WHO MODEL RMP ASSESSMENT GUIDELINE

TO SUPPORT NATIONAL REGULATORY AUTHORITIES IN ASSESSING RISK MANAGEMENT PLANNING DOCUMENTS

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ABBREVIATIONS

ACCESS	Collaborative consortium including the following regulatory authorities MHRA, HSA, TGA, Swissmedic and Health Canada
AE	Adverse Event (or effect)
ADR	Adverse Drug Reaction
AEFI	Adverse Event Following Immunization
AMA	African Medicine Agency
ANSM	Agence Nationale de sécurité du médicament et des produits de santé (France, EU Member State)
aPVM	Additional Pharmacovigilance Method (in addition to routine activities)
aRMM	Additional Risk Minimization Measures/Activities (in addition to routine activities)
CCSI	Core Company Safety Information
CHMP	Committee for Medicinal Products for Human Use (of the EMA)
CIOMS	Council for International Organizations of Medical Sciences
CRP	Collaborative Registration Procedure
CSA	Country-Specific Annex
DEC	Drug Event Combinations
DHCPC	Direct HCP Communication
EMA	European Medicine Agency
US-FDA	Food & Drug Administration (of the United States of America)
GBT	WHO Global Benchmarking Tool
EC	European Commission (of the EU)
EMRN	European Medicine Regulatory Network
EU	European Union
GBT	WHO Global Benchmarking Tool
GPvP	Good Pharmacovigilance Practice (customizable guideline for MAHs)
GVP	Good Vigilance Practice
HC	Health Canada (Santé Canada)
HCP	Health Care Professionals
HPRA	Health Products Regulatory Authority, Republic of Ireland
HSA	Health Sciences Authority (of Singapore)
HQ	Headquarter(s)
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Reports (according to ICH-E2A guideline)
LMIC	Low- and Middle-Income Country (World Bank terminology)
MAH	Market Authorization Holder
MHRA	Medicines and Healthcare products Regulatory Agency of the United Kingdom
ML	Maturity Level (WHO-GB terminology)
MNPC	Multi-National Pharma Company
NDA	New Drug Application
NRA	National Regulatory Authority
PAR	Public Assessment Report (e.g. Australian AusPAR)
PASS	Post-Authorization Safety Studies
PBRER	Periodic Benefit-Risk Evaluation Report (PSUR according to ICH-E2C(R2) guideline
PIDM	WHO Programme for International Drug Monitoring
PMDA	Pharmaceuticals and Medical Devices Agency (of Japan)
PQ	WHO Prequalification
PRAC	Pharmacovigilance Risk Assessment Committee (of the EMA)
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report (according to ICH-E2C and E2C(R1) guidelines

PV	Pharmacovigilance
RMI	Risk Minimization Intervention (= additional risk minimization)
RMM	Risk Minimisation
RMP	Risk Management Plan document (according to ICH-E2E guideline)
SPC	Summary of Product Characteristics (or SmPC)
SOI	Standard Operating Instruction
SOP	Standard Operating Procedure ("the SOP) refers to the SOP associated to this Guideline
TGA	Therapeutic Good Administration (of Australia)
UK	United Kingdom of Great Britain and Northern Ireland
UMC	Uppsala Monitoring Centre (WHO-Collaborating Centre for International Drug Monitoring)
VL	Vigilance (used for pharmacovigilance in WHO-GBT terminology)
WHO	World Health Organization
WLA	WHO-Listed Authority (tWLA refers to a *transitional* WLA)
W&P	Warning & Precaution section of the CCSI
XML	Extensible Markup Language (standardized transmittable electronic file)

"Guideline" written with a capital letter refers to this Document.

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I. EXECUTIVE SUMMARY

This Guideline provides a structured approach to support National Regulatory Authorities (NRAs) in the assessment of Risk Management Plans (RMPs) for medicines and vaccines. Its primary objective is to strengthen regulatory decision-making in low- and middle-income countries (LMICs) by enabling reliance on evaluations performed by WHO Prequalification (PQ), WHO-Listed Authorities (WLAs), and other reference NRAs while ensuring adaptation to local health system needs.

Risk management planning is a proactive pharmacovigilance strategy introduced through the ICH E2E guideline (2004). RMPs combine two complementary elements:

- Pharmacovigilance activities to further characterize identified and potential risks and address missing information.
- Risk minimization measures to prevent or mitigate safety concerns and protect patients.

The Guideline emphasizes that while reliance can reduce duplication and optimize resources, local assessment remains essential. Risk minimization strategies developed for high-income settings may not always be feasible in LMIC contexts, necessitating tailored approaches that reflect national health system capacities, epidemiology, and population-specific factors.

Four main assessment scenarios are described:

- Situation A – WHO-PQ RMP available.
- Situation B – RMP endorsed by a WLA or other reference authority.
- Situation C – No PQ or WLA RMP available; reliance on publicly available sources.
- Situation D – Country-specific RMP submitted directly to the NRA.

To guide assessors, the document introduces the WHO Model RMP Assessment Template, structured around:

- Product information
- Epidemiology
- Indication
- Safety concerns (important identified risks, important potential risks, missing information)
- Pharmacovigilance plan (routine and additional)
- Risk minimization measures
- Assessment of benefit–risk balance

The Guideline further highlights the importance of good reliance practices, legal provisions for RMP submission, and the use of tools such as the WHO Global Benchmarking Tool (GBT). It also stresses the value of multi-stakeholder consultation, including expert committees, healthcare professionals, and patient representatives, to ensure feasibility and ownership of safety decisions.

By applying this Guideline, NRAs can:

- Conduct proportionate and efficient RMP assessments.
- Optimize the use of reliance pathways while ensuring local adaptation.
- Strengthen pharmacovigilance systems and protect public health through timely, evidence-based regulatory action.

II. FOREWORD

WHO aims to assure the safety of medicines and vaccines by ensuring reliable and timely exchange of information on safety issues, promoting pharmacovigilance activities throughout the Organization and encouraging Member States' participation in the WHO Programme for International Drug Monitoring (PIDM). This Guideline is developed to support National Regulatory Authorities (NRAs) in assessing risk management plans (RMP) as part of both marketing authorization and post-authorization changes. The application of the Guideline can be customized based on local RMP requirements (Country-Specific Annex).

The ultimate goal of pharmacovigilance (PV) is to ensure that medicinal products maintain a positive benefit-risk balance by preventing the occurrence of adverse effects inherent to those products or otherwise mitigating them.

Pharmacovigilance focuses on monitoring, assessing, compiling and analysing adverse reactions in order to identify safety signals and support decisions that prevent further harms.

Introduced in 2004 with the ICH-E2E guideline, the risk management planning (RMP) approach aims at anticipating the risks of new medicinal products and manage these..

The RMP approach combines a) a proactive PV strategy aimed at collecting additional information to better characterize important identified risks, or further investigate potential risks, and address missing information, and b) a proactive risk minimization strategy aimed at preventing the occurrence of important identified risks or mitigating their impact. Implementing RMP, including its risk minimization strategies, ensures that potential safety concerns are systematically identified, characterized, and addressed from the earliest stage of authorization, thereby helping to protect patients.

From this perspective, reliance on WHO-Listed Authorities (WLAs) or other Reference Regulatory NRAs is essential, as it allows NRAs to focus their resources on aspects specific to their own health care systems while avoiding unnecessary duplication of efforts. Access to RMP-relevant information from reference authorities is therefore crucial for NRAs when making their regulatory decisions, as it enables reliance. However, the submission of a RMP may not be required for all medicinal products, depending on national legal provisions and regulatory guidelines.

It is important to recognize that risk minimization methods designed for the health care systems of high-income countries (HICs) or other parts of the world may not always be feasible or effective in the context of low- and middle-income countries (LMICs). While reliance on the overall RMP assessment reports of a WLA or a reference authority provides a valuable foundation, additional country-specific consideration of the benefit–risk balance within the local healthcare system may be required, ensuring that safety decisions are optimized and tailored to national specificities and needs. This Guideline should not be viewed as a simplified summary of the methods used by WLAs. Rather, it is specifically designed for NRAs in LMICs, enabling them to make maximum use of assessment work already conducted by reference authorities, while focusing their own efforts and resources on areas where reliance is not feasible and on country-specific aspects.

The process described in this Guideline and related documents is organised to support four types of situations where an RMP is required under national regulations:

Situation A: WHO Prequalification (PQ) RMP available

When an RMP resulting from the WHO Prequalification (PQ) process is available, the NRA may conduct a simplified assessment.

Example: Assessment of an RMP for a WHO-prequalified product submitted under the WHO Collaborative Registration Procedure (CRP) for medicines and vaccines.

Situation B: RMP endorsed by a WLA or other reference authority

When an RMP has been reviewed and endorsed by a WLA or other reference authority and is accessible to the NRA, reliance can be applied.

Example: Assessment of an RMP during product authorization via a Collaborative Registration Procedure (CRP) that uses evaluations from a WLA or a recognized reference authority.

Situation C: No RMP accessible from PQ or WLAs/SRAs

When none of the above RMPs are available, the NRA may need to rely on publicly available RMP documents as a basis.

Example: Developing a risk management strategy for a generic product when neither the manufacturer nor the NRA has access to the originator's RMP. Ideally, this situation should be addressed through an agreement with a WLA, to get access to the approved RMP of the originator, thereby shifting the case to Situation B.

Situation D: Country-specific RMP submission

When a marketing authorization holder (MAH) submits country-specific RMP documentation directly to the relevant NRA, and none of the situations (A-C) apply, the NRA must conduct a full national assessment.

Under Situation D, the NRA may need to conduct a full, independent assessment of the RMP. This requires evaluating both the global evidence provided by the MAH and the locally relevant factors—such as health system capacity, epidemiology of the target disease, pharmacovigilance infrastructure, and the feasibility of proposed risk minimization measures. Because resources in many LMIC settings are limited, this situation can be particularly challenging. At the same time, it also provides the NRA with an opportunity to ensure that the benefit–risk balance and the design of risk minimization measures are fully adapted to local circumstances, leading to safety decisions that are optimized for the local context.

Example: Evaluation of a locally developed medical product for which no approved RMP exists elsewhere. A new product requiring an RMP is submitted for marketing authorization in an LMIC where neither WHO PQ nor WLA/other reference authority's RMPs are available. In such case, the NRA need to critically assess the RMP submitted by the MAH and provide recommendations adapted to local implementation.

The assessment of RMPs should make the best use of available expertise, including national and/or regional expert committees. Consultation of key stakeholders beyond MAHs, such as patient/consumer association and relevant healthcare professional associations/boards or learned societies can also be required to ensure feasibility and ownership of the final recommendations.

II. CONTEXT OF RISK MANAGEMENT PLANNING

Pharmacovigilance Planning represents a proactive strategy introduced in 2004 to enhance the original pharmacovigilance framework. Hence, the term *Pharmacovigilance* refers to a broad spectrum of pharmacovigilance activities, including risk management planning. However, pharmacovigilance is also commonly used to refer to the routine and additional activities related to the collection and analysis of cases of adverse reactions. The following figure provides an overview of the broad scope of pharmacovigilance activities including the specific pharmacovigilance activities performed in routine conditions or in the context of a Risk Management Plan.

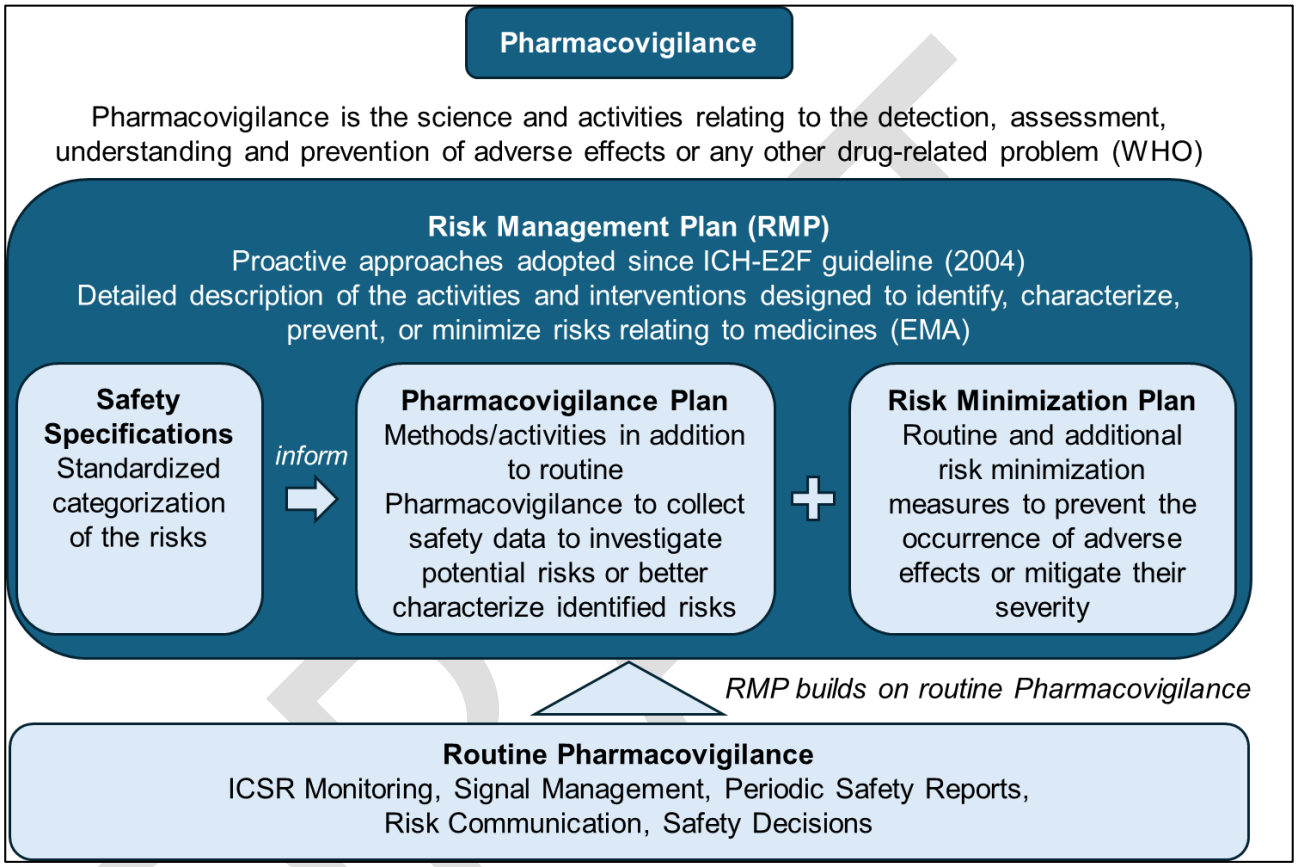

Figure 1. The comprehensive scope of Pharmacovigilance encompassing a) routine pharmacovigilance practices, b) pharmacovigilance planning, and c) risk minimization planning.

1. Routine pharmacovigilance

The purpose of routine pharmacovigilance, which is required for all authorized medicinal products, is to monitor the safety of authorized medicines to make safety decisions as early as possible. It includes:

1. **Collection of Individual Case Safety Reports (ICSRs)**: Gathering reports of suspected Adverse Drug Reactions (ADRs) for all different categories of medicines including vaccines (reported as Adverse Events Following Immunization, AEFIs).

2. **Data entry:** Entering **ICSRs** into a database structured according to the ICH-E2B international standard. Many NRAs use *VigiFlow, the online ICSR reporting management* system provided by the WHO-Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre (UMC).

3. **Data exchange:** Sharing of ICSRs by MAH with the NRA in the required international (E2B) format

4. **Global data sharing**: Based on NRA decision, ICSRs are transmitted from *VigiFlow* or equivalent national database to *VigiBase,* the global adverse events reports database maintained by the UMC on behalf of WHO and its Member States.

5. **Assessment of ICSRs:** NRAs evaluate individual and clustered case safety reports to explore potential causal associations between the suspected medicines and the reported ADRs.

6. **Signal detection:** Safety signals (i.e., new or changing associations suggesting a possible causal relationship between a medicinal product and an adverse event) are identified by analysing Drug-Event Combinations (DECs). A DEC represents the pairing of a specific medicinal product (or active substance) with a reported adverse event term. Each DEC may appear in one or more Individual Case Safety Reports (ICSRs). DECs form the basic analytical unit in signal detection because they allow regulators to examine whether a certain adverse event is reported more frequently with a given medicine compared to background expectations. Many NRAs use *VigiLyze,* the WHO-UMC safety data management system, to support systematic signal detection and prioritization.

7. **Assessment of Periodic Safety Update Reports (PSURs):** NRAs review PSURs that Market Authorization Holders (MAHs) are required to submit according to a pre-defined schedule and requirements. Under the current l ICH-E2C(R2) guideline, each PSUR must include a re-assessment of the benefit-risk profile, reason why PSURs are referred to as Periodic Benefit vs Risk Evaluation Reports (PBRERs).

8. **Reliance on reference assessments:** NRAs with limited resources may rely on PSUR evaluations performed by reference NRAs, while focusing on their own review of the analysis of domestic data and its implications within their health care systems. Because PSUR evaluation is resource-intensive, NRAs should carefully prioritize the products for which such review is required. Additionally, considering good regulatory practices, the application of reliance can help improve the efficiency of NRAs in general by avoiding duplication of efforts.

9. **Safety decisions:** Regulatory decisions on safety signals are an essential outcome of pharmacovigilance and risk management activities. Such decisions are based on the assessment of emerging safety concerns identified through diverse sources, including:
   - Individual case safety reports (ICSRs), whether single cases of serious harm or clusters suggesting a new safety signal
   - Periodic Safety Update Reports (PSURs/PBRERs)
   - Signal detection activities (local, regional, or global)
   - Scientific literature, media reports, or findings from observation studies
   - Alerts and regulatory decisions issued by the WHO and UMC or reference NRAs.

   While these sources provide the evidence base, the critical step for NRAs is determining the type of regulatory decision required to ensure patient safety. Decisions may include:

   - Requesting additional pharmacovigilance activities (e.g., Post-Authorization Safety Studies [PASS], pregnancy registries, enhanced surveillance).

- Introducing or strengthening risk minimization measures (RMMs), either routine (e.g., product information updates) or additional (e.g., controlled access, educational programs).
- Safety variations to product labelling, including updates to the SmPC, PIL, or packaging (e.g., new warnings, contraindications, dose restrictions).
- Issuing safety communications, such as Direct Healthcare Professional Communications (DHPCs), press releases, or guidance to health programs.
- Administrative measures up to and including suspension, restriction, or revocation of the marketing authorization.

These decisions should be proportionate to the level of risk, take into account the local healthcare system's capacity to implement measures, and, where possible, be aligned with reliance on decisions by WHO or trusted reference NRAs.

The sequential activities outlined above exemplify a reactive pharmacovigilance approach aimed at preventing the recurrence of observed adverse effects. Timely execution of these activities enables earlier safety-related regulatory decisions to safeguard patients receiving specific medicinal products in the country and timely information of healthcare professionals.

2. Towards Risk Management Planning

Risk Management is a proactive approach designed to anticipate and address potential safety concerns associated with a medicine from the earliest phase of market authorization. As evidence accumulates during the post-authorization phase, the RMP is revised to reflect the re-evaluation of better-characterized risks or the identification of any newly emerging risks.

Although the structure of RMPs may differ on specific NRA requirements, RMP documents typically include the following components: a) a product overview, including indication(s) and unmet medical needs within the relevant healthcare context, b) the safety specifications of the medical product, c) the pharmacovigilance plan, and d) the risk minimization plan.

Table 1: Essential Components of a RMP document

Product overview and indications	Summary of product information including how the product can meet target medical needs in the context of the health care system of the country under scope	
Safety specifications	• Important identified risks • Important potential risks • Missing information • Summary of safety concerns	
Pharmacovigilance plan	Routine Pharmacovigilance	• Additional pharmacovigilance • Post-authorization data generation
Risk minimization plan	Routine Risk minimization measures	• Additional safety interventions • Other risk minimization interventions (RMI) • Evaluation of risk minimization effectiveness

3. Context of RMP Assessment

3.1. RMP requirements and legal provisions

3.1.1. Products under scope

This guidance applies to medicines only; medical devices are outside the scope.

The categories of medicinal products under the scope for RMP submission vary across regulatory jurisdictions. It is therefore essential that these categories are explicitly stated in the national guidance for MAHs, preferably within Good Vigilance Practices (GVPs) and, where possible, also in the legal provisions for pharmacovigilance.

In most regulatory systems, biological products (including vaccines) and innovative/first-in-class medicines are included within the scope of RMP submission. By contrast, many high-income countries (HICs) do not generally require RMPs for generics, except in specific situations if there is an identified safety concern or additional risk minimization requirements are in place for the reference product, or the post-authorization safety data indicate that enhanced monitoring is required.

For LMICs, it is particularly important to specify whether requirements also apply to generic products. Providing such direction helps ensure proportionate regulatory expectations while maintaining adequate safeguards for patient safety. Where RMP submission is required for generics, MAHs should provide an adapted RMP or summary document addressing locally relevant safety concerns, with cross-references to the reference product's RMP when available. This allows the NRA to focus on verifying the completeness, relevance, and feasibility of proposed risk minimization activities within the local health-care context.

3.1.2. Stakeholders required to submit an RMP

RMPs are expected to be submitted by the MAH or by an applicant seeking marketing authorization in the country of commercialization. Depending on the regulatory requirements in the country, this may include the manufacturer, the local affiliate of the originator company, or an appointed distributor responsible for ensuring compliance with national requirements.

3.1.3. Legal provision for Risk Management Planning

A clear legal basis for RMP-related activities is essential for empowering the NRA to request the MAH to submit an RMP according to the requirements in accordance with the GVP, and ensure effective implementation of pharmacovigilance and risk minimization commitments.

The following provisions are recommended to be included in the national regulation:

- **Submission of core product information:** The summary of product characteristics (SmPC), the Patient Information Leaflet (PIL), and the packaging information at the time of Marketing Authorization with mandatory updates whenever changes occur. These documents form the foundation for any risk minimisation activity.

- **Advance notification of safety communications:** The obligation to submit to the NRA, prior to dissemination, any safety communication intended for healthcare professionals (e.g., Direct Healthcare Professional Communications, DHPCs).
- **Regulatory decisions from other authorities:** The obligation for the Marketing Authorization Holder (MAH) to submit timely information on safety-related regulatory decisions issued by other regulatory authorities.
- **Submission and updating RMPs:** The obligation to submit an RMP for designated categories of products as part of a New Drug Applications (NDA), or as a result of a benefit-risk review, as well as its update in case of any change in benefit vs risk balance.
- **Post-authorization safety studies (PASS) and data collection:** The obligation to conduct adequately designed safety studies or data collection programmes to address safety concerns requiring further investigation when requested by the NRA.
- **Risk minimization activities:** The obligation to implement adequately designed risk minimization measures (routine and additional) to address identified safety concerns, and to evaluate and demonstrate their effectiveness when requested by the NRA.

3.1.4. Regulatory requirements applicable to MAHs

It is recommended that a guideline be developed for the submission of RMP documents, to provide clear and consistent instructions to MAHs and other relevant stakeholders. This Guideline should specify the categories of products for which RMP submission is required, such as biologicals, biosimilars, vaccines, and innovative medicines.

Special consideration should be given to the generic products, with clear criteria defined for when an RMP is required.

3.2. Reliance on WHO-Listed Authorities (WLAs)

The WHO promotes regulatory reliance as a general principle to help NRAs make optimal use of available resources and expertise[1]. Reliance allows NRAs to focus on value-added regulatory activities that cannot be delegated, such as post-authorisation product-safety monitoring and products not authorised by reference authorities. In line with WHO's Good Reliance Practice (GRP), NRAs are encouraged to incorporate reliance into processes such RMP evaluation and related pharmacovigilance and risk-minimisation planning while taking into consideration the local context and specificities.

In the Annex 10 of the WHO Technical Report Series, No. 1033 (2021) defines reliance as *"The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent,*

[1] World Health Organization. (2021). *Annex 10: Good reliance practices in the regulation of medical products: High level principles and considerations* (WHO Technical Report Series, No. 1033). https://www.who.int/publications-detail/9789240021258

responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others". Its scope includes medicines, vaccines, blood and blood products and medical devices including in-vitro diagnostics.

Compared to reliance, *recognition* refers to a more formalized approach whereby one NRA recognizes the decisions of another NRA or Regional Regulatory System (RSS). Recognition usually requires formal and binding legal provisions.

3.2.1. Authorities qualified to serve as reference for reliance

Where appropriate, NRAs can rely on the work of WHO-Listed Authorities (WLAs). The current list of WLAs is available at the WHO website: https://www.who.int/initiatives/who-listed-authority-reg-authorities.

Annex 10 of the WHO Technical Report Series No. 1033 (2021) highlights common barriers to reliance, particularly the limited access to complete assessment reports from reference regulatory authorities. Ideally, such reports should be made publicly available. Where this is not the case, NRAs may obtain them through the MAH (if the company has access) or by submitting a direct request to the reference authority. In addition, confidentiality agreement between NRAs can facilitate exchange of assessment information, further effective reliance.

3.2.2. Global Benchmarking Tool

In the Vigilance (VL) section of the WHO Global Benchmarking Tool (WHO-GBT), attention to risk management planning is reflected in several sub-indicators. These address critical components of a functional regulatory system, such as

- existence of adequate legal provisions for a national vigilance system, including the regulations and guidelines for planning, conducting, monitoring, and reporting of vigilance activities
- NRA staff having access to essential information resources including RMPs, Periodic Safety Update Reports (PSURs) and Periodic Benefit- Risk Evaluation Reports (PBRERs).

The most relevant WHO-GBT sub-indicators for risk management planning are:

- VL04.04 – Legal provisions in place for pharmacovigilance activities
- VL04.05 – Availability of regulations and guidelines for pharmacovigilance, including risk management planning
- VL04.08 – Mechanisms for the assessment and monitoring of RMPs and risk minimization activities
- VL05.02 – Access of NRA staff to key information resources (e.g., RMPs, PSURs, PBRERs)
- VL06.01 – Processes in place to assess the effectiveness of risk minimization measures

III. RMP ASSESSMENT METHODS

1. Methods Used for Benefit-Risk Assessment and RMP Assessment

1.1. Identifying the RMP-relevant elements of the submission package

The content of an RMP submission may vary depending on context and should be defined in the applicable GVP.

As much as possible, the MAH should take responsibility for preparing and submitting the RMP in line with local requirements. Specifically, the MAH should ensure that:

- Submission package contains the latest version of all RMP-relevant documents.
- Documents are consistent with those endorsed by the reference authorities (where available).
- A clear comparison is provided between the reference RMP and the locally submitted version.
- A structured discussion of local relevance is included, following an agreed format (e.g. addressing local epidemiology, healthcare system capacity, and feasibility of proposed risk management measures).

The role of the NRA, particularly in settings where resources are limited, should primarily focus on the critical review of the MAH's submission. This review should ensure that the package is complete, accurate, and appropriately adapted to the local context.

Once the RMP package has been clearly identified, the review should confirm its completeness by focusing on key elements such as the product summary, indication(s), and target population, expected therapeutic benefits, safety specifications, pharmacovigilance activities, risk minimization plans, and the overall benefit–risk evaluation.

1.2. Screening for safety concerns

Safety concerns are defined as specific risks or knowledge gaps that may have an important impact on the benefit–risk balance of a medicinal product and therefore warrant further evaluation or risk minimization. These are typically summarized in the Safety Specification section of Risk Management Plans (RMPs) or other RMP-relevant documents, such as Public Assessment Reports (PARs). The Safety Specification provides a structured overview of what is known and unknown about a product's safety profile at the time of submission.

Some risks may not be highlighted in RMPs or PARs because they are considered adequately managed through routine pharmacovigilance—that is, the standard, ongoing safety monitoring activities such as spontaneous adverse event reporting, literature review, and inclusion of warnings in product information. Because the adequacy of routine activities may differ across health-care systems, it is therefore recommended to also review the Warnings and Precautions section of the Product Information (for prescribers) endorsed by the reference authority to ensure a complete list of all relevant safety concerns is considered.

According to the ICH-E2E guideline on pharmacovigilance planning, the safety concerns described in the Safety Specification section of the RMP should be categorized as follows:

1. Important Identified Risks: risks for which additional risk minimization may be needed.
2. Important Potential Risks: possible risks that require further evaluation; and
3. Important missing information: gaps in knowledge (e.g., use in special population) where additional pharmacovigilance or post-authorization studies may be warranted.

1.3. Assessing the pharmacovigilance and risk minimization plan of a WLA RMP assessment report in the context of the local health care system

This RMP assessment method is outlined in the following table (Table 2). The first step is a comparative evaluation of the benefit-risk balance as established or endorsed by the reference WLA. This consists of evaluating the extent to which the parameters used in the WLA's benefit-risk assessment are relevant to the local health care system, and whether local conditions might modify the outcome of the benefit-risk assessment (e.g. increased benefits or higher risks, unique healthcare system specific factors). Where differences are identified, a country-specific risk minimization strategy may be needed to ensure that the benefit-risk balance remains positive in the local setting.

For any safety concern requiring additional pharmacovigilance or risk minimization interventions, the next step is to assess whether the interventions requested or approved by the WLA are relevant, feasible, monitorable, and implementable, and likely to be effective within the context of the local healthcare system. If these criteria are not met, alternative approaches adapted to the local context should be considered. For instance, in some settings, it may be more effective for patient education and risk communication to be delivered by pharmacists or nurses at the point of care, depending on local healthcare infrastructure and practice patterns.

Table 2. Stepwise approach to assess RMP in a context of reliance

WLA serving as a reference	NRA relying on a WLA
Benefit-Risk Assessment established for a well-resourced economy	Assess the relevance of the benefit-risk balance, the PV Plan and the Risk minimization plan endorsed by the WLA in the context of the local health care system.
Routine methods considered sufficient for pharmacovigilance, safety communication, and risk minimization.	Assess whether routine pharmacovigilance activities can be adequately implemented in the target country. If not, then some form of enhancement of routine activities may be required to address the insufficiencies in the local context.
Routine methods insufficient, requiring implementation of an aRMM	Evaluate whether aRMM required by the WLA is suitable in the local context. If not, consider alternative methods more suitable for local implementation.
aRMM insufficient, requiring more restrictive measures	Evaluate whether the more restrictive aRMM required by the WLA is suitable locally. If not, consider alternative risk minimization strategies tailored to the local healthcare system.

To support the above comparative evaluation, particularly when alternative approaches may need to be considered, the following summary of routine and additional pharmacovigilance and risk minimization methods can serve as a useful reference (Table 3).

Monitoring the effectiveness of risk minimization measures (RMMs), both routine and additional (aRMMs), is important. While process indicators (e.g., logistical or implementation metrics) are generally straightforward to collect, assessing the actual impact of a risk minimization intervention often requires a statistically robust epidemiological study, which can be resource intensive. Measuring clinical or patient-level outcomes directly is even more challenging, given the methodological complexity and data limitations.

Table 3. Common pharmacovigilance and risk minimisation methods		
	Routine activities	Additional activities (interventions)
Product Vigilance	▪ Collection, follow-up and reporting of suspected adverse drug reactions, ▪ Continuous monitoring of the Benefit vs Risk profile	▪ Clinical trials ▪ Post-Authorization Safety Studies ▪ Patient registries ▪ Additional monitoring
Risk minimization	Routine ▪ Product labelling ▪ Product information for HCP ▪ Product information for patients ▪ Packaging information ▪ Package size ▪ Medicine scheduling	▪ Direct HCP communication ▪ Educational programmes or tools for HCPs and/or Patients/Care givers ▪ Controlled Access Programmes ▪ Pregnancy Prevention Programmes ▪ Other risk minimization programmes

1.4. Evaluating the Benefit vs Risk in a context of reliance

Under reliance, there is no need for duplicating the benefit-risk assessment performed by a WLA or WHO-PQ. The essential step of reliance pathway, proposed in this Guideline is a tailored local benefit-risk assessment that considers country-specific safety concerns, and the feasibility and expected effectiveness of the locally implemented pharmacovigilance and risk-minimization measures.

Methods (proposed steps)

1. Therapeutic context: Describe the pre-existing therapeutic options for the target disease in the local healthcare system.
2. Product characterization: Summarize the indication(s), target population, conditions of use, expected benefits, important risks and uncertainties of the medicine under review
3. Benefit-risk conclusion: Provide a concise summary weighing benefits vs risks in the local context.

The method applies to both initial marketing authorization (MA) and renewal. For renewals, the therapeutic context must reflect products introduced since the initial MA and the analysis should incorporate post-authorization safety and effectiveness data.

The Benefit vs Risk Summary is expected to be a comprehensive, concise and critical analysis of the product's benefit-risk balance. The benefit-risk balance should be assessed separately for each indication and for each population likely to receive the product. The assessment should explicitly include the strengths, limitations, and uncertainties of the evidence used. Potential misuse and medication errors need to be also considered. When off-label (non-approved) use is foreseeable, conduct a risk evaluation and propose appropriate mitigations.

The following three-step process is proposed to guide the benefit-risk assessment process (Table 4).

Table 4. Benefit vs Risk Assessment Process	
Part 1: Disease context and current therapeutic offer	
Item 1	Disease and condition intended to be addressed
Item 2	Current therapeutic options to address the above
Item 3	Remaining medical need under current therapeutic options
Part 2: Medical product under review	
Item 1	Target indications of the medical product
Item 2	Key characteristics
Item 3	Key benefits
Item 4	Uncertainties regarding benefits
Item 5	Safety profile: (Key risks and non-key risks)
Item 6	Uncertainties regarding risks
Item 7	Risk management needs
Part 3: **Benefit vs risk assessment summary**	

In case of reliance, the below table (Tabel 4-1) can be used after checking 1) version/date of the reference decision, 2) version/date of the MAH submission (Core RMP, and any Country-Specific Annex) and latest safety/label updates.

Table 4-1. Benefit vs Risk Assessment Process (Reliance)	
Part 1: Disease context and current therapeutic offer	
Item 1	Disease/condition: Check if local epidemiology and clinical practice match the reference setting and highlight key differences that could alter benefit or risk balance
Item 2	Current therapeutic options: Check if locally available therapeutic options differ from the reference authority's context
Item 3	Unmet need: Specify whether the unmet need is comparable
Part 2: Medical product under review	
Item 1	Indications: Confirm alignment with reference NRA by identifying target population difference (e.g. paediatrics) and state any local restrictions
Item 2	Key characteristics: Flag use-conditions that may differ locally (e.g. cold chain)
Item 3	Key benefits: State the reference efficacy/effectiveness conclusion, then check if local epidemiology would amplify or attenuate the benefits
Item 4	Benefit uncertainties: Check which uncertainties remain relevant locally and how to monitor them

Item 5	Safety profile: (Key risks and non-key risks): Check local risk factors (co-medication, genetics, nutrition, or co-endemic disease, etc.)
Item 6	Uncertainties regarding risks: Check if there are any risk uncertainties in the local context
Item 7	Risk management needs: State which RMMs are adopted as-is and which RMMs are not feasible for implementation. Check if any additional RMMs are needed.
Part 3: **Benefit vs risk assessment summary**	

1.5. RMP Source Documents for NRAs

Depending on the context and situation, the RMP-relevant document to be assessed by the NRA may differ as shown in the below tabulated summary of some examples (Table 5).

Table 5. Examples of RMP types and other RMP-relevant documents

	Accessibility	Remarks
WHO-PQ RMP	A signed agreement with WHO-PQ is required. Agreement with the manufacturer of the PQ product may also be required.	The company RMP or the approved RMP from a reference NRA is to be assessed to ensure it aligns with the conditions and needs of the local healthcare system , including the suitability of proposed risk minimization methods or need for additional ones.
EU-RMP	Confidentiality agreement required unless accessible from EMA website (or through SRA-CRP)	Elaborated by the MAH and subsequently approved by the EMA. Designed to fit with the healthcare system of the EU.
USFDA-REMS (Risk Evaluation and Mitigation Strategies)	Publicly available	Approved REMS documents are publicly available on the FDA website through the REMS@FDA database.
Part VI of EU-RMP	Publicly available	Summary of EU-RMP including a summary description of the safety concerns, pharmacovigilance plan, risk minimisation plan and post-authorisation studies.
Company RMP	Submitted by the MAH filing the NDA application.	Commonly names “Core RMP”. Reflect the opinions of the Manufacturer/MAH. When such RMPs are submitted, the NRA should request the MAH to provide the latest EMA-approved version of the EU-RMP.
Country-Specific Annex to the RMP	May be submitted by the MAH filing the NDA application in addition to the RMP	Intended to explain and justify the difference between the RMP submitted and the pharmacovigilance and/or risk minimization plans intended to be implemented in the country under scope.
WLA-RMP	A signed agreement with the WLA used as reference may be required.	Elaborated by the MAH and subsequently approved by a WLA. Designed to fit with the healthcare system of the Country of submission.

CTD Part 5	Provided by the MAH filing the NDA application.	Compared to an RMP, Part 5 of the CTD may not include as many details on the intended pharmacovigilance plan and risk minimisation plan.
EUPAR	Publicly accessible	European Public Assessment Reports. May not be available for all EMA-authorized medicines.
UK PAR	Publicly accessible	Available only for a limited number of products.
SwissPAR	Publicly accessible	For limited products, SwissPAR reports are available in English, French, German, Italian, searchable by trade name.
AusPAR	Publicly accessible	Australian Public Assessment Reports usually include a benefit-risk assessment discussion. Not available for all TGA-authorized medicines.
Product Monographs Canada	Publicly accessible	When relevant, the Warning & Precaution Sections and Contra-Indication section may refer to PV and RM measures stated in the RMP but lacking the necessary details for an assessment.
Prescriber's Information SmPC	Publicly accessible	WLA-endorsed Product Information for Prescribers are publicly accessible from the respective Health Authority website. When relevant, the Warning & Precaution, Contra-Indication or other safety sections may refer to PV and RM measures stated in the RMP but lacking the necessary details for an assessment.

IV. RMP ASSESSMENT PROCESS

1. Essential aspects to consider

When assessing or designing a risk management planning strategy in a context of reliance, the following essential aspects should be carefully considered (Table 6).

Table 6: Essential points to consider in assessing RMP in a context of Reliance	
Differences Between Health Care Systems	The RMP approved by the reference authority such as a WLA may have been designed for a healthcare system that differs significantly from the one in the local context. These differences should be carefully considered when assessing the RMP.
Scope of Safety Concerns	The RMP from the reference authority (example, WLA) may only address safety concerns that require additional pharmacovigilance or risk minimisation measures specific to its healthcare system. To avoid overlooking important risks, review all safety concerns listed under Contraindications and Warnings & Precautions in the product information, even if they are not addressed by additional interventions in the reference RMP.
Effectiveness of Local Pharmacovigilance	Routine pharmacovigilance practices in the local healthcare system may not be as robust as those in the reference healthcare system. Therefore, even if routine monitoring was deemed sufficient by the reference authority (example, WLA), it may not be adequate in the local setting to reach the objective of the post-authorisation safety monitoring.
Applicability of Routine Risk Minimisation	Routine risk minimisation methods (e.g., warnings in product information) that are sufficient in the reference healthcare system may not be effective under local conditions. Always evaluate whether these methods are expected to work as intended in the local healthcare system or whether additional strategies are needed.
Feasibility of Additional Risk Minimisation Measures (aRMM)	aRMMs developed for the reference healthcare system may be difficult to implement or ineffective in the local healthcare environment. In such cases, alternative measures that are more practical and likely to succeed locally should be identified and considered.

1.1. Overview of the different RMP assessment situations

As summarized in Table 7, the RMP assessment should be tailored—and, where appropriate, streamlined—according to the type of RMP or RMP-relevant document available. The RMP assessment process can be optimised depending on the availability of RMP-relevant document.

Table 7: Overview of the different RMP Assessment situations encountered			
Situation A	**Situation B**	**Situation C**	**Situation D**
"PQ RMP" available to the NRA	RMP approved by WLA or other recognized reference authority available to the NRA	Only public RMP-related documents (e.g. EU-RMP Part VI or other WLA Public Assessment Reports) available	Country/Region-specific RMP submitted with NDA; No approved RMP available
Example: PQ-CRP New Drug Application (NDA)	Example: SRA-CRP NDA	Example: local generic product without access to the innovators' RMP or a	Example: NDA without approved RMP available

		legacy product authorized before RMP requirements	
Remarks: The Marketing Authorization Holder (MAH) applying for WHO Prequalification is expected to provide a Risk Management Plan (RMP) accepted or reviewed by a reference authority or WHO-Listed Authority (WLA).	**Remarks:** The Marketing Authorization Holder (MAH) should provide a Risk Management Plan (RMP) with evidence of approval by a reference authority or WHO-Listed Authority (WLA).	**Remarks:** Documents used as a basis for assessment should be those recognized or endorsed by the National Regulatory Authority (NRA). If RMPs reflect only the Marketing Authorization Holder's (MAH's) internal assessments—without review or approval by a WLA, then these may not be appropriate for use in reliance-based regulatory decisions.	**Remarks:** In the absence of an approved RMP, a country/region-specific Risk Management Plan should be submitted in accordance with local regulatory requirements.
Safety Specifications: The NRA can rely on the content of the "PQ-RMP".	**Safety Specifications**: The safety sections (e.g. Warnings & Precautions and Contra-indications) of the SmPC should be screened in addition.	**Safety Specifications**: The safety sections (e.g. Warnings & Precautions and Contra-indications) of the SmPC should be used as basis.	**Safety Specifications**: The NRA needs to conduct complete and thorough assessment of the RMP.
Pharmacovigilance Plan **Risk Minimization Plan** The NRA may consider the WHO Prequalification RMP (PQ-RMP) as a primary reference, while ensuring tailoring to the local health system conditions and regulatory expectations.	**Pharmacovigilance Plan** **Risk Minimization Plan** The NRA may consider the RMP (approved by WLA or other recognized reference authority)- as a primary reference, while ensuring tailoring to the local health system conditions and regulatory expectations.	**Pharmacovigilance Plan** **Risk Minimization Plan** The published parts of a WLA-approved RMP (e.g., EU-RMP Part VI) or public assessment reports should be used as references to reconstruct key components of the RMP. The proposed methods can be evaluated for their appropriateness, feasibility, and potential impact within the local healthcare setting. Alternative measures may be developed as needed.	**Pharmacovigilance Plan** **Risk Minimization Plan** The NRA should undertake a thorough evaluation of the submitted RMP, ensuring that all proposed pharmacovigilance and risk minimisation activities are appropriate, feasible, and aligned with national healthcare system capacities and risk profiles.

2. RMP Assessment using the WHO Model RMP Assessment Template

2.1. Product Information

When reviewing the product information section, assessors can confirm the completeness, clarity, and consistency of key product details that may impact risk evaluation and risk minimization strategies.

Note: Assessors can utilise following questions to review the section if approved RMP is not available for *Reliance*.

Guiding questions:

Basic Product Identification

- Is the INN (International Nonproprietary Name) provided?
- Is the reference/originator product specified?
- Is it a fixed-dose combination? If so, are all active components listed?

Regulatory & Authorization Context

- Is it approved in other regions (e.g., EU, US)?
- Are all authorized indications listed (as per SmPC)?
- Are off-label or expected off-label uses considered (e.g., paediatrics, elderly)?
- Is the information consistent with SmPC/regulatory documents, and are risks/RMMs appropriately linked to product characteristics?

Clinical Use & Risk-Relevant Characteristics

- Are the recommended dose and route of administration clearly stated?
- Are there known dose-dependent risks?
- Is there a need for titration, and are monitoring requirements specified?
- Are indication-specific risks addressed (e.g., immunosuppression in oncology)?
- Are known abuse, misuse, or dependence risks highlighted?

Special Populations

- Are vulnerable populations (renal/hepatic impairment, children, pregnant women, elderly) addressed?

Storage, distribution and other risk linkage

- Are there risks associated with temperature excursions (e.g., vaccine potency)?
- Are storage and handling conditions relevant for the healthcare setting (e.g., hospitals vs. community)?
- Are there any safety concerns that arise directly from this product information?
- Are the identified risks and risk minimization measures linked to these product characteristics?

2.2. Epidemiology

When reviewing the epidemiology section, assessors can review the benefit-risk balance of the product in the context of local use and population characteristics. This will help assessors to identify whether the disease burden justifies the use of the product and assess whether certain risks may be higher or lower in the local setting. Assessors can ensure the proposed risk minimisation measures are relevant and tailored to the actual users. The section also helps to identify any subpopulations (e.g., children, elderly, immunocompromised) that may have unique safety concerns. The section also helps to identify commonly used medicines that may interact with the product, increasing the risk of adverse effects or reducing effectiveness.

Note: Assessors can utilise following questions to review the section if approved RMP is not available for *Reliance*.

Guiding questions:

Disease Burden & Epidemiology

- What is the incidence and/or prevalence of the disease in the relevant regions or populations?
- Is the epidemiological data up to date and referenced properly?
- Is the disease burden described (e.g., morbidity, mortality, quality of life)?
- Are there regional, ethnic, or demographic differences in disease epidemiology?

Target population

- Who are the intended recipients of this treatment (e.g., age group, sex, special populations)?
- Are vulnerable populations included (e.g., paediatrics, elderly, pregnant women, immunocompromised)?
- Are genetic or metabolic differences relevant to efficacy or safety in the local population?

Risk factors and subgroups

- Are there subgroups with a higher baseline risk of adverse events?
- Are special subgroups identified that may require tailored safety monitoring?
- Does the target population profile raise specific needs for risk minimization (e.g., limited literacy, health system capacity)?

Concomitant therapies and interactions

- What are the most common concomitant therapies used with this product?
- Does the drug have known interactions with other medicines?
- Could concomitant use increase the risk of AEs (e.g., QT prolongation, bleeding)?

2.3. Indication

When reviewing the indication section, assessors can ensure that the benefit–risk profile remains appropriate for the target population and setting and consider what studies / additional risk minimisation measures could be required to this end. Also, the assessors can identify population-specific risk factors as certain subgroups within the indicated population may be at higher risk (e.g., pediatrics, elderly, patients with comorbidities).

Note: Assessors can utilise following questions to review the section if approved RMP is not available for *Reliance*.

Guiding questions:

Scientific and clinical justification

- Is there a clear unmet medical need or advantage over existing therapies?
- Does the benefit–risk balance remain positive within the proposed indication?

Scope and target population

- Does the indication clearly define for each age group the medicine is indicated for?
- Who are the intended recipients of this treatment (e.g., age group, sex, special populations)?
- Is the indication too broad or too narrow compared to the clinical trial population?
- Are any subgroups (e.g., elderly, children, pregnant women) included without sufficient supporting data?
- Does the proposed indication include high-risk populations (e.g., immunocompromised, elderly, patients with co-morbidities)?
- Does it imply a large or vulnerable target population, increasing exposure and risk?

Regulatory Consistency

- Should the indication be modified, restricted, or clarified to ensure safe and appropriate use?
- Is the proposed indication consistent with the SmPC (Summary of Product Characteristics)?
- Is it the same or different from the indication approved in other regulatory jurisdictions (e.g., FDA, EMA)?

Risk Management & Pharmacovigilance Considerations

- Does the indication suggest off-label use potential (e.g., vague wording or broad population)?
- Will the indication require additional risk minimization measures or pharmacovigilance activities?

- Is there an intention to include pediatric population, pregnant or breastfeeding women, and patients with renal or hepatic impairment? (e.g. Is a pediatric Investigation Plan in place?)
- Does the indication raise population-level concerns, such as herd immunity, resistance, or misuse?

2.4. Safety Concerns and Methods to Address them

This section includes three key categories of safety concerns:

Important Identified Risks: Adverse reactions for which there is sufficient evidence of an association with the product. These risks have been observed in clinical trials, post-marketing experience, or published literature and are considered clinically significant for patient safety.

Important Potential Risks: Safety concerns for which there is reasonable scientific suspicion of an association with the product, but where the evidence is not yet conclusive. These require further evaluation and monitoring to confirm or rule out the risk.

Missing Information: Gaps in knowledge about a medicinal product's safety profile related to use in certain populations or under specific conditions. Some common examples include the use during pregnancy, breastfeeding, elderly, patients with renal or hepatic impairment, long-term use).

Assessors should ensure that all clinically significant risks and gaps in knowledge are clearly documented and appropriately categorized. This categorization enables regulators to understand the product's safety profile and to ensure specific pharmacovigilance methods (e.g., post-marketing studies, adverse event monitoring) are in place to monitor or further characterize each listed safety concern.

This section also helps assessors to determine whether risks can be managed through routine RMMs (e.g., product labelling, package leaflet) or whether additional RMMs (e.g., controlled distribution, restricted access, prescriber or patient educational tools) are needed.

In the case of missing information, assessors should evaluate if additional studies or registries are needed to generate new data in under-studied areas or populations (e.g., pregnancy, elderly, specific co-morbidities).

Finally, assessors should track changes to the list of safety concerns throughout the product life cycle and evaluate the effectiveness of the risk management strategies in place.

Note: If no approved RMP is available for *Reliance*, assessors can use the following guiding questions to review this section.

Guiding questions:

Safety Concerns

- Are the risks appropriately categorized (identified vs. potential vs. missing)?
- Are there any important identified or potential risks, or missing information overlooked?
- Are the proposed risk minimization and pharmacovigilance activities aligned with the nature and severity of each concern?
- Do any safety concerns require further clarification, refinement, or additional evidence?

<u>Important identified risks</u>

- Is the risk clearly defined and medically plausible?
- What is the nature, severity, and frequency of the adverse event?

- Is there robust evidence supporting a causal relationship?
- What risk minimization measures are proposed? Are they adequate and proportionate (routine vs. Additional)?

Important potential risks

- Is there a biological or pharmacological plausibility for the suspected risk?
- Are interim risk minimization measures appropriate given the uncertainty?

Missing information

- Are there clear plans to address the missing information? Are there plans for post-authorization studies or registries? Is there a Pediatric Investigation Plan (PIP)?
- Are there important uncertainties in the local population / healthcare system that need studying (e.g. pregnancy, elderly, comorbidities)?
- Are current measures adequate to manage the uncertainty while data are being collected?

Pharmacovigilance (PV) Plan

- Are there locally relevant special populations that may impact risk (e.g., pediatrics, pregnancy, higher prevalence of renal/hepatic impairment/diabetes)?

Routine Pharmacovigilance:

- Is routine PV (e.g., spontaneous reporting, literature review, signal detection) considered sufficient to monitor the identified risk?
- Are local reporting systems capable of detecting and assessing the identified risk?

Additional Pharmacovigilance:

- Is additional pharmacovigilance needed in the local context (e.g., registries, post-authorization safety studies (PASS), enhanced surveillance)?
- Is the design of additional PV activities appropriate (objectives, population, duration)?
- Are there any local requirements for safety data (e.g., ethnicity-related metabolism differences)?
- Are there clear timelines, endpoints, and methods for data collection defined?

Risk minimization plan/measures

- Are the proposed risk minimization measures adequate and proportionate to the level of risk?
- Are there needs for additional risk minimization measures considering the local clinical context (e.g., diagnostic capabilities, monitoring practices, treatment alternatives)?

2.5. Important information in pre- and post-marketing authorization

When reviewing the indication section, assessors should evaluate whether the submitted studies are scientifically justified, well-designed, feasible, and proportionate to the level of risk. Assessors should also verify that the proposed or approved post-authorisation safety and efficacy studies (PASS/PAES) are appropriately designed to address identified safety concerns and missing information. The evaluation of such studies often requires the expertise of an epidemiologist.

Note: Assessors can utilise following questions to review the section if approved RMP is not available for *Reliance*.

Guiding questions:

Relevance and Scope:

- Does it address important safety concerns, missing information, or residual uncertainties?
- Will the study include the local population where the product will be used?

Scientific and Methodological Quality:

- Are the design and methodology robust enough to meet their objectives?
- Is the study design appropriate for the objectives (observational, interventional, registry-based, cohort, case-control, randomized, etc.)?
- Has the applicant proposed a reasonable follow-up duration to observe outcomes?

Data Quality and Validity:

- Are data likely to be of sufficient quality and completeness for reliable conclusions?
- Is there a risk of bias, confounding, or loss to follow-up that could affect results?

Feasibility:

- Is the study feasible in the proposed setting?

2.6. Assessment of the Benefit-Risk Balance

When reviewing the indication section, assessors should critically evaluate whether the therapeutic benefits of a product outweigh its known and potential risks, taking into account the proposed risk management measures and any residual uncertainties. Also, the assessment should consider both the overall population and relevant subpopulations.

Note: Assessors can utilise following questions to review the section if approved RMP is not available for *Reliance*.

Guiding questions

General Benefit-Risk Assessment

- Is the overall benefit–risk balance positive, uncertain, or negative?
- Do the benefits outweigh the risks in the proposed indication?
- Is the benefit–risk balance favorable in all relevant subpopulations (e.g. children, elderly, patients with comorbidities)?
- Are further data needed post-authorization to maintain or improve confidence in the benefit–risk profile?
- Are additional risk minimization measures required to ensure a positive benefit-risk balance in the whole population defined by the indications?

Assessment of Benefit

- What are the main therapeutic benefits of the product?
- How does the product compare to existing treatments? (Superior, non-inferior, or complementary?)
- Is there a benefit to public health, particularly in addressing unmet medical needs?
- Are there gaps or uncertainties in efficacy data?

Assessment of Risks

- What are the key risks, and do they include high-impact risks (e.g., fatal, disabling, or irreversible events)?
- Is the overall safety profile acceptable for the proposed indication and population?
- Are routine pharmacovigilance and risk minimization measures sufficient?
- Are additional activities (e.g., PASS, educational programs, controlled access) needed?

3. Applications of *Reliance*

When NRAs review an RMP, the following principles should be considered, particularly in resource-limited settings.

1. Leveraging existing RMPs to optimize resources:
National Regulatory Authorities (NRAs) are encouraged to rely on Risk Management Plans (RMPs) developed in the context of WHO Prequalification (PQ) or those approved by a recognized reference authority such as the WHO Listed Authority (WLA). This approach allows NRAs to focus their efforts on assessing aspects of the RMP that require local adaptation to suit the specific conditions of the national healthcare system, while avoiding duplication of work.

2. Clear regulatory expectations for RMP submissions:
To facilitate effective reliance and ensure that appropriate information is received, national regulations and guidance should clearly specify the RMP-related documents that must be submitted by the Marketing Authorization Holder (MAH). This helps avoid misunderstandings and supports a consistent and efficient review process.

3. Access to adequate expertise and consultation with relevant stakeholders:
For effective reliance and proportionate RMP assessment, NRAs should ensure access to the necessary expertise and engage in structured consultation with relevant stakeholders. Internal expertise includes trained pharmacovigilance staff, regulatory reviewers, epidemiologists, and clinical specialists to interpret benefit–risk profiles and assess feasibility of risk minimization measures. External or regional expertise includes advisory committees, academic experts, and regional regulatory networks to provide additional perspectives and support where internal capacity is limited.

4. Use of Approved vs. Core Company RMPs:
RMPs prepared solely as part of a company's internal global safety strategy, but not reviewed or approved by WHO PQ or a recognized reference authority such as a WLA may not be appropriate as a basis for reliance. In such cases, further evaluation or additional documentation may be required to ensure alignment with regulatory expectations.

5. Consideration of the scope and focus of RMPs:
RMPs approved in other jurisdictions (e.g., EU-RMPs) often focus on safety concerns requiring additional interventions within that specific health care system. To ensure the assessment of local context, NRAs relying on RMPs from other jurisdictions should review all safety concerns listed in the safety sections (e.g. Warnings & Precautions and Contraindications sections) of the product information, even if they were not subject to additional measures in the reference RMP.

6. Adapting Risk Minimisation Measures to local context:
A safety concern that warrants additional risk minimisation in a well-resourced setting is likely also relevant elsewhere. However, the choice of measures should be adapted to the local healthcare system to ensure they are practical, feasible, and effective. Where original measures are not

applicable or implementable, alternative approaches tailored to local conditions should be considered.

ANNEX 1 KEY DEFINITIONS

DEFINITION OF TERMS
RELAVANT FOR RISK MANAGEMENT PLANNING

Source of information: Council for International Organisations of Medical Sciences (CIOMS) Cumulative Glossary with focus on Pharmacovigilance Version 2.1, CIOMS, Geneva 2023.

GENERAL TERMS	REFERENCE
Acceptable risk: The degree of risk (likelihood of an adverse event or outcome) that a person or group is prepared to take or considers reasonable. However, what may be acceptable for one person or group may not be to another.	CIOMS XI (2022: Patient involvement)
Active surveillance system: A system for the collection of case safety information as a continuous pre-organised process. Active surveillance can be 1.) Drug based: identifying adverse events in patients taking certain products; 2.) identifying adverse events in certain healthcare settings where they are likely to present for treatment 3.) Event based: identifying adverse events that are likely to be associated with medicinal products, e.g., liver failure.	CIOMS DILI (2020)
Additional risk minimisation measure (= **Additional risk minimisation activity**) (= **Risk Minimisation Intervention** (RMI) (See also Risk minimisation measure and Routine risk minimisation measure: A risk minimisation measure which is in addition to the routine risk minimisation activities which apply to all medicinal products in a particular region or territory.	CIOMS XI (2022: Patient involvement
Adverse event of special interest (= **Targeted medical event**): An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such an event may require further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties may also be needed (e.g., regulators).	CIOMS VI (2005) Clinical trial safety information
Benefit: An estimated gain for an individual or a population.	WHO (2002): The Importance of PV
Benefit: Usually refers to a gain (positive result) for an individual or a population. ''Expected'' benefit can be expressed quantitatively, and this would ordinarily incorporate an estimate of the probability of achieving the gain. Some definitions of benefit may include reference not only to clinical improvement but also to quality of life and economic consequences.	CIOMS IV (1998) Benefit-risk.
Boxed warning (= **Black box warning**): A warning that appears on a prescription drug's label and is designed to call attention to serious or life-threatening risks. Not all health authorities implement boxed warnings in the label, however some health authorities do (e.g., those of the U.S., the United Kingdom and Japan). In the U.S., boxed warnings are ordinarily used to highlight for prescribers one of the following situations: (1) There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening, or permanently disabling adverse reaction) that it is essential it be considered in assessing the risks and benefits of using the drug, OR (2) There is a serious adverse reaction that can be prevented or reduced in severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoid certain concomitant therapy, addition of another drug or managing patient in a specific manner, avoiding use in a specific clinical situation), OR (3) FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (…) Infrequently, a boxed warning can also be used in other situations to highlight warning information that is especially important to the prescriber (e.g., reduced effectiveness in certain patient populations). Infrequently, a boxed warning can also be used in other situations to highlight warning information that is especially important to the prescriber (e.g., reduced effectiveness in certain patient populations).	CIOMS DILI (2020)
Burden of a risk minimisation activity: Burden is defined as the additional load that a risk minimisation activity imposes on (1) patients, (2) carers, (3) the healthcare system including	CIOMS IX (2014): Risk minimisation

health care professionals, (4) others such as regulatory authorities, pharmaceutical companies, the supply chain, and those involved in access and supervision of the use of medicines. The burden may impact, for example: a.) Patients by adversely affecting their access to prescribed medicines and/or needed healthcare services, daily activities, or routines; b.) Healthcare providers by adding steps or services that are normally, c.) Not required in the day-to-day management of their medical area; d.) The health care system by requiring extra human and/or financial resources; d.) Other entities of the healthcare system by including additional, e.) scientific evaluation of the risk minimisation plan, its implementation, and its effectiveness.	
Burden to patients: The additional load that a clinical activity imposes on patients above that which would be experienced under normal clinical practice.	CIOMS XI (2022): Patient involvement
Cohort Event Monitoring (CEM): A surveillance method that requests prescribers to report all observed adverse events, regardless of whether or not they are suspected adverse drug reactions, for identified patients receiving a specific drug. Also called prescription event monitoring.	CIOMS VIII: Signal detection 2010 and Glossary of terms used in PV. WHO-UMC.
Cohort study (prospective or retrospective): Cohort studies are studies that identify subsets of a defined population and follow them over time, looking for differences in their outcome. Cohort studies can be performed either prospectively, that is simultaneous with the events under study, or retrospectively, that is after the outcomes under study had already occurred, by recreating those past events using medical records, questionnaires, or interviews.	CIOMS IX (2014): Risk minimisation
Company Core Safety Information (CCSI). All relevant safety information contained in the Company Core Data Sheet prepared by the MAH (Marketing Authorisation Holder) and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.	CIOMS VII (2006) DSUR
Direct Healthcare Professional Communication (DHPC): A direct healthcare professional communication (DHPC) is a communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorisation holder or by a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. For example, a DHPC may aim at adapting prescribing behaviour to minimise particular risks, and/or to reduce the burden of adverse reactions with a medicinal product.	CIOMS IX (2014): Risk minimisation and EU GVP: Module XVI (2014) Risk-min. measures: selection of tools and effectiveness indicators
Dominant risk: The risk that is considered to be the major contributor to the overall risk profile.	CIOMS IV (1998): Benefit-risk
Educational tool: Material designed to impart awareness, knowledge, and aid comprehension of specific information.	CIOMS IX (2014): Risk minimisation
Effect modifier: A feature of study individuals such that a treatment or risk factor has different effect at different levels of the feature, i.e. that there is an interaction between the feature and the treatment. The term is mostly used in an epidemiological context.	CIOMