of the safety profiles for pharmaceutical products and any new safety worries.
- Having control over the pharmacovigilance quality system, which includes regular compliance reports, procedural documents, agreements with partners and third parties, database operations, adherence to essential pharmacovigilance and related processes, audit reports, and training of personnel in pharmacovigilance.
- Being aware of any requirements or promises made as part of marketing authorizations and other agreements relating to product safety or safe usage, including but not limited to safety variants.
- Being aware of risk minimization techniques and having appropriate control over the information in risk management strategies.
- Having awareness of post-authorisation safety studies requested by a competent authority including the results of such studies.
- Ensuring process of signal detection is managed in compliance with legislation in place including review of all identified signals as per the Safety Review Meetings in place.
- Ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the legal requirements and GVP.
- Ensuring the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to the competent authorities in Members States and the Agency.

- Ensuring that the process of medical information is managed in compliance with legislation in place including support of medic for any technical responses
- Ensuring that reference safety information (RSI) is available for all registered products and molecules across the entire portfolio in the form of the reference SmPC or in any other format as defined by internal processes, and that it is regularly reviewed to ensure compliance with reference products
- Ensuring a full and prompt response to any request from the competent authorities in Members States and from the Agency and any other information to the competent authorities, for the provision of additional information necessary for the benefit risk evaluation of a medicinal product.
- Providing input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals) as defined in the internal processes.
- Overview and monitor compliance for all pharmacovigilance activities on regular basis.
- Possessing a system for pharmacovigilance audits that is reviewed, approved, and fully supports inspections, including CAPAs, in order to achieve ongoing quality and compliance monitoring of the pharmacovigilance system.
- Participate in the creation and review of all SOPs/OPIs relating to Pharmacovigilance System.
- Assistance in managing PSURs, ACOs, and RMPs (in coordination with RAD) for all registered medicines, including final approval based on fully completed QC and medical assessment by designated members of the European Union Pharmacovigilance Team.
- The Qualified Person Responsible For Pharmacovigilance will oversee company and individual user registration in the EudraVigilance system and ensure that the system is properly communicated with (ICSRs, EVPRMs).
- Overview of Safety data exchange agreements/ Technical Agreements with PV Clause with any business partners followed by the final sign off.
- Oversight of pharmacovigilance training and approval of the european union pharmacovigilance training materials.

The Qualified Person Responsible For Pharmacovigilance is supported by the European Pharmacovigilance Team (hereafter referred to as European Union Pharmacovigilance), the Outsourced Pharmacovigilance Team, and local Responsible People for Pharmacovigilances (Responsible Person For Pharmacovigilances), who collaborate closely and have clearly defined Job responsibilities and duties.

According to the pharmaceutical statement that is part of the Summary of Pharmacovigilance System, the Qualified Person Responsible For Pharmacovigilance and, in their absence, the deputy of the Qualified Person Responsible For Pharmacovigilance, have enough power to affect the effectiveness and compliance of the Pharmacovigilance System.

b. <u>Local Responsible Person for Pharmacovigilance</u>

Pharmaceuticals must appoint or subcontract such responsibilities to suitably qualified individuals in accordance with local legal requirements for territories where they intend to obtain or already have an MA and where local/EMA legislation requires the presence of Local Qualified Person Responsible For Pharmacovigilance/Responsible Person For Pharmacovigilance at the national level.

Pharmacovigilance activities are carried out at the national level in accordance with the local PV criteria of the competent authorities, and local responsible persons for pharmacovigilances are qualified in both the theoretical and practical understanding of these activities. The PSMF does not retain the CV of the local responsible person for pharmacovigilances.

The relevant SOP: Duties of Responsible Person for Pharmacovigilance outlines the duties of the EU Responsible Person For Pharmacovigilances/Deputy Responsible Person For Pharmacovigilances (Responsible Person For Pharmacovigilance).

The PSMF contains information about the local responsible person for pharmacovigilances who has been designated to represent the EU countries at the national level.

This is a description of the position and duties of the local responsible person for pharmacovigilances.

- Creation, upkeep, and management of a nationwide pharmacovigilance system for pharmaceutical.
- The main point of contact for the neighborhood regulatory body and pharmaceutical, available around-the-clock.
- A backup system should be in place for the local responsible person for pharmacovigilance in the event of his or her absence.
- As and when necessary, prompt and efficient communication with local regulatory authorities for any safety-related concerns relating to pharmaceutical products.
- Act in compliance with local regulation and in accordance with Local PV Procedures when applicable.
- Keep track of pertinent safety profiles and any new safety issues in respect to the pharmaceutical's national authorizations.
- Communication regarding any safety-related issues, regulatory authority requests or actions, updates regarding national legislation/guidelines, and regulatory inspections with the Qualified Person Responsible For Pharmacovigilance/EU Pharmacovigilance.
- Keeping tabs on the marketing status, any product withdrawals (due to whatever reason), and commitments around the product. Sharing updates with the pharmaceutical industry and/or the Qualified Person Responsible For Pharmacovigilance.
- Supervision of Risk Management Plans pertinent to their specific markets. Risk minimization measures (RMMs) are reviewed (including their effectiveness and national language translations), coordinated with the relevant national authorities, and their distribution strategy is approved. The distribution plan and all associated actions must be carefully monitored and recorded in accordance with national standards.
- Oversees functioning of local Pharmacovigilance system in all relevant aspects including local SOPs, Quality Management systems, trainings, records & archival.
- Support audits and Inspections conducted for Local pharmacovigilance activities.
- Gathering locally suspected AE/ADR or potential AE/ADR reports received at the national level (such as but not limited to product complaints, medical inquiries, and

regulatory assessment reports), and sending them to European Union Pharmacovigilance and the Qualified Person Responsible For Pharmacovigilance.

- Perform follow up, if required for local product complaints, medical enquiries, case report received from national competent authority/pharmacovigilance centres, HCP or patients, which are reported to local office.
- Performing local literature screening according to EU and local requirements (if applicable).
- Co-ordinate with Local distributors (if available) for all Pharmacovigilance related activities and oversight of all safety related issue occurred at national level.
- Local administration and supervision of risk-reduction actions relating to time-sensitive safety limits and newly discovered safety problems.
- Report any modifications to local marketing authorizations and product withdrawals that might have an impact on the pharmacovigilance surveillance to the qualified person responsible for pharmacovigilance/pharmaceutical.
- Local pharmacovigilance documentation archiving
- Provide translation of any safety documents from local language to English if required.
- Notifying the European Union Pharmacovigilance of any local safety issues, concerns, or safety recalls.

5. Organisational design

Summary of the Organization

The European pharmaceutical firm has its main office in the EU and marketing authorizations in Europe.

The European Union is the system's base of operations. The European Pharmacovigilance Department, which is based in the European Union (European Union Pharmacovigilance), is in charge of overseeing the Pharmacovigilance System. This includes managing PV activities for markets where a Responsible Person For Pharmacovigilance has not been designated because it is required by law.

The local outsourced PV person, the outsourced pharmacovigilance department, as well as the quality assurance department (QA) and regulatory affairs department (RAD) situated in the EU, support the authorized EU pharmacovigilance operations as well as the outsourced PV pharmacovigilance activities.

Each nation where a European pharmaceutical business or one of its affiliates has marketing authorizations has local responsible persons for pharmacovigilance (RPPs) in place.

A common safety database is shared by the qualified person responsible for pharmacovigilance, EU pharmacovigilance, outsourced pharmacovigilance, and designated team members of RA and QA.

Sites for pharmacovigilance operations

The European Union Pharmacovigilance site houses the qualified person responsible for pharmacovigilance and their deputies, whereas the medical information, regulatory affairs, and quality assurance departments are located in a third-party nation.

Additionally, the Qualified Person Responsible For Pharmacovigilance/deputy may delegate certain pharmacovigilance activities to other departments (quality assurance, regulatory affairs), which are based in Europe, as well as to local Responsible Person For Pharmacovigilances for pharmacovigilance activities in each country where

pharmaceuticals have registered products, including (if local or EU legislation requires it), but not exclusively, the EU market.

The right service agreements are in place to guarantee that the chosen service provider will fulfill their obligations related to pharmacovigilance.

European Union-based European Pharmacovigilance Department (european union pharmacovigilance).

The European Union Pharmacovigilance team oversees the following operational pharmacovigilance aspects:

- European Union Pharmacovigilance physician, qualified person responsible for pharmacovigilance and deputy qualified person responsible for pharmacovigilance activities
- Establishing and managing the PSMF
- Setting up and overseeing the Signal Detection
- Management of aggregate reports (PBRER, ACOs, PSUR) generated by European Union Pharmavigilance, comprising overview of tracking and monitoring as managed by RAD, final medical assessment included, as well as sign off
- Tracking and monitoring of the RMPs including regular overviews of compliance of whole process of the RMPs, creation, submission and management in liaison with RAD
- Tracking and monitoring of compliance for RMMs within EEA/EU when applicable
- Overview of the Signal Detection Reports and signal detection process via participation in Safety Review Meetings, including detailed overview of the Signal Detection activity by Qualified Person Responsible For Pharmacovigilance or Deputy of Qualified Person Responsible For Pharmacovigilance
- Overview of the reference SmPC, including review as part of RAD's management duties, updating the reference SmPC and/or RSI as needed, and creating Change Request any necessary SmPC updates and adjustments.
- Safety variation overview for all products with EEA licenses, under RAD's administration
- Evaluation and approval of answers to any PV-related requests (including safety) from EEA Competent Authorities and EMA.

