



A Study on Regulatory Requirements of Risk Management Plan for Pharmaceuticals in Europe, U.S. and Brazil

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ABSTRACT: Risk is associated in every single aspect in pharmaceuticals from development of a molecule to its way to the customer. So, to minimize or manage risk associated with pharmaceutical product, a contingency plan should be present and made with past experiences and expert references. A Risk management plan helps to find out the possible risks involved in every aspect of research, development, manufacture and marketing. Risk Management Plan is handled differently from country to country. In Europe, U.S and Brazil have established Risk Management plan which illustrate the increasing importance of managing risk of pharmaceutical product during research, development, manufacture and marketing. A different component of Risk Management Plan in three countries gives ideas about information that should be submitted in risk management plan during marketing authorization. © 2016 iGlobal Research and Publishing Foundation. All rights reserved.

INTRODUCTION

Pharmacovigilance [1-2]:

The World health Organization (WHO) defines “Pharmacovigilance as the science and activities relating to the detection, evaluation, understanding and prevention of adverse reaction to medicines or any other drug related problems”.

Pharmacovigilance Activities

Different Kind of Pharmacovigilance activates are shown in Figure I.

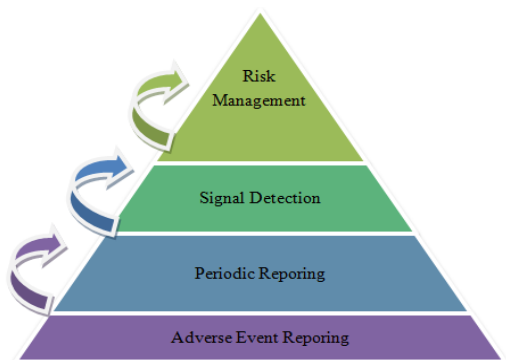


Fig I. Pharmacovigilance Activity Pyramid

Risk Management:

Risk is associated in every single aspect in pharmaceuticals from development of a molecule to its way to the customer. There are different kinds of Risk in Pharmaceutical Industry and they are following.

Risk management is a process for identifying, characterizing, evaluating, monitoring, communicating and mitigating risks that may arise from the normal conditions of use for a medical product. Risk Management Cycle Shown in Fig II.

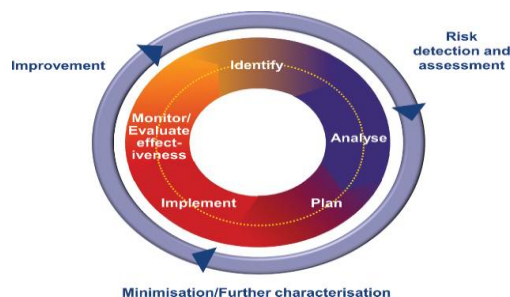


Fig II Risk Management Cycle

RISK MANAGEMENT PLAN

A Risk management plan is detailed description of risk management system [3-5].

Need of Risk management Plan:

At the time of authorization, information on the safety of a medicine is relatively limited. This is due to the limitations of clinical trials, including:

- Relatively small numbers of subjects in clinical trials compared with the intended treatment population
- Restricted population in terms of age, gender or ethnicity
- Restricted co morbidity
- Restricted co medication
- Restricted conditions of use
- Relatively short duration of exposure and follow-up
- Statistical problems associated with assessing many different outcomes

A Risk management plan helps to find out the possible risks involved in every aspect of research, development, manufacture and marketing.

Objectives of a Risk Management Plan

- Identify or characterize the safety profile of the medicinal product(s) concerned;
- Give indication to characterize further the safety profile of the medicinal product(s) concerned;
- Document measures to prevent or minimize the risks associated with the medicinal product including an assessment of the effectiveness of those interventions;
- Document post-authorization obligations that have been imposed as a condition of the marketing authorization
- An RMP (or RMP update) will normally be expected with applications involving a significant change to an existing registration, such as a: Significantly different population, Pediatrics indication, New dosage form or route of administration with inherently higher risk, New manufacturing process of a biotechnologically derived product, Other significant change in indication.

RISK MANAGEMENT PLAN FOR PHARMACEUTICALS IN EUROPE [6-12]

In the EU, the concept of a risk management plan was formally crystallized in an amendment to Directive 2001/83/EC on the Community code relating to medicinal products for human use (Code for Human Medicines Directive) by Directive 2004/27/EC on the Community code relating to medicinal products for human use (Code for Human Medicines Second Amendment Directive).

A European Risk Management Plan describes the risk management system of a product, or multiple products, containing the same active substance. Good Pharmacovigilance Module V on Risk Management Systems provides detailed guidance about the EU-RMP.

Risk Management Plan Submission and Review

Risk Management Plan submitted as pdf within eCTD Submission to the European Medicine Agency along with NDA/ANDA/BLA. In

EMA Pharmacovigilance Risk Assessment Committee is Responsible for review of Risk Management Plan. PRAC will appoint PRAC Reporter for review of individual RMP. Here, PRAC is Responsible for Review and Assessment and after that Report is submitted to Committee for Medicinal Products for Human Use.

Timeline for the Marketing authorization procedure

Time Period for marketing authorization for new drug in Europe is shown in Fig III.

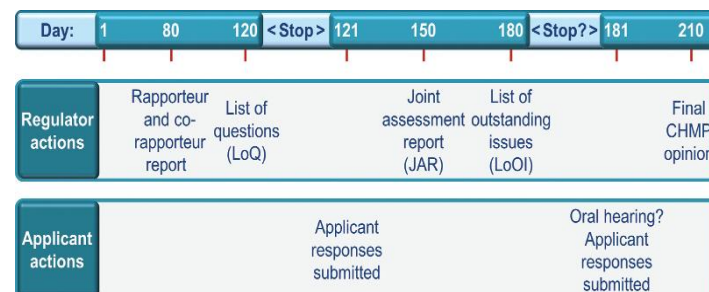


Fig III .Timeline for the Marketing authorization procedure in Europe

Structure of Risk Management Plan

A. Part I: Product Overview

This Part provides the administrative information on the RMP and an overview of the product(s) covered within it. The information should include:

Administrative information on the RMP

- o Data lock point of the current RMP;
- o Date submitted and the version number;

For each medicinal product included in the RMP:

- o Authorization procedure (central, mutual recognition, decentralized, national);
- o Invented name(s) in the European Economic Area (EEA);
- o Brief description of the product including:
- o Important information about its composition
- o Indications:
- o Dosage:
- o Pharmaceutical forms and strengths

B. Part II: Safety Specification

The purpose of the safety specification is to provide a synopsis of the safety profile of the medicinal product(s) and should include known and not known about the medicinal product(s). Summary of the important identified risks of a medicinal product, important potential risks, and missing information mentioned in Safety Specifications.

C. Part III: Pharmacovigilance Plan

A PV plan describes a structured approach for monitoring the safety concerns of a product, usually during the post- authorization phase. It may better characterize important identified risks, verify important potential risks, and fill in the gaps of (important) missing information.

Pharmacovigilance Activities divided into

- o Routine Pharmacovigilance Activity
- o Additional Pharmacovigilance Activity

□ Routine Pharmacovigilance Activity:

This section presents a summary of the routine pharmacovigilance system by specifying the processes. The processes usually include the collection and medical evaluation of Individual Case Safety Reports (ICSRs), expedited reporting of adverse drug reactions (ADRs) and suspected unexpected serious adverse reactions (SUSARs) to the competent authorities in a predetermined period, regular signal detection and signal evaluation, weekly or monthly screening of the scientific literature for ADR reports, maintenance of the pharmacovigilance quality management system and standardized processes to define and decide on adequate measures for crisis management and risk minimization.

□ Additional Pharmacovigilance Activity:

Additional Pharmacovigilance activities may be non-clinical studies, clinical trials or non- interventional studies.

The objective of additional pharmacovigilance activities normally differ according to safety concern to address. For Important identified and potential risk, objective may be measure the incidence rate in large or a different population, to measure the ratio or rate different in comparison to reference medicinal products, to examine the risk varies with different doses and duration of exposure, to identify risk factor or to assess a causal association.

D. Part IV: Plan for Post Authorization efficacy studies

Efficacy, as assessed at the time of authorization, is based on data from clinical trials which, by their nature, are of relatively limited duration. The benefit risk balance must be positive for a medicine to be authorized. Whereas it is recognized that many risk will be identified post authorization, there is an implicit assumption that efficacy remain relatively constant over time. However, there may be circumstances where efficacy may vary over time and also patients in whom this assumption of constant efficacy may not be true and where longer term efficacy data post authorization is necessary.

E. Part V: Risk Minimization Measure

On the basis of safety specification marketing authorization holder/applicant assesses the risk minimization activities needed for each safety concern. The risk minimization plan provides detail information about to reduce risk associated with each individual safety concerns.

Risk minimization activities may consist of Routine risk minimization or additional risk minimization activities. All risk minimization should review at regular intervals and their effectiveness assessed.

□ Routine Risk minimizations

Routine Risk minimization is those activities which apply to every medicinal product. These relates to:

- o The summary of Product characteristic;
- o The Labeling;
- o The Package Leaflet;
- o The Package size;
- o The legal status of Product;

The summary of product characteristic and package leaflet are important tools for risk minimization.

□ Additional Risk minimization

Additional risk minimization activities are those risk minimization measure which are not routine risk minimization activities. Additional risk minimization activities should only suggested when essential for the safe and effective use of medicinal product and these should be science based, and developed provided by suitably qualified people. Many additional risk minimization tools are based on communication which aims to augment the information in the summary of product characteristic and package leaflet.

F. Part VI: Summary of activities in the risk management plan by medicinal product

A summary of the RMP for each medicinal product shall be made publically available.

The summary must include key elements of the RMP with a specific focus on risk minimization activities. With regard to the safety specification of the medicinal product concerned, it should contain important information on potential and identified risks as well as missing information. For products authorized under the centralized procedure, the Agency currently publishes a full scientific assessment of the dossier in the format of a European Public Assessment Report (EPAR).

G. Part VII: Annexes

The RMP should contain the annexes listed below. Annexes 1-3, 10 and 11 should be provided for each medicinal product within the RMP. If no information is available for a given annex this should be stated. If a single study is addressing issues in both parts III and IV of the RMP, it should be included in RMP annex 6 with a cross reference in RMP annex 8.

RMP Annex 1: Interface between RMP and Eudravigilance/EPITT (electronic only)

RMP Annex 2: Current (or proposed if product is not authorized) local (centralized/mutual recognition/decentralized/national) summary of product characteristics (SmPC) and package leaflet. If multiple versions are included, they should show in which Member State(s) they are applicable. If available, a core SmPC should be provided with an overview of the changes applicable to the SmPC in each Member State.

RMP Annex 3: worldwide marketing authorization status by country (including EEA). This should include: Current license status (approved/refused under review/ suspended/expired/withdrawn);

RMP Annex 4: Synopsis of on-going and completed clinical trial program.

RMP Annex 5: Synopsis of on-going and completed pharmacoepidemiological study program.

RMP Annex 6: Protocols for proposed and on-going studies in categories 1-3 of the section “Summary table of additional pharmacovigilance activities” in RMP part III.

RMP Annex 7: Specific adverse event follow-up forms.

RMP Annex 8: Protocols for proposed and on-going studies in RMP part IV.

RMP Annex 9: Synopsis of newly available study reports for RMP parts III-IV.

RMP Annex 10: Details of proposed additional risk minimization activities (if applicable).

RMP Annex 11: Mock up examples in English (or the National language if the product is only authorized in a single Member State) of the material provided to healthcare professionals and patients as a requirement of Annex II of the Commission Decision or as a

requirement of national authorizations including those using the mutual recognition or decentralized procedure as applicable.

RMP Annex 12: Other supporting data (including referenced material).

Parts of Risk management Plan for Pharmaceuticals to be submitted for different pharmaceutical products shown in Table I.

Type of new application	Part I	Part II, Module SI	Part II, Module SII	Part II, Module SIII	Part II, Module SIV	Part II, Module SV	Part II, Module SVI	Part II, Module SVIIa	Part II, Module SVII	Part II, Module SVIII	Part III	Part IV	Part V	Part VI	Part VII
New active substance	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Similar biological	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Informed consent ¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	★	★	✓	★	✓
Generic medicine	✓						✓	✓	✓	✓	★	★	✓	★	✓
Hybrid medicinal products	✓	✓	△	△	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fixed combination	✓	✓	△	△	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Well established use ²	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
"Same active substance"	✓	✓	★	★		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

¹ Application under Article 10(c) of Directive 2001/83 as amended

² Application under Article 58 of Regulation 726/2004 as amended

△ May be omitted under certain circumstances

★ Modified requirement

Table I. Parts Submitted for Different Pharmaceuticals

RISK EVALUATION AND MITIGATION STRATEGY FOR PHARMACEUTICALS IN U.S. [13-20]

On September 2007, President signed into law the Food and Drug Administration Amendment Act of 2007.

Title IX, Subtitle A, Section 901 of this statute created new section 505-1 of the FDCA, which authorize FDA to require person to submitting along with REMS to ensure that benefits of drug outweigh the risk of Drug.

Risk Evaluation and Mitigation Strategy are required risk management plans that use risk minimization strategies beyond the professional labeling to ensure that the benefits of certain prescription drugs outweigh their risks.

In U.S Risk Evaluation and mitigation strategy applies to certain drugs and biological products submitted for approval or approved under section 505(b) or 505(j) of the federal food, drug and cosmetic act.

Condition for Requirement of REMS:

Following are the requirement that the FDA is required to take into account by the legislation when REMS is needed for a product is:

- The size of the patient population;
- The seriousness of the underlying disease/condition being treated;
- The expected benefit of the product;
- The anticipated treatment duration;
- The seriousness of known or potential adverse events that may be related to the drug, and their background incidence in the likely patient population;
- New molecular entity (NME).

Timeline for Marketing Authorization:

Time Period for marketing authorization for new drug in Europe is shown in Fig IV.

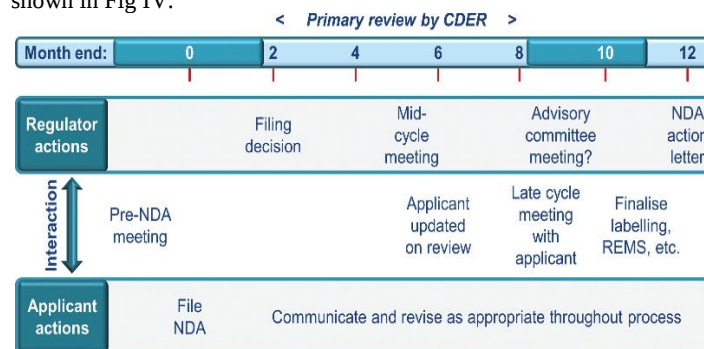


Fig IV. Timeline for the Marketing authorization procedure in Europe

Parts of Risk Evaluation and Mitigation Strategy

A. Medication Guide and /or Patient package inserts:

Medication guides are paper handouts that include FDA-approved information about the safe and effective use of a drug. As one elements of REMS, the FDA may require the development of a Medication guide, as provide for under 21 CFR part 208, which set requirement for patient labeling for human prescription drug products, including biological product, that FDA determines poses serious and significant public health concerns requiring the distribution of FDA approved patient information.

In addition, FDA may require patient package inserts as part of a REMS if the FDA may determines that patient package inserts may help to mitigate a serious risk of drug.

Copies of Medication guide or Patient package inserts that are parts of REMS should be appended top proposed REMS.

B. Communication Plan

FDA determines that communication plan targeted at healthcare providers is necessary elements of REMS. The communication plan include following:

- o Sending letter to healthcare provider;
- o Disseminating information about REMS elements to encourage implementation by healthcare provider; or
- o Explain certain safety protocol such as medical monitoring by periodic laboratory test
- o Disseminating information to healthcare provider through professional societies about any serious risks of the drugs and any protocol to assure safe use.

C. Elements to assure safe use

Elements to assure safe use are intended to provide safe access for patients to drug with known serious risk. Required ETASU are put in place to mitigate a specific risk listed in the labeling of drug.

Before requiring one or more ETASU, the FDA must make the following determination:

- o Drug that show effectiveness but associated with serious adverse drug experience, can be approved only if, or would be withdrawal unless, such elements required ; and
- o Drug that approved initially without ETASU, other possible elements of REMS are not sufficient to mitigate such serious risk.

Copies of all relevant materials should be appended to the proposed REMS. The following lists the elements to assure safe use that may include in the REMS.

- a. Healthcare provider prescribe the drug have particular training or experience, or are specially certified
- b. Pharmacies, practitioner, or healthcare setting that dispenses the drug are specially certified.

Section 505-1(f) (3) (B) pertains method of drug dispense. Elements under this category might require certification of training of specific knowledge before the pharmacy, practitioner, or healthcare setting is enrolled in program that allows the practitioner to dispense product.

- c. The drug is dispensed to patient only in certain healthcare setting, such as hospitals.

Section 505-1(f) (3) (C) pertains to restriction on dispensing the products to patient in specific healthcare setting.

- d. The drug is dispensed only to patient with evidence or other documentation of safe use conditions, such as laboratory test.
- e. Each patient using the drug is subject to certain monitoring.
- f. Each patient using drug is enrolled in a registry.

Section 505-1(f) (3) (F) pertains to enrolling patients into program as part of an overall strategy to mitigate a specific serious risk listed in the labeling of drug.

Drug access may be contingent on patient enrollment. The types of information that may be collected on enrolled patient may include:

- o Information on clinical outcomes
- o Clinical and laboratory data
- o Safety information
- o Data on compliance with prescribed management and prescribing protocols
- o Data on the impact of tools on ensuring compliance and outcomes
- o Implementation System

Section 505-1(f) (4) of the FDCA gives the FDA authority require an implementation system for a REMS that include ETASU describe under Section 505-1(f) (3) (B), (C), and (D). Through the implementation system, the applicant may be accepted to take reasonable step to monitor and evaluate implementation by healthcare provider, pharmacies, and other parties in the healthcare system who are responsible for implementing those elements, and work to improve their implementation.

FDA may require the implementation system to include a description of how applicant product distributed. In addition, as part of the implementation system, FDA may require the certification of Wholesaler who distributes the product to ensure that the product is distributed only to certified pharmacies, practitioner, or healthcare setting that dispense drug, or only to patient who meet the requirement of REMS.

D. Timetable for submission of assessment of the REMS

This subsection of REMS should describe the proposed timetable for submission of assessment of the REMS. REMS for NDAs and BLAs must include a timetable for submission of the REMS.

Each timetable for submission of assessment of REMS must at a minimum include assessment submitted by 18 Months and 3 years after REMS is initially approved and in the 7th Year after the REMS is initially approved.

The timetable specifies when the assessment will be submitted to FDA, not when the assessment will performed. This subsection should specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60days before the submission date for that assessment.

PHARMACOVIGILANCE AND RISK MINIMIZATION PLAN FOR PHARMACEUTICALS IN BRAZIL [21-24]

National Health Surveillance Agency has published a regulatory guide to pharmacovigilance plans and risk minimization plans in English in 2009. This guidance was developed based on the ICH E2E, EMA Volume 9A and FDA Risk MAP guidelines, as well as the relevant legal requirements.

Safety Specifications

The PVP and the RMP should present associate initial section denominated Safety Specifications, that may be a outline of the legendary safety profile of the merchandise and includes exposure information from clinical studies and from post-marketing use. Any safety concerns are discussed in this section, once they're a potential risk, as well as other aspects related to the products use, such as misuse, abuse, and off label use.

An important consideration on safety specifications is the epidemiology section, which should present information on the population that will probably be exposed to the product (target population) and the relevant co-morbidities of this population.

A. Pharmacovigilance Plan

The Pharmacovigilance Plan is specifically elaborated for a product and describes in detail the pharmacovigilance measures related to the potential risks and the ones identified in the safety specification.

Routine Pharmacovigilance Practices

Routine pharmacovigilance should be conducted for all medicinal products, regardless of whether or not additional actions are appropriate as part of a Pharmacovigilance Plan. This routine pharmacovigilance should include the following:

- o Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- o The preparation of reports for regulatory authorities: Expedited adverse drug reaction (ADR) reports; and Periodic Pharmacovigilance Reports (PPRs).
- o Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities;
- o Other requirements, as defined by local regulations.

Action Plan for Safety Issues

The Plan for each important safety issue should be presented and justified according to the following structure:

- o Safety issue;
- o Action(s) proposed;
- o Objective of proposed action(s);
- o Rationale for proposed action(s);
- o Monitoring by the MAH for safety issue and proposed action(s);
- o Milestones for evaluation and reporting.

Pharmacovigilance Plan Summaries

At the end of this section, there should be a summary of the PVP presented.

Evaluation of the need to elaborate the Risk Minimization Plan

This section should have a discussion on the need of a RMP or not, in addition to the PVP, on safety concerns.

B. Risk Minimization Plan (RMP)

After establishing the Pharmacovigilance Plan, the need or not of a Risk Minimization Plan should be assessed. The Risk Minimization Plan (RMP) should be developed in addition to the Pharmacovigilance Plan, in safety situations where additional actions are needed. In this plan, the company should explain how it will assess the effectiveness of its actions to minimize their products' risks. The RMP referred to in this article aims at managing new risks in the post-approval period, or even following up known risks in already studied populations. It also aims at being applied to situations where the product will have a probable use that was not adequately studied in the pre-approval period.

Risk Minimization Activities

The Risk Minimization Activities may comprise actions that aim at providing information on the product and actions related to the drug use control.

Effectiveness of Risk Minimization Activities

Methodologies to assess the effectiveness of the actions proposed should be developed for each risk minimization plan. The effectiveness indicators are related to the actions taken. Therefore, they will be specific for each plan.

COMPARISON

Comparison Risk management Plan for Pharmaceuticals in Europe, US and Brazil is Shown in Table II.

CONCLUSION

Risk Management Plan is the document which is submitted to regulatory authorities to ensure that ensure that the benefits of Pharmaceuticals outweigh their risks. Regulatory requirements of Risk Management Plan in Europe, US and Brazil are varying from each other so it is challenging for companies to develop and making risk management plan requirement and comply with requirement of different countries. From the comparison of three concern countries it can be conclude that European Risk Management Plan Documentation during Marketing Authorization is strict compare to Europe, U.S and Brazil.

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Table II Comparison of Risk Management Plan for Pharmaceutical in Europe, U.S and Brazil

	Europe	U.S	Brazil
Regulatory Authority	European Medicine Agency	U.S Food and Drug Administration	Agência Nacional de Vigilância Sanitaria
Guidelines	Good Pharmacovigilance- Module V	Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies	Guideline on Pharmacovigilance Plan and Risk Minimization Plan PVP/RMP
Prescription Information	- Name of the medicinal product - Qualitative and quantitative composition - Pharmaceutical form - Clinical particulars: - Therapeutic indications - Posology and method of administration - Contraindication - Special warnings and precautions for use - Interaction with other medicinal products and other forms of interaction - Fertility, pregnancy and lactation - Effects on ability to drive and use machine - Undesirable effects - Overdose - Pharmacological properties: - Pharmacodynamic properties - Pharmacokinetic properties - Preclinical safety data - Pharmaceutical particulars: - List of excipients - Incompatibilities - Shelf- life - Special precautions for storage - Nature and contents of Container - Special precautions for Disposal - Marketing authorization holder	Boxed warning (<i>if appropriate</i>) - Indications and usage - Dosage and administration - Dosage forms and strengths - Contraindications - Warnings and precautions - Adverse reactions - Drug interactions - Use in specific populations: - Pregnancy - Labor and delivery - Nursing mothers - Pediatrics use - Geriatric use - Drug abuse and dependence - Over dosage - Description - Clinical pharmacology - Non- clinical toxicology - Clinical studies - References - How supplied/storage and handling - Patient counseling information	- Name of product (trademark or generic) - Pharmaceutical form - Number of units in package - Active ingredients - Complete formula of the product with quantitative composition - Name and address of manufacturer - Responsible pharmacist - License number and date of issue - Batch number - Expiration date and date of manufacture - Storage instructions - For prescription products, statement that it is supplied on prescription only - Indications - Side effects & Precautions, if any

	• Marketing authorization number(s) • Date of first authorization/ renewal of the authorization • Date of revision of the text		
Safety Specification	Wide- ranging safety specification that includes detailed consideration of important identified risks, important potential risks and missing information	Background section of the REMS Supporting Document should Describe is known thing to minimize risk.	Wide- ranging safety specification that includes detailed consideration of important identified risks, important potential risks and missing information
Pharmacovigilance Plan	Incorporates a detailed pharmacovigilance plan	A REMS assessment must include information about the status of post-marketing requirements/ commitments, and other studies/ trials undertaken to investigate a safety issue	Incorporates a detailed pharmacovigilance plan
Post Authorization Efficacy Studies	Takes into account benefits and the need for post- authorization efficacy studies	Background section of the REMS Supporting Document should include description of benefits	Not Mentioned
Risk Minimization Measure	The need for risk minimization should be considered for each safety concern	Background section of the REMS Supporting Document should explain Requirements of REMS is and justification of the selected tools/elements	The need for risk minimization should be considered for each safety concern
Risk Minimization Elements	• Routine risk minimization ○ SmPC and PL ○ Labeling ○ Pack size and design ○ Legal (prescription) status of the product • Additional risk minimization ○ Educational program ○ Educational tools targeting HCPs. ○ Educational tools targeting patients and/or caregivers ○ Controlled access program ○ Other risk minimization measures Such as PPP & DHPC	• Medication Guide/Patient Package Insert • Communication plan (for HCPs) • Elements to assure safe use (ETASU) ○ Healthcare providers who prescribe the drug have particular training or experience, or are specially certified. ○ Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified. ○ The drug may be dispensed to patients only in certain healthcare settings, such as	• Routine Risk Minimization • Additional Risk Minimization

		hospitals. ○ The drug may be dispensed to patients with documentation of safe- use conditions, such as laboratory test results. ○ Each patient using the drug is subject to certain monitoring. ○ Each patient using the drug is enrolled in a registry.	
ICH E2E	significantly influenced the safety specification and PV plan	Little influence of ICH E2E	significantly influenced the safety specification and PV plan
Time for Assessment	Carefully planned prior to initiation.	Fixed assessment timelines (normally 18 months, 3 years and 7 years)	Not Mentioned

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