- Review of Response to Safety Assessment Reports from Competent Authorities, including permission from Qualified Person Responsible For Pharmacovigilance if necessary.
- The European Union's primary tool for pharmacovigilance is the management of compliance presentations and compliance meetings. Monitoring of compliance with minimal oversight of all PSMF KPIs as defined.
- Pharmacovigilance Assessments related to risk to patient safety
- Overview towards the Management of PV audits in liaison with QA team and full support of PV Inspections including CAPA covering internal audits as well as audits of third parties and service providers
- Managing the application of corrective and preventive measures (CAPAs) for the EEA in accordance with the current pharmacovigilance quality system of the European Union (with exception of local CAPA on the Responsible Person For Pharmacovigilance level)
- A summary of the Audit Schedule and the Log of Completed Audits
- Coordination and monitoring of EEA risk minimization measures, including Post-Authorization Safety Studies (PASS), when applicable.
- Regular screening of EEA and relevant authority websites for safety issues, including issuing Weekly Bulletin and informing all involved departments of European pharmaceutical company
- Outline of the QA-managed Pharmacovigilance/Service Agreements (EEA) with service providers
- Communication with the Regulatory Affairs Department (RAD) for labeling updates and medical/PV support of safety variants throughout the EU
- Overview of SDEAs with Partners as managed by QA
- Management of ICSRs processing, assessment, and reporting to the Authorities upon receipt from the Local Responsible Person For Pharmacovigilances/local nominated PV contact person (e.g., Responsible Person For Pharmacovigilances/NCP);
- Management of ICSRs processing, assessment, and reporting to the Authorities upon identification during the Global Literature Search and Local Literature Search;
- Medical review and support for medical information services

- Monitoring the official websites and sending an overview to all teams involved in the PV operation
- Preparation of EU procedures including management of the process and actual tracking of all changes, creating european union pharmacovigilance SOP Development Plan
- Review and Approval of Pharmacovigilance training on GVP Modules and european union pharmacovigilance SOPs for the PV personnel performing european union pharmacovigilance activities (regardless their location) and EU Responsible Person For Pharmacovigilances
- Management of the Summary of the Pharmacovigilance System (EEA)
- Administration of business data, including Eudravigilance's Qualified Person Responsible For Pharmacovigilance/Deputies information.
- Pharmacovigilance training for any PV staff participating in European Union Pharmacovigilance activities, including assigned tasks, and storage of training records at European Union Pharmacovigilance.
- Governance Board Committee Meeting - production of a summary report or presentation with a focus on PV compliance and PV issues, coordination, and action monitoring of regular Meetings with a minimum monthly frequency

Out-sourced Pharmacovigilance Department

The following pharmacovigilance operational aspects are managed activities by Out-sourced PV team:

- Evaluation of worldwide literature search results in accordance with service provider's search to ensure that all product benefits and risks, as well as any potential adverse drug reactions, are tracked, recorded, and/or reported in accordance with legal requirements.
- Tracking and administration of the entire signal detection process, including the compilation of the signal detection reports, quality control, and submission of the finalized reports with a list of all verified signals via Safety Review Meetings.
- As agreed upon during monthly TC meetings with european union pharmacovigilance, support for the compilation of necessary data by that organization for aggregate reports (PBRER, ACOs, and PSUR).

- Management of all monitored sources, including but not limited to EV, MLM, and EVDAS, for potential ICSRs.
- Management, assessment and tracking of Obligation reports

Local Partners/Local Pharmacovigilance Representatives

In order to fully support European Union Pharmacovigilance, the EU Responsible Person For Pharmacovigilances functionally reports to the Qualified Person Responsible For Pharmacovigilance.

The scope of the role for local people is defined in the countries/markets specific JD (as per delegated PV activities by Qualified Person Responsible For Pharmacovigilance) and can include the following activities. In addition to the pharmacovigilance activities performed by european union pharmacovigilance, certain activities are performed completely locally by the national affiliate/local Responsible Person For Pharmacovigilance.:

- ICSR collection and distribution to the European Union Pharmaceutical Vigilance team for case processing and expedited reporting
- ICSR follow-up as needed
- ICSR distribution to partners as needed
- Reconciliation of ICSRs with the European Union Pharmaceutical Vigilance and partners, where necessary
- Local medical and scientific literature screening for ICSRs and safety related issues, where applicable
- Enquiry and complaint screening to identify potential ICSRs and other safe alternatives
- Submission of RMPs as needed; PBRER and ACO/Renewal submission at the local level as needed; and a summary of safety variation submissions for SmPC and PIL for all local products
- Act as a local contact for local Pharmacovigilance Agreements with third parties as needed. Review local Pharmacovigilance legislation, local competent authority websites, and notify Qualified Person Responsible For Pharmacovigilance.

Implement local Risk Minimization Measures as necessary, including PASS in coordination with european union pharmacovigilance.

- Where necessary, keeping track of the success of the use of local risk reduction measures
- Management of local Pharmacovigilance Agreements with Licensing Partners and third parties, if not covered by QA
- Providing data for the preparation of compliance reports covering all completed european union pharmacovigilance delegated activities; notifying european union pharmacovigilance of the need for local Pharmacovigilance/Service Agreements with service providers; managing local SOPs; training any relevant local staff in pharmacovigilance and archiving training records at the local level; and providing information to support the creation of the PSMF and its supporting documents.
- Before any local pharmacovigilance operations (such as Dear Doctor letters or changes to prescribing information) are carried out, they must be coordinated with european union pharmacovigilance.
- Handling local medical information inquiries in coordination with European Union Pharmacovigilance when necessary
- Communicating with and serving as the local Pharmacovigilance contact person to competent authorities when necessary
- Ensuring support for local pharmacovigilance inspections by competent authorities and local internal audits
- Arranging translations of any safety documents from local to European Union Pharmacovigilance when necessary

Governance Management Board Committee

The Governance Board Committee has been established at EEA territory and includes the following members:

- Managing Director / Senior Management Representative of Pharmaceutical
- Qualified Person Responsible For Pharmacovigilance
- Deputy Qualified Person Responsible For Pharmacovigilance and/or European union pharmacovigilance team member

- Other Governance Management Board Committee members may also include representatives from Quality Assurance, Regulatory Affairs, selected local affiliate Responsible Person For Pharmacovigilance, and any other departments relevant to the subject matter being discussed

The Governing Board Committee's responsibility is to:

- Ensure that efficient pharmacovigilance quality and healthcare compliance systems are maintained, improved, and supported. These systems are created for timely detection, correction, and prevention activities to ensure the delivery of safe pharmaceuticals and to comply with pharmacovigilance laws, regulations, and/or Company policies and standards.
- Ensure that pharmaceuticals' senior management is well informed about the pharmacovigilance obligations, demands, and difficulties placed upon pharmaceuticals and its subsidiaries as the Marketing Authorization Holder.
- Ensure that the Qualified Person Responsible For Pharmacovigilance receives enough support in carrying out their pharmacovigilance duties.
- Verify that medications have the ability to react quickly and successfully in the mitigation of patient health risks.
- Review and approve pharmacovigilance financial operating plans including the resourcing requirements.
- Review and approve major pharmacovigilance initiatives and compliance activities, especially substantial changes in the PSMF (e.g., change of the Qualified Person Responsible For Pharmacovigilance).
- To address any serious PV non-compliances and have a clear oversight of all key CAPAs implemented or proposed.
- Ensure oversight of risk and crisis management, legal and ethical conduct with respect to pharmacovigilance matters

The Governance Board Committee meets on a regular basis, but no less frequently than once a year.

Additionally, an ad hoc meeting may be called as needed to ensure prompt and effective decision-making in the event of:

- recommendations of Safety Review Committee with regards to:

    - identified and potential serious risk to patient health,
    - significant safety issues that may necessitate regulatory actions, such as product recall or withdrawal.
- major non-routine pharmacovigilance activities

A brief summary is presented below of the activities related to pharmacovigilance as performed by other departments.

6. Medical Information

European Union Pharmacovigilance is responsible for creating and managing medical information, with assistance from local Responsible Person For Pharmacovigilances within the EU in some markets. Members of the PV team's specialized teams manage complicated support for medical information for their specific markets. A designated phone line has been set up and is run by the PV team with frequent testing. The PV team answers any medical inquiries through this line, keeping track of all questions received, spotting potential ADRs, and sending product complaints to the QA team for further handling. The PV team should make sure that any medical inquiries that are addressed and handled.

In order to react to medical inquiries, product information is used (approved SmPC, PIL), or if more assistance is needed, a designated physician is consulted. Any identified ADRs are processed by PV team.

7. Regulatory Affairs Department (RAD)

Regulatory Affairs (RAD) covering the following activities:

- Regular maintenance and updates to PV of product data pertaining to the actual submission, approval, and implementation for product licenses, renewals, variations (including safety variants), and changes to product labeling; Patient Information Leaflets and a Summary of Product Characteristics (using Reference SmPC as the primary source of safety data, with PV team management as part of the Signal Detection Process).
- Making sure that any update of the SmPC and PIL for marketed products will be carried out through the submission and implementation of the safety variation as discovered by PV team via Weekly Search or from Signal Detection procedure and/or frequent update of the SmPC with chosen reference SmPC /RSI.
- Inform PV of any enquiries received from Competent Authorities or EMA relating to safety information as well as regulatory actions
- Responding to Competent Authority/EMA requests, as appropriate, in close liaison with PV, Qualified Person Responsible For Pharmacovigilance/Deputy Qualified Person Responsible For Pharmacovigilance
- Preparation, submission and tracking of safety variations.
- Submission and tracking of submission of the Aggregate reports (PBRER/PSUR, ACOs) as required for EEA
- Submission of RMPs
- Preparation of summarised information on delegated PV activities for Compliance Report and participation on TC meetings where reconciliation with PV is being conducted
- Support to European and local PV with regard to registration status of whole product portfolio and provide notification of new approvals and withdrawals
- Population and maintenance of the Article 57 Database including monitoring of compliance
- Provide relevant regulatory information for PBRERs, RMPs and ACOs
- Submission (after review and approval from Qualified Person Responsible For Pharmacovigilance/Deputy Qualified Person Responsible For Pharmacovigilance) of the Summary of Pharmacovigilance System

Provision of information to support the production and maintenance of the PSMF

8. Quality Assurance Department (QA)

Involvement in matters relating to product quality that could or might not result in an ICSR. Any AE/ADR connected to a complaint or quality flaw must be forwarded to QA for processing by the local responsible person for pharmacovigilance. QA conducts a review to guarantee that all ICSRs have been recorded and sent to european union pharmacovigilance.

Investigation of quality complaints is under the purview of quality assurance (QA). In the event that an accompanying ICSR is received, the complaint will first be registered on the local system before being directed to QA for data input and the QA department for inquiry.

All product recalls are handled locally with the help of contract manufacturers and/or Quality Assurance (QA), who communicate with the quality assurance team at the manufacturing site.

According to national and European recall processes, the Qualified Person Responsible For Pharmacovigilance/deputy and european union pharmacovigilance will be notified if a product recall is connected to any safety issue.

The following are additional delegated European Union Pharmaceutical Vigilance initiatives sponsored by the Quality Assurance Department:

- Management of the QMS for market and all relevant activities performed for market
- Management of audits and Inspections including CAPA covering internal audits as well as audits of third parties and service providers.
- Overview of the implementation of corrective and preventative actions (CAPAs) for EEA
- Maintenance and planning of the Audit schedule and completed audits log in liaison with european union pharmacovigilance
- Management of Pharmacovigilance/Service Agreements with service providers (EEA)
- Management of all product complaints including review for potential ADRs

- Quality review of SDEAs by european union pharmacovigilance including management and tracking, actual approval of the SDEAs/TA with PV clause, sign off by Qualified Person Responsible For Pharmacovigilance/Deputies
- Monitoring and tracking of safety variation implementation as per data collected from BRS
- Support and execution for PV training of the local affiliates in liaison with european union pharmacovigilance.
- Preparation of local procedures for delegated european union pharmacovigilance activities

9. Safety Data Exchange Agreements (SDEAs)

SDEAs or Technical Agreements with PV Clause are prepared between the pharmaceutical and their partners at time of business contract between them, but prior to the product being placed on the market. the sdea details the responsibilities of the partner for maintaining a local tracking database/sheet to record incoming medical inquiries and ae/adrs, which must be forwarded to the pharmaceutical as per timeline agreed in sdea.

The following types of sdeas/tas with pv clause are prepared based on relationship type with pharmaceutical/distributor partner as:

Pharmaceutical and licensing partner; pharmaceutical and own label distributor; pharmaceutical and manufacturer.

Licensing Partner Type:

SDEAs with the license partners holding a MA in one or more territories for DCP/MRP licenses where the pharmaceutical is the license holder in Reference member state or Concern member states, is prepared according to the Pharmacovigilance responsibilities.

Own label distributor:

When pharmaceutical partner is a distributor, who sells/distributes pharmaceutical products on their behalf/own label, pharmaceutical and own label distributor sdea with pharmaceutical partner is prepared, which describes the Pharmacovigilance responsibilities.

Manufacturer Type:

When pharmaceutical partner is the manufacturer (contract manufacturing organization (cmo)) who provides/will provide finished products to pharmaceutical - BRS, TA with PV Clause is prepared, which describes key Pharmacovigilance responsibilities.

Management of the SDEA and TA is responsibility of the Quality Assurance team including partners assessment and evaluation as well as reconciliation with partners. Designated document shows all Safety Data Exchange Agreements between companies and their partners.

Outsourced Activities

Nominated external persons contracted as local Responsible Person For Pharmacovigilances, are included here.

All service providers are being monitored and are audited regularly as required. The periodicity of the audit schedule is decided based on the PV risk assessment and following 2 – 5 years periodicity, unless immediate PV audit is required.

a. <u>Sources of Safety Data</u>

ICSRs are received (locally and globally) from the following sources:

- Spontaneous reports
    - Healthcare professionals
    - Consumers
    - Consumer representatives
- International and local medical and scientific literature
- Competent Authorities/EMA/Eudravigilance (including MLM service)
- Studies
    - Clinical trials (BA/BE)
    - Post Authorisation Safety Studies (PASS)
    - Post Authorisation Efficacy Studies (PAES)
    - Patient support programs
    - Registries
    - Non-interventional studies
- Media

These can be received into company via the following routes:

- European Pharmacovigilance Department (european union pharmacovigilance)
- Local Responsible Person For Pharmacovigilance

- Medical Information
- Quality Assurance (product technical complaints, covered by QA at manufacturing sites, and QA teams within Local Responsible Person For Pharmacovigilance)
- Commercial personnel (Sales and marketing)
- Licence partners
    - Distributors
    - Manufacturers
    - Joint procedures
- Service providers
- General staff

A brief description of the different sources is given below.

b. <u>Impromptu Reports</u>

Medical Information (directly from the european union pharmacovigilance Medical Information team or by the local Responsible Person For Pharmacovigilance), Manufacturing site Quality Assurance, sales representatives, general staff, and from partners are the sources of ICSRs from healthcare professionals and consumers. If the responsible person for pharmacovigilance does not receive the reports directly, they are sent to the local responsible person for pharmacovigilance for local follow-up before being sent to European Union Pharmacovigilance for processing. ICSRs are sent directly to European Union Pharmacovigilance for processing after being received by service providers serving as Responsible Person for Pharmacovigilances. European Union Pharmavigilance manages the ICSRs tracker.

c. <u>International and National Literature</u>

The results of the search are provided to the designated staff of the Outsourced pharmacovigilance on a weekly basis, who are monitoring the safety information for the entire product portfolio. The service provider searches the global literature on a weekly basis via designated sites/databases/sources (covering also MLM search). Full text articles are

ordered as needed, then analyzed by designated staff members for outsourced pharmacovigilance.

The ICSRs obtained from literature must be regularly reconciled by an outsourced pharmacovigilance team. The reconciliation is documented, the Qualified Person Responsible For Pharmacovigilance is in charge, and this process' quality control is handled by european union pharmacovigilance.

As mutually agreed upon with the qualified person responsible for pharmacovigilance, european union pharmacovigilance, and Outsourced pharmacovigilance based on publications dates and frequency of publications, relevant local literature would be screened by the responsible Responsible Person For Pharmacovigilances/Local service providers (if required by local legislation), and forwarded to Outsourced pharmacovigilance for assessment and processing. European Union Pharmavigilance is in charge of reporting any ICSRs produced by literature.

d. <u>Competent Authorities</u>

Local Responsible Person For Pharmacovigilances or european union pharmacovigilance can monitor the local authority databases or receive competent authority reports by post, email, or other means. for processing on the eudravigilance, these are sent to european union pharmacovigilance.

European authority reports can be obtained through outsourced pharmacovigilance by monitoring the authority databases. the european union pharmacovigilance and/or the qualified person responsible for pharmacovigilance/deputy oversee the processing and tracking of these in the competent authorities case tracker (obligation report safety tracker), as well as the assessment and monitoring of these during the signal detection process.

Outsourced pharmacovigilance is responsible for managing cases that pharmaceutical gets directly from authorities via eudravigilance.

e. Computerised Systems and Databases

Computerized Systems & Databases

Hard copies:

The ICSRs are collated and the database (Excel) maintained by the designated personnel of the european union pharmacovigilance, QCed by the designated PV Physician. The source documents are stored in a fire-resistant locked cabinet (when applicable) as well as archived as electronic copies.

The electronic archive is located on Cloud-station where the data is shared with Qualified Person Responsible For Pharmacovigilance/deputy, Out-sourced pharmacovigilance and european union pharmacovigilance mi team.

Electronic copies:

Companies use a Microsoft Excel and Word software packages for our adverse event queries, product complaints and regulatory affairs data, all electronic copies are archived on share drive of the companies.

Microsoft Word and Excel as Part of Microsoft Office.

f. EudraVigilance

The pharmaceuticals comply with internationally agreed standards for electronic submissions of ICSRs via EVWEB to the EudraVigilance database.

All pharmaceuticals are in production with the EMA as required.

10. Pharmacovigilance Processes

The pharmaceutical company's quality management system is made up of a number of procedural documents, including SOPs and OPIs for all crucial pharmacovigilance procedures. ICSR management, literature searches, change control, signal detection, medical information, management of reference safety information and reference SmPC, safety data exchange agreements, safety data archiving, pharmacovigilance auditing, compliance monitoring and quality control, pharmacovigilance training, safety variation, and other processes are included in the pharmacovigilance processes.

This quality management system includes SOPs for activities linked to product recall, audits, SOP creation, risk assessment, and local training, among other pharmaceutical-specific processes.

Support of Governance board will be required to ensure adequate funds and resource available for Pharmacovigilance activity.

Description of processes

Risk management system(s) and monitoring of the outcome of risk minimisation measures

At the time of all new marketing authorization applications or as per regulatory authority request, Risk management plan is prepared as per the applicable current RMP templates and submitted it as a separate part of the scientific dossier of a product. If RMP is required by national authorities outside of the EU territory, the template defined by national legislation will be followed (e.g., the Out-Sourced market).

11. RMP Preparation Procedure:

When an RMP is necessary for a new application, renewal, or update to an existing RMP, as applicable, or if necessary at the request of the agency or national competent authority, or each time a PASS is performed or a new signal for the molecule is detected, the Regulatory Department notifies European Union Pharmacovigilance.

If an RMP is required, a designated individual within the European Union Pharmacovigilance, delegated medically, will prepare the report. The RMP is subject to a quality review for scientific content by qualified European Union pharmacovigilance specialists, who also verify that all safety hazards are effectively addressed. The European Union Pharmacovigilance evaluates any additional risk minimization measures that are not covered by the regular pharmacovigilance activities, and the Qualified Person Responsible For Pharmacovigilance or Deputy Qualified Person Responsible For Pharmacovigilance approves the evaluations. Both the Qualified Person Responsible For Pharmacovigilance and the Deputy of Qualified Person Responsible For Pharmacovigilance can also be responsible for medical assessment, as doctors (European Union Pharmacovigilance Physician). European Union Pharmacovigilance oversees the monitoring of risk mitigation strategies using an RMM tracker if required.

The designated reviewer, medically competent staff from the European Union pharmacovigilance team, shall conduct a quality evaluation of the RMP to verify data quality and integrity. The results shall be notified to the author for any necessary adjustments. Unless otherwise specified by the delegation from the qualified person responsible for pharmacovigilance to the European Union Pharmacovigilance Physician itself, the author shall submit the draft document to the qualified person responsible for pharmacovigilance or the deputy qualified person responsible for pharmacovigilance (both of whom are medically qualified) for final review and approval.

The process of the quality, accuracy, and scientific integrity of RMP will be supervised by a qualified person responsible for pharmacovigilance or a deputy qualified person responsible for pharmacovigilance. The final RMP must be duly signed by the qualified person responsible for pharmacovigilance, the deputy qualified person responsible for pharmacovigilance, or other designated medically qualified pharmacovigilance personnel in the European Union, and it must be sent to the regulatory affairs department (RAD) for submission to the national competent authority. Any new RMP submission or

clearance must be reported to the European Union Pharmacovigilance by RAD within the designated timeframes. Information pertaining to the submission of the RMP and its approval must be gathered by European Union Pharmacovigilance and recorded in the relevant RMP tracker.

The pharmaceutical should maintain records of when RMPs were submitted to National Competent Authority and the significant changes between each version of the RMP. Compliance of all RMP submissions will be managed by european union pharmacovigilance team as well as part of the monthly compliance meetings.

Upon the RAD notification of approval of the RMP(s), prepared by european union pharmacovigilance, the Summary of Safety Concerns are submitted to the CMDh as described.

In close coordination with the local Responsible Person For Pharmacovigilance (if appointed; otherwise, directly to be managed by Qualified Person Responsible For Pharmacovigilance/deputy or designated European Union pharmacovigilance member), and in accordance with the regulations, implementation of RMMs (when required) will be carried out as per specified timelines agreed in RMP and recorded in the RMM Distribution Plan.

The agreed-upon Distribution Plan of RMM, which includes a detailed distribution method and the date when the educational material and DHPC will be implemented, must be followed by the RAD and the Responsible Person For Pharmacovigilances/designated member of the European Union Pharmacovigilance Team.

The intricate RMM implementation will be meticulously documented and followed by the European Union Pharmacovigilance in accordance with the relevant Safety Review Meetings.

Any requirement for RMM will be reviewed at monthly compliance meetings and conveyed by the European Union Pharmacovigilance Team to all involved local PV team members, including the Responsible Person For Pharmacovigilances/Local PV Contact Person.

European Union Pharmacovigilance will monitor the real RMM's commitment execution, ensuring that the activities' results are appropriately appraised and that, where needed, changes to the RMM's documentation are implemented promptly and precisely.

Pharmacovigilance within the European Union must make sure that any violations of RMPs, RMMs, or safety communications are addressed with corrective and preventive measures. The Qualified Person Responsible For Pharmacovigilance and/or deputy regularly evaluate PV CAPAs.

a. <u>Signal generation, detection and evaluation</u>

By continuously monitoring the safety profiles, the signal management activity identifies any new safety signals and assesses the benefit-risk balance of pharmaceutical products, determining the necessary actions to be taken in response.

The task of performing the Signal Detection process has been assigned to an outsourced team, who is also responsible for producing the Signal Detection report, ensuring the SDR's quality, and maintaining the Signal detection Calendar. The production of the pertinent presentation of the evaluated SDR data and any other pertinent material, as well as participation in the Safety Review meetings, are also the responsibility of Out-Sourced.

The Qualified Person Responsible For Pharmacovigilance/deputy and the Designated Member of the European Union for Pharmacovigilance should be aware of the procedure, any discovered and validated signals, and process compliance.

Timelines for Signal management activity

All active compounds for which the aforementioned medications possess MAs shall undergo routine signal detection and evaluation.

Signal management schedule

The designated individual in outsourced creates the schedule for signal management (SMC). Version control will be used. The schedule must take into account the risk of the product in question, the PBRER/PSUR timeline as per the EURD list, the length of time the product has been on the market, ongoing safety concerns, the product's known safety profile, and any additional risks that may be present. Regular schedule revision will take place within agreed-upon internal parameters based on the risk assessment completed for each molecule, with periodicity ranging from 6 months (for products with active RMM in place and under additional monitoring) to 12 months for marketed and non-marketed products, respectively.

All goods will be subject to a signal detection schedule/tracker that will be given to the European Union pharmacovigilance team for final assessment and agreed upon with the Qualified Person Responsible For Pharmacovigilance/deputy.

Signal Management Process

Signal detection, signal validation, evaluation and analysis, prioritization, and coordination with pharmaceuticals are all parts of the signal management process that must be completed before regulatory authorities are notified in writing (if any emergent safety issue results from the activity or if the benefit-risk balance of the products changes). On demand, additional information will be given to the regulatory authorities and will be outsourced. With oversight from the european union pharmacovigilance and the Qualified Person Responsible For Pharmacovigilance, the management of the tracking of the actions taken and any recommendations made is also outsourced.

The medical reviewer will carry out qualitative signal detection while taking into account all potential sources of safety data for review and assessment in the signal management process. This work will be done by designated staff from an outside source.

A possible signal must be verified for clinical utility and prior knowledge after being identified. If the observed potential signal is not confirmed, has not been disproved, and merits continued examination, it will be continuously and closely monitored. The possible signal will be analysed, given a priority, and evaluated for potential follow-up actions if it is validated.

Major criteria used in determining the priority of a potential signal for evaluation include seriousness, the impact on patients and public health, including use in special populations, the strength and consistency of the evidence supporting an association, increased frequency or severity of a known adverse effect, and expectedness. Also, the effectiveness of the medication will be evaluated in terms of how it affects the targeted disease based on the seriousness, chronicity, and degree of the disease's control. Evaluation of a validated signal will be carried out in order to determine the impact on the product's benefit-risk balance.

A validated signal's priority should be discussed with the pharmaceutical company so that everyone can agree on any necessary measures to be made within the specified time

frames. Pharmacists or other qualified individuals in charge of pharmacovigilance must notify the appropriate authorities of any urgent safety issue, provide all necessary supporting documentation, and suggest appropriate actions and timelines.

During the safety review meeting, the Qualified Person Responsible For Pharmacovigilance will examine the validated signals from the finalised SDR. In the event that the product's risk-benefit ratio changes, the Qualified Person Responsible For Pharmacovigilance will advise pharmaceutical of the best course of action (e.g., Risk minimization activities such as changes to labelling, enhanced follow-up, institution of RMP etc.). The "Signal detection tracker" is used to keep track of all the detection and validation phases as well as the actions done.

After the safety review committee has identified and assessed a potential or real crisis situation, a subsequent crisis management meeting (containing of the Governance Board and the Qualified Person Responsible for Pharmacovigilance) shall be scheduled, ideally within one working day. This meeting's/primary TC's duty would be to decide and offer suggestions on the safety issue. A pharmaceutical product's benefit-risk balance may alter at any time, and Regulatory Authorities will be notified right away. Action proposals will be made, together with any necessary adjustments, in coordination with RAD, who will be in charge of submission.

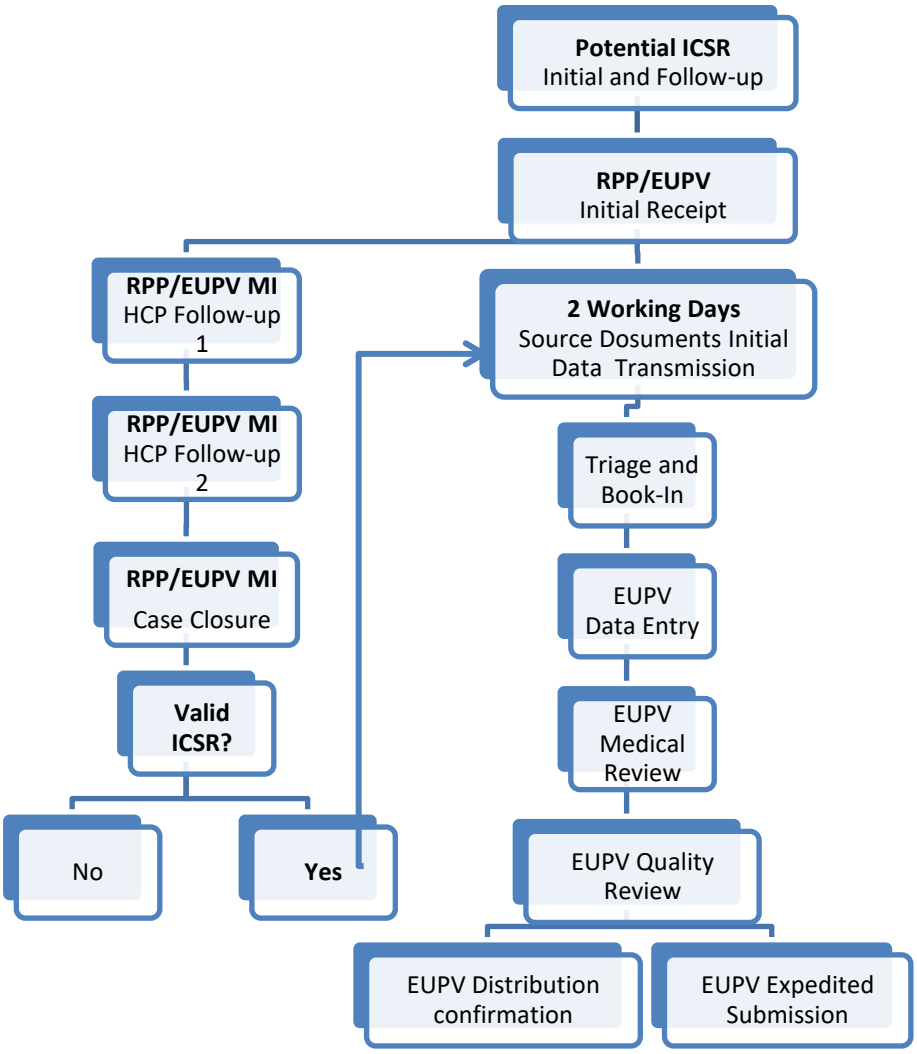
The pharmaceutical Regulatory Affairs, affiliate offices, or commercial partners will communicate with the competent authorities on their behalf as necessary (as appropriate). Pharmaceutical will inform healthcare professionals, patients, or the general public after receiving regulatory approval regarding the change in benefit risk of the product as agreed and approved by the Competent Authority (including but not limited to: Direct Healthcare Professional Communications - DHPC, patient alert safety cards, educational materials, press releases, any electronic and/or media awareness). The pharmaceutical industry is required to inform all distributors and licencing partners. Pharmaceutical will archive all regulatory notifications, direct discussions with healthcare professionals, and public communications.

b. ICSR data gathering, aggregation, monitoring, evaluation, and reporting

Collection and processing of ICSRs

Medical Information (gathered by the local responsible person for pharmacovigilances and/or the European Union pharmacovigilance MI team), the Quality Assurance Department (QA), the Commercial Team, and general personnel as well as anyone who is exposed to receive any communication which may contain any potential ADR/AE in relation to pharmaceuticals' products are where ICSRs from healthcare professionals and consumers are received. The local responsible person for pharmacovigilance and/or the European Union Pharmacovigilance are receiving these reports for processing and follow-up. According to specific agreements, ICSRs received from partners are either sent to the regional responsible person for pharmacovigilances or to the European Union pharmacovigilance.

The Responsible Person For Pharmacovigilance forwards all ICSRs to the European Union Pharmacovigilance for processing, evaluation, and reporting. If not excluded, European Union Pharmacovigilance is in charge of keeping track of and reporting on cases, and it gives all necessary details, such as the ADR number allocated, to the Responsible Person For Pharmacovigilances (if applicable). The ICSRs processing is reflected in the below flow-chart:



Pharmacovigilance of the European Union and Out-Sourced oversee the procedure for the identification of ICSRs from international literature, and it is outlined in the pharmacovigilance.

The Responsible Person For Pharmacovigilances oversees the procedure for the identification of ICSRs from local literature, which is detailed in local pharmacovigilance SOPs (if local SOPs are in place). The firm safety case management workflow is used to continuously check the ICSR processing system's compliance, and pharmacovigilance for the European Union also regularly creates a compliance report.

As reporting of the ICSRs is the responsibility of the European Union Pharmacovigilance for all markets, it is responsible for reconciling local instances, local and global literature obtained from local affiliates, and global literature.

1) ICSRs received as Medical Enquiries

Medical, pharmaceutical, and technical inquiries, including AEs and ADRs, can be received, handled, and archived using the protocols in place.

A designated member of the european union pharmacovigilance team evaluates and keeps track of medical inquiries received by pharmaceutical, pharmaceutical local Responsible Person For Pharmacovigilances, and/or pharmaceutical european union pharmacovigilance MI team. Every medical enquiry is tracked.

A qualified, competent, and delegated individual responds to all medical inquiries using product labelling, literature searches, and available source papers. If the answer to a medical question is to be based on the product label and no assessment by a medical reviewer is required, then it can be given by trained employees in accordance with the information on the product that has been approved.

Every correspondence pertaining to the medical investigation is archived in hard copy, electronic copy, and/or electronic tracking sheet formats.

When adverse events or adverse drug reactions are discovered through medical inquiries, they are treated as potential ICSRs. At least two follow-up attempts must be made (depending on the category of the ICSRs and the completeness of the data), in order to obtain more information about the case and, if necessary, obtain a medical opinion confirming the validity of the potential ICSRs.

2) ICSRs received from Regulatory Authorities

The EMA sends out ICSRs via EudraVigilance, including but not limited to:

- Receiving ICSRs from the database of competent authorities (in RTF, CIOMS, and XML format).

The chosen individual downloads ICSRs from the EudraVigilance database's EVWEB (or any local ICSR gateway).

12. PBRERs/PSUR

For all EU/EEA and outsourced permitted products, European Union Pharmacovigilance, in collaboration with RAD, is in charge of scheduling and preparing PBRERs and ACOs based on information that has been mutually confirmed.

European Union Pharmacovigilance creates PBRER/PSURs, which are then examined and authorised by the Qualified Person Responsible For Pharmacovigilance. The European Union Pharmacovigilance Physician conducts the medical review. When the PBRER/PSUR repository (EMA in the case of the EU and MHRA PBRER/PSUR repository in the case of outsourced permitted products) has received the final, signed copy within the specified timeframes, it is the responsibility of RAD to seek confirmation of submission. The Qualified Person Responsible For Pharmacovigilance and European Union Pharmacovigilance shall receive confirmation of submission from RAD together with any assessment and probable LoDs/RFIs generated by the authorities. Based on data from the RAD, the European Union Pharmacovigilance is responsible for tracking PBRER/PSUR submissions.

The procedure for producing, monitoring, managing, and controlling PBRERs/PSUR.

The Qualified Person Responsible For Pharmacovigilance is in charge of monitoring the PBRERs/PSUR and ACO schedule tracker, which is run by the European Union Pharmacovigilance with assistance from RAD in accordance with information on submission, for the planned PBRER/PSUR submission schedule, actual submission dates, and actual compliance.

The Qualified Person Responsible For Pharmacovigilance receives assessment reports from responsible authorities, is advised of discrepancies in PBRER/PSUR filings, and evaluates the authorities' responses.

Any non-compliance with the submission of PBRERs/PSURs and ACOs and any CAPA initiated for such non-compliance are reported to and preserved to the Qualified Person Responsible For Pharmacovigilance.

In order to ensure the compliance with the provided data for the given report, the Quality Review for ACO/PSUR should be carried out by a member of the European Union

Pharmacovigilance or by a Qualified Person Responsible For Pharmacovigilance/Deputy Qualified Person Responsible For Pharmacovigilance in parallel with the medical review.

Safety Issues

The European Union Pharmacovigilance receives any safety issues reported by the company or through a responsible body for management, tracking, and overview by the Qualified Person Responsible For Pharmacovigilance. During the monthly or ad hoc Safety Review Meetings, where required actions are agreed upon, including assessment and evaluation of necessity of safety variations, the Safety Review Committee evaluates the safety issues identified from various sources, such as regular pharmacovigilance monitoring, signal detection activities, and safety issues raised by the authorities.

Moreover, PBRERs/PSURs and RMPs record and evaluate safety-related complaints.

The Qualified Person Responsible For Pharmacovigilance (or her designate in her absence) serves as chair of the Safety Review Committee, which has complete authority over all safety requests made by competent authorities. European Union Pharmacovigilance makes ensuring that requests are completely addressed quickly and that any pledges made to the appropriate authorities are followed up on. All safety notifications to authorities must first have clearance from the Safety Review Committee; if an urgent communication is needed, the approval of the Qualified Person Responsible For Pharmacovigilance/deputy is crucial.

Following approval by the Qualified Person Responsible For Pharmacovigilance, newly discovered safety issues that may affect the risk-benefit ratio of a marketed product are immediately reported to the appropriate authorities in Member States of the EU, as well as to EMA and MHRA for outsourced territory.

The duties of the Qualified Person Responsible For Pharmacovigilance, the European Union Pharmacovigilance, and the local Responsible Person For Pharmacovigilances with relation to the review, management, and implementation of RMPs and RMMs.

Any direct communications between healthcare providers and patients are created by the European Union Pharmacovigilance and approved by Competent Authorities, the Safety Review Committee, the Qualified Person Responsible For Pharmacovigilance/Deputy Qualified Person Responsible For Pharmacovigilance, and the Qualified Person Responsible

For Pharmacovigilance. The European Union Pharmacovigilance and RAD have approved the risk communication plan. The local affiliates receive the approved communication materials and suggested action plan for submission to their regional Competent Authorities for approval prior to dissemination. The local execution of risk minimization measures, as well as monitoring of efficacy at the local level, are both the responsibility of the responsible person for pharmacovigilances.

Safety Variations

With the assistance of European Union Pharmacovigilance, wherein European Union Pharmacovigilance and the Qualified Person Responsible For Pharmacovigilance/Deputy of Qualified Person Responsible For Pharmacovigilance are maintaining an overview of the procedure and compliance, Safety Variations within the EU and Outsourced Territory are Fully Managed by the RAD. The local Responsible Person For Pharmacovigilance, or RAD, is in charge of preparation, submission, and coordination with the appropriate authorities to get approval. They are also in charge of keeping track of the entire process. According to data provided by RAD, European Union Pharmacovigilance is in charge of conducting periodic reviews of this process's compliance and actual execution. the management and use of safety variation.

The Quality Assurance team manages the information regarding the actual implementation of the change of patient information artwork using the tracking sheet for Change Control, which is overseen by the Qualified Person Responsible For Pharmacovigilance.

European Union Pharmacovigilance notifies QA, RAD, and/or Responsible Person For Pharmacovigilances (where necessary) of safety variance updates discovered by routine PV activities for EU and outsourced goods. European Union Pharmacovigilance regularly screens and monitors a number of global and EU Competent Authorities (such as EMA, MHRA, HMA, and WHO) to spot any emerging safety issues. This covers all safety concerns or suggestions made by competent authorities, such as PRAC recommendations, CHMP referral procedures such as article 30 and article 31 referrals, and paediatric work sharing procedures (Art. 45 or Art. 46).

Weekly PV Bulletins containing written reports about safety monitoring are distributed to all key stakeholders, including but not limited to the Qualified Person Responsible For Pharmacovigilance, the Deputy of the Qualified Person Responsible For Pharmacovigilance, RAD, QA, and, if necessary, specific members of the Governance Board. All identified necessary safety variations should be followed up with by European Union Pharmacovigilance, and RAD should also advise them if any requests for safety variations have been made directly to them by EU or external Competent Authorities.

European Union Pharmacovigilance tracks all requests resulting from Weekly Authority Search (e.g., EMA website, MHRA official website, HMA-CMDh website) and direct communications (Authority Requests) in a Competent Authority request tracker. Additionally, all safety variations are recorded and tracked in a Safety Variation tracker, and frequently monitored by European Union Pharmacovigilance to ensure compliance.

As necessary by their respective national competent authorities, the Responsible Person For Pharmacovigilances must advise RAD and the European Union Pharmacovigilance of country-specific safety variations. European Union Pharmacovigilance completes the Compliance Report's reconciliation of all variations.

All safety variants are prepared, presented, and carried out by RAD as necessary within the time frames established by local legislation.

European Union Pharmacovigilance regularly monitors safety variation compliance within the EU and in outsourced settings based on data from RAD, and regularly updates the Qualified Person Responsible For Pharmacovigilance/deputy. The list of safety variations that were prepared, followed up on, submitted, and implemented (such as artwork for PILs, cartons) in the previous month is provided to european union pharmacovigilance on a monthly basis by RAD and the Responsible Person For Pharmacovigilances (if such activity has been delegated to them). RAD oversees and carries out the actual process of amending the Product Information Leaflet (PIL) and SmPC in compliance. The required deadlines are compared to those established by the regional responsible body. The monthly compliance report will keep track of compliance with the safety variation submission under the supervision of the Qualified Person Responsible For Pharmacovigilance/deputy.

Reference SmPC, which is managed by European Union Pharmacovigilance in collaboration with RAD, is the source of Reference Safety Information - Core Safety information for the product. RAD makes sure that European Union Pharmacovigilance has

the most recent information on reference SmPC - product for the entire product portfolio. Using a process of routine SmPC comparison between reference SmPC and current SmPC as part of the signal detection process and in accordance with the Signal Management Calendar, European Union Pharmacovigilance will ensure that all SmPC and RSI/CSI of the product are in accordance with the most recent approved safety information.

For every identified change of the SmPC for marketed goods, the European Union Pharmacovigilance team will produce a Change Request and submit it to QA for further processing together with updated product information.

RAD is in charge of making sure that any requested safety variants are produced, submitted, and approved on schedule. RAD is also in charge of communicating submission information and any LoD or RFI from Authorities to the pharmacovigilance team of the European Union.

Prior to the launch of the product in the market, SmPC must be updated in accordance with all updates identified from SmPC Comparison for non-marketed products (unless the update is required by the Authorities, in which case it is incorporated regardless of whether the product is in the market or not). RAD and/or QA will make sure that this update is started prior to launch by performing a product information gap analysis with adopted brand-leaders and taking into consideration the latest version.

The QA team is in charge of managing the implementation of the safety variant, and it regularly updates the pharmacovigilance team of the European Union.

The qualified person responsible for pharmacovigilance/deputy and european union pharmacovigilance will identify any non-compliance issues in the submission and implementation of safety variations (as per provided data from QA/RAD) in the compliance review meetings, and appropriate CAPAs will be implemented in accordance.

a. Safety Data Exchange Agreements (SDEA)

Commercial and safety/technical agreements, such as the Technical Agreement (TA) with PV Clause or the Safety Data Exchange Agreement, outline the roles and obligations of pharmaceuticals and their partners in licencing as well as manufacture and distribution (SDEA).

Pharmacovigilance Agreements provide a description of the steps involved in creating and managing SDEAs (including SDEAs).

Following any non-compliance noted for any PV partner by the QA team, regular PV risk assessments are carried out for all PV partners as per the established timetable (authorised by Qualified Person Responsible For Pharmacovigilance) and initiated by risk-based questionnaires. PV Risk assessment is done using a questionnaire, and if necessary, a PV audit that requires approval from a qualified person in charge of pharmacovigilance before being shared with the partner might result in a full analysis of the PV partners' system.

In the SDEA Tracker, SDEAs and TA with PV Clause are tracked, along with partners' PV Risk assessments.

The strategic PV audit schedule, which is constantly updated by QA and approved by a qualified person responsible for pharmacovigilance, includes a regular timetable for the PV partners audit.

Each and every SDEA and TA with a PV clause covers the EU and is outsourced. With supervision and approval from the qualified person responsible for pharmacovigilance and the deputy qualified person responsible for pharmacovigilance, they are monitored and tracked by QA.

Pharmacovigilance System Performance (KPI)

To provide the necessary oversight of the performance of the system's primary outputs, a set of performance indicators for tracking key pharmacovigilance system activities has been put in place. These basic KPIs will also be reviewed through monthly compliance meetings. All PV KPIs have a target compliance level of 100%, and the action compliance level is 95% or less.

Also, each active Responsible Person For Pharmacovigilance, Qualified Person Responsible For Pharmacovigilance/Deputy, and European Union Pharmacovigilance continuously and frequently check internal compliance with established evaluation protocols. The local pharmacovigilance responsible person creates a Compliance Report/Form and regularly sends it to the European Union Pharmacovigilance. Depending on the scope of responsibilities, the Compliance Report/Form can be prepared and provided to the European Union pharmacovigilance team on a quarterly or up to (maximum of) annual

basis in territories where pharmaceutical has products on the market, as opposed to territories where products are not placed on the market.

In order to give the Qualified Person Responsible For Pharmacovigilance/deputy a thorough and complete overview of all pharmacovigilance actions, European Union Pharmacovigilance is in charge of creating a consolidated monthly compliance report.

Regular Monthly Compliance and Safety Review Meetings via TCs are held by the European Union Pharmacovigilance Team with the participation of the Qualified Person Responsible For Pharmacovigilance and/or deputy Qualified Person Responsible For Pharmacovigilance to review and discuss all actively performed local pharmacovigilance functions, compliance monitoring, and/or any identified safety issues with all concerned parties, including but not limited (as per requirement), to QA, RAD and out-sourced team.

ICSRs - Expedited Reporting

For ICSRs eligible for expedited reporting, the date of initial receipt and reporting date are tracked. It is determined how many days there are. Every late submission necessitates the completion of a deviation report.

The Qualified Person Responsible For Pharmacovigilance oversees the summary, which includes the number of expedited reports and the number of late reports, and reviews the process compliance on a monthly basis. The Qualified Person Responsible For Pharmacovigilance/Deputy Qualified Person Responsible For Pharmacovigilance oversees the management of CAPAs on behalf of the European Union. Action threshold for compliance is 95% or below.

A sample of ICSRs that qualify for expedited reporting and those that do not is examined by european union pharmacovigilance to determine whether the proper determination has been made if the processing and reporting of ICSRs is not handled by the qualified person responsible for pharmacovigilance or their deputy.

13. PBRERs and ACOs

The European Union Pharmacovigilance or Qualified Person Responsible For Pharmacovigilance/Deputy regularly monitors compliance with PBRERs and ACOs submissions, as well as through compliance reports.

Deviation and CAPA will be created by the European Union Pharmacovigilance for any late PBRER filings, and will be approved by the Qualified Person Responsible For Pharmacovigilance/deputy. The Qualified Person Responsible For Pharmacovigilance evaluates the performance. Action threshold for compliance is 100% or below.

Safety Variations

The qualified person responsible for pharmacovigilance/deputy or european union pharmacovigilance reviews and approves (if necessary) the safety variations that need to be submitted. RAD assists pharmacovigilance in this process. QA oversees the tracking of the actual implementation with the assistance of RAD. The actual creation of the safety variant is based on data obtained from either external sources or the pharmacovigilance of the European Union.

- Competent Authority requests for safety variation filing as received by the local responsible person for pharmacovigilance, the European Union responsible person for pharmacovigilance, the qualified person responsible for pharmacovigilance/deputy, etc.
- The results of referrals
- Signal management operations
- PBRER/PSUR Evaluation reports
- Frequent reviews of websites run by Competent Authorities.
- PRAC suggestions and/or CMDh judgements

A CAPA will be created by the European Union Pharmacovigilance for any late submissions, and it will be approved by the Qualified Person Responsible For Pharmacovigilance/deputy. The Qualified Person Responsible For Pharmacovigilance/Deputy evaluates the performance.

a. Risk Management Plan Commitments

The European Union Pharmacovigilance is responsible for monitoring RMP submissions with the help of RAD, and it is also responsible for monitoring additional risk minimization measures with the help of the local Responsible Person for Pharmacovigilance.

The European Union Pharmacovigilance is in charge of managing CAPAs for any noncompliance, and the Qualified Person Responsible For Pharmacovigilance and Deputy Qualified Person Responsible For Pharmacovigilance give their approval. 100% or less is the action threshold for RMP submissions that are in accordance with the designated national competent authority date. This activity's metrics are accurately recorded.

PSMF Submission

Pharmacovigilance for the European Union (EU) is in charge of ensuring compliance with the requirement for submission of the PSMF to the Competent Authority. A standard submission deadline of seven calendar days is established unless otherwise stated by the Competent Authority. The Qualified Person Responsible For Pharmacovigilance/Deputy must approve all PSMF filings. 100% compliance is the desired level.

This activity's metrics are accurately recorded.

At monthly compliance reports and compliance review meetings, metrics for this activity are shared and addressed.

14. Quality System

Document and Record Control

The Quality System includes a series of Standard Operating Procedures (SOP).

Standard Operating Procedures (SOPs):

Describe the procedure that will be followed and completed. The SOP is divided into the following sections: purpose, scope, procedure, roles in decisions and actions, and references to related papers that are relevant to the process as defined.

Paper copies and master copies of every SOP are maintained and monitored. The SOPs are distributed within the company in electronic form.

Local Procedures (SOPs): norms that apply to a certain nation, office, or affiliate.

- Reviewed, approved, and distributed by local functions, local procedures may be adapted to their own Quality Management System format and controlled by the local Quality Assurance function, if applicable, or local PV functions. They may cross-reference European procedures.

Depending on the duties outlined in the SOP, the SOPs are kept on the shared business server and Cloud-Station and made accessible to the appropriate parties. Selected local affiliate/office/responsible person for pharmacovigilances, european union pharmacovigilance staff, and others have access to a common cloud. a qualified individual who is in charge of pharmaceutical vigilance or a constable qualified individual.

The local PV functions plan and oversee local PV procedures. The Qualified Person Responsible For Pharmacovigilance/Deputy and European Union Pharmacovigilance are informed of any new or amended local procedures.

Below is a list of all current procedural documents that apply to pharmacovigilance.

The SOP Development Plan includes the procedures that are being developed and improvements that are being implemented.

The European Union Pharmacovigilance department handles documents that are archived in hard copy and soft copy and stored electronically on a local server and cloud server.

All electronic documents received, such as contacts with authorities, are saved on shared drives in the cloud or given to the pharmacovigilance team of the European Union, who will arrange for archiving.

All physical copies are kept in secured locations. The crucial pharmacovigilance records are stored in a fire-resistant cabinet.

In the European Union Pharmacovigilance, the following primary categories of pharmacovigilance source papers are stored in hard copies.:

- Training records including job description and CVs
- Compliance documentation, (e.g., CAPA and Deviation forms)
- European Pharmacovigilance SOPs (e.g., PVE and PVEQA)
- Aggregated reports (ACO, RMP and PSUR)
- ICSRs (EU and OUT-SOURCED)
- The PSMF and PSMF Annexes
- Medical information – enquiries

At the out-sourced PV/out-sourced site (QA/RAD), there are the following types of hard copies of source materials for pharmacovigilance:

- Product complaints
- Local pharmacovigilance SOPs, as applicable
- Local Training records, CVs and job descriptions for local personnel
- SDEA's
- Audit and inspection reports
- Local compliance documentation, (e.g., CAPAs)

a. <u>Quality Control</u>

To prevent non-compliance with regulatory requirements and to maintain effective pharmacovigilance practise, a number of quality control procedures have been devised at various levels and areas.

QC measures are implemented throughout the workflow for each ICSR recorded into the Competent Authority PV Safety Databases (such as EudraVigilance) with regard to content, data entry quality, and processing time.

A quality checklist is in place for all reports to document performed quality control, and PBRER, ACOs, RMP, CSI/RSI, and/or SmPC are regularly checked for quality with relation to content and data accuracy. By using the chosen KPIs listed in the SOPs, European Union Pharmacovigilance regularly reviews PBRER/PSUR, ACOs, and RMP and evaluates compliance monitoring.

The European Union Pharmacovigilance Team maintains SmPC for marketed drugs, and quality is monitored by routine SmPC updates and comparison with local originator - latest safety information updates. To ensure that the most recent safety information has been represented in the Core Safety Information/Reference Safety Information of each API, RSI is maintained for both marketed and unmarketed products (and with consideration of pharmaceutical form) Prior to product introduction, the most recent iteration of RSI will be used to update the product, which is licenced under pharmaceutical SmPC.

The European Union Pharmacovigilance Monthly Compliance Report keeps track of the performance status monitoring of the pharmacovigilance system on a regular basis using a set of several specified quality measures.

Through regular compliance and reconciliation reports, information from TCs and other regular meetings with European Union Pharmacovigilance/Responsible Person For Pharmacovigilances, and summarised European Union Pharmacovigilance, the Qualified Person Responsible For Pharmacovigilance is informed about important quality issues. A monthly compliance report is in place to regularly track the real firm PV compliance.

All deviations and CAPAs that affect EU Pharmacovigilance regulatory compliance are handled in accordance with EU Pharmacovigilance SOPs; however, deviations and CAPAs that affect local PV systems are handled in accordance with local quality management systems and QA SOPs.

Deviation

When there has been a documented deviation from any Pharmacovigilance SOPs, GVP Modules, or PV laws, there has been an internal non-compliance. Responsible Person For Pharmacovigilances/outsourced/European Union Pharmacovigilance notifies the

appropriate staff members at this organisation, who are filling out the necessary documents, of all deviations. The Qualified Person Responsible For Pharmacovigilance/Deputy approves the agreed-upon remedial and preventive measures.

Pharmacovigilance in the European Union keeps track of all deadlines for PV-related tasks and actions.

CAPA

Following external non-compliance brought on by audit findings, inspections, or deviations, CAPA is raised. The person in charge of pharmacovigilance/pharmacovigilance for the European Union notifies all CAPAs. The CAPA form is completed, given a CAPA number, and administered by staff members appointed by the European Union for Pharmacovigilance. The agreed-upon remedial and preventive measures are approved by the Quality Committee, the Qualified Person Responsible For Pharmacovigilance, or both.

All PV-related actions and deadlines are tracked by European Union Pharmacovigilance in the PV CAPA tracker. An overall trend analysis and CAPA and Deviation overview are created for the Safety Review conference.

List of procedures

A summary of particular steps and processes relating to the operations of pharmacovigilance and how they interact with other processes.

Training

In accordance with Pharmacovigilance Training, a training and development programme is in place to ensure that individuals engaged in pharmacovigilance activities and post-marketing surveillance of products are informed of the most recent pharmacovigilance needs. Internally or by attending formal group training sessions, adequately competent persons provide training and development. Ongoing documentation is kept of the training resources and assessments of the effectiveness of the training.

Training on pharmacovigilance practises is provided to all personnel in the European Union Pharmacovigilance Outsourced, Responsible Person For Pharmacovigilances, and Service Providers Acting as Responsible Person For Pharmacovigilances (SOPs). This is based on the training needs associated with the duties of their jobs.

Written records of the training are kept and utilised for tracking. If deviations from a prescribed technique are noticed, retraining may be necessary. Such retraining must be recorded.

The European Union Pharmacovigilance Training documentation, CVs, and job descriptions are kept up to date for all pharmacovigilance staff. The European Union Pharmacovigilance or Responsible Person For Pharmacovigilance/local office maintains up-to-date training records for all pharmacovigilance staff.

Local pharmacovigilance training is the responsibility of the Responsible Person For Pharmacovigilances. To make sure that all personnel has received fundamental training in pharmacovigilance, concerned departments are sent a common set of training materials.

Any newly hired non-pharmacovigilance staff members will get local basic pharmacovigilance training. Refresher training is conducted at least every two years or if there are major changes.

b. Quality Assurance and Auditing

Scheduled audits and assessments fulfil the strategic and tactical audit requirements of the organisation with a risk-based approach.

In collaboration with the European Union Pharmacovigilance and the Qualified Person Responsible For Pharmacovigilance/deputy, QA established the audit schedule, which is then maintained by QA.

The audit and assessment schedule, which covers all local responsible persons for pharmacovigilances, major sites of pharmacovigilance activities, as well as service providers, is agreed upon with the european union pharmacovigilance/QA and approved by the qualified person responsible for pharmacovigilance/deputy. It is planned to conduct an internal audit of the primary PV sites on a regular basis, as well as the other PV sites and service providers (e.g., the Responsible Person For Pharmacovigilances, third parties), in

accordance with the audit schedule and taking into account the aforementioned risk factors, on a cycle every two to five years depending on the actual PV risk assessment evaluation. Any modifications to the audit schedule must be agreed upon by QA and European Union Pharmacovigilance and approved by the Qualified Person Responsible For Pharmacovigilance/Deputy. The frequency might be changed based on the most recent risk assessment.

Independent PV auditors/contractors do audits for service partners, own affiliates, and outsourced pharmacovigilance for the European Union.

The results of each audit are documented in a thorough audit report that is shared with the European Union Pharmacovigilance, the Qualified Person Responsible For Pharmacovigilance, and the Deputy Qualified Person Responsible For Pharmacovigilance.

The Qualified Person Responsible For Pharmacovigilance/Deputy Qualified Person Responsible For Pharmacovigilance reviews and approves corrective and preventative actions resulting from audits.

European Union Pharmacovigilance and QA regularly review audit requirements, outcomes, findings, and CAPAs under the supervision of the Qualified Person Responsible For Pharmacovigilance/Deputy.

Service Providers

Audits are planned according to the strategic and tactical audit strategy as well as a risk-based approach. The management of audits of service providers carrying out any pharmacovigilance operations for businesses or medicines falls under the purview of QA. European Union Pharmacovigilance provides a detailed description of the procedure.

The Qualified Person Responsible For Pharmacovigilance/Deputy Qualified Person Responsible For Pharmacovigilance or Quality Committee must always authorise corrective and preventative measures emerging from audits.

Business Partners

Business partner audits are started based on risk assessment evaluations completed for all SDEA partners; QA is in charge of managing the audits of SDEA partners and their risk assessment evaluations.

Audit Note

A Pharmacovigilance audit note is placed in this area of the PSMF where important audit findings are noted. Substantial discoveries are those that meet the EU's requirements for important or critical findings. Until the corrective and/or preventative measure(s) have been fully taken, the notation on major findings will stay in the PSMF. The remark is only deleted once the corrective action and substantial improvement can be demonstrated or has been independently verified. If corrective and preventative action(s) for a specific audit or finding have not yet been agreed upon, a note stating that such action(s) is/are to be agreed upon shall be made. The logbook keeps track of the additions and deletions of audit notes.

15. Conclusion

The practise of monitoring, identifying, evaluating, and preventing side effects or any other drug-related issues connected with the use of pharmaceutical products is known as pharmacovigilance. To ensure that the advantages of medicines outweigh their hazards and to increase patient safety is the ultimate goal of pharmacovigilance.

There are various pharmacovigilance business models, and the following are some of its salient features.:

Service Provider Model: The most typical pharmacovigilance business model involves enterprises offering pharmacovigilance services to pharmaceutical firms, contract research organisations (CROs), and regulatory organisations. Adverse event reporting, signal identification, risk management, and regulatory compliance are some of these services. The amount of pharmaceuticals, patients, or events that a company monitors can determine how much it charges, or it can set a fixed rate for each project or contract.

In-house Model: Having an internal pharmacovigilance team to manage all facets of drug safety monitoring is a decision made by some pharmaceutical corporations. Long-term savings and more process control are potential benefits of this technique. Yet, it necessitates a substantial expenditure on staff and infrastructure.

Hybrid Model: Using a hybrid approach, some businesses use in-house staff for the most important aspects of pharmacovigilance while contracting out some of the less important duties to a service provider. More flexibility and cost effectiveness are made possible by this paradigm.

Outsourcing Model: Some businesses contract out their whole pharmacovigilance department to a separate service provider. Small to mid-sized pharmaceutical companies that lack the resources or knowledge to perform pharmacovigilance internally frequently utilise this model. The service provider can manage all facets of medication safety monitoring, including risk management and the reporting of adverse events.

Collaborative Model: Pharmaceutical corporations sometimes work together with academic institutions, patient advocacy organisations, and regulatory organisations to carry out pharmacovigilance initiatives. The findings of drug safety studies could be improved with the use of this paradigm, which can also encourage patient engagement.

In conclusion, it should be highlighted that the pharmacovigilance business model is labyrinthic and that there are numerous ways to ensure patient safety. The literature on the topic emphasises how crucial it is to choose the best optimal model depending on the size, resources, and goals of the company.

16. List of Abbreviations

ACO – Addendum to Clinical Overview

ADR – Adverse Drug Reaction

AE – Adverse Event

BA/BE – Bioavailability / Bioequivalence clinical studies

CA – Competent Authority

CAPA – Corrective and Preventive Action

CHMP – Committee Medicinal Products for Human use

CMO – Contract Manufacturing Organisation

CIOMS – Council for International Organisations of Medical Sciences

CSI – Core Safety Information

CV – Curriculum vitae

DCP – Decentralized Procedure

EC – European Commission

EEA – European Economic Area

EMA – European Medicinal Agency

EU – European Union

EUPV – European Pharmacovigilance Department

EURD – (List of) European Union Reference Dates and frequency of submission of periodic safety update reports

EV – EudraVigilance

EVDAS – EudraVigilance Data Analysis System

EV WEB – EudraVigilance World Wide Web

GVP – Good Pharmacovigilance Practises

HCP – Health Care Professional

ROW – rest of the world

RSI – Reference Safety Information

ICSR – Individual Case Safety Report

IR – the Implementing Regulation

JD – Job description

KPI – Key Performance Indicator

MA – Marketing Authorisation

MAH – Marketing Authorisation Holder

MD – Medical Doctor

MLM – Medical Literature Monitoring

MFL – Master File Location

NHCP – National Health Communication Policy

PAES – Post-authorisation Efficacy Studies

PASS – Post-authorisation Safety Studies

PIL – Patient Information Leaflet

PRAC – Pharmacovigilance Risk Assessment Committee

PSMF – Pharmacovigilance System Master File

PSUR – Periodic Safety Update Report

PBRER – Periodic Benefit Risk Evaluation Report

PubMed – US National Library of Medicine

PV – Pharmacovigilance

QA – Quality Assurance

QC – Quality Control

QS – Quality System

QMS – Quality Management System

QPPV – Qualified Person for Pharmacovigilance

RAD – Regulatory Affairs Department

RMP – Risk Management Plan

RMM – Risk Minimisation Measures

RPP – Responsible Person for Pharmacovigilance

RTF – Rich Text Format

MRP – Mutual Recognition Procedure

SDEA – Safety Data Exchange Agreement

SmPC – Summary of Product Characteristics

SOP – Standard Operating Procedure

OPI - Operational Instructions

TA – Technical Agreement

TC – Teleconference

XML - eXtensible Markup Language

17. Reference Literature

1. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use Text with EEA relevance OJ L 348, 31.12.2010, p. 74–99.
2. Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council Text with EEA relevance OJ L 159, 20.6.2012, p. 5–25.
3. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Text with EEA relevance): Regulations originating from the EU 2004 No. 726, TITLE II, Chapter 2, Article 20.
4. *Segura-Bedmar I, Martinez P.* Special issue on mining the pharmacovigilance literature. J Biomed Inform. 2014; 49: 1–2.
5. Europe Pharmacovigilance Market Research Report - Segmented By Clinical Trial Phase, Service Provider, Method & Country (UK, France, Spain, Germany, Italy, Russia, Sweden, Denmark, Switzerland, Netherlands, Turkey, Czech Republic and Rest of Europe) - Industry Analysis, Size, Share, Trends, COVID-19 Impact & Growth Forecast (2022 to 2027). Published: March, 2023; ID: 7548; https://www.marketdataforecast.com/market-reports/europe-pharmacovigilence-market
6. Report of CIOMS (Council for International Organisations of Medical Sciences) Working Group III, Guidelines for Preparing Core Clinical-Safety Information on Drugs, Geneva. 1995.
7. *Jeetu G, Anusha G.* Pharmacovigilance: a worldwide master key for drug safety monitoring. J Young Pharm. 2010;2(3):315–320.
8. World Health Organization (WHO). The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products Geneva: World Health Organization; 2002. https://apps.who.int/iris/handle/10665/42493.
9. World Health Organization (WHO). Clinical trials Geneva: World Health Organization; 2022. https://www.who.int/health-topics/clinical-trials#tab=tab_1.

10. NIH National Institute on Aging. What Are Clinical Trials and Studies? Baltimore, MD.: National Institutes of Health (NIH) National Institute on Aging (NIA); 2020. https://www.nia.nih.gov/health/what-are-clinical-trials-and-studies.
11. *Brewer T, Colditz GA.* Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. JAMA. 1999;281(9):824–829.
12. *Montastruc JL, Sommet A, Lacroix I, Olivier P, Durrieu G, Damase-Michel C, et al.* Pharmacovigilance for evaluating adverse drug reactions: value, organization, and methods. Joint Bone Spine. 2006;73(6):629–632.
13. Pharmacovigilance Market (By Clinical Trial Phase: Preclinical Phase I, Phase II, Phase III, and Phase IV; By Service Provider: In-house and Contract Outsourcing; By End User: Hospitals, Pharmaceutical Companies, and Others) - Global Industry Analysis, Size, Share, Growth, Trends, Regional Outlook, and Forecast 2021 – 2030; https://www.precedenceresearch.com/pharmacovigilance-market
14. *Harmark L, van Grootheest AC*. Pharmacovigilance: methods, recent developments and future perspectives. Eur J Clin Pharmacol. 2008;64(8):743–752.
15. *Babigumira JB, Stergachis A, Choi HL, Dodoo A, Nwokike J, Garrison LP*. A framework for assessing the economic value of pharmacovigilance in low- and middle-income countries. Drug Saf. 2014; 37: 127–134.
16. *Edwards IR*. Who cares about pharmacovigilance? Eur J Clin Pharmacol. 1997;53(2):83–88.
17. Guideline on good pharmacovigilance practices (GVP) – Module II (Rev 2)EMA/816573/2011 Rev 2; https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-ii-pharmacovigilance-system-master-file-rev-2_en.pdf
18. *Gyllensten H, Hakkarainen KM, Hägg S, Carlsten A, Petzold M, Rehnberg C, et al.* Economic Impact of adverse drug events—a retrospective population-based cohort study of 4970 adults. PLoS ONE. 2014.
19. European Medicines Agency (EMA). Pharmacovigilance London: European Medicines Agency (EMA); 2015. https://www.ema.europa.eu/en/documents/leaflet/pharmacovigilance_en.pdf.
20. *Mammì M, Citraro R, Torcasio G, Cusato G, Palleria C, di Paola ED*. Pharmacovigilance in pharmaceutical companies: an overview. J Pharmacol Pharmacother. 2013;4 (Suppl 1):S33–S37

21. *Peters T, Soanes N, Abbas M, Ahmad J, Delumeau JC, Herrero-Martinez E, et al*. Effective pharmacovigilance system development: EFPIA-IPVG consensus recommendations. Drug Saf. 2021;44(1):12.
22. European Medicines Agency (EMA). Good pharmacovigilance practices Amsterdam: European Medicines Agency (EMA); 2022. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c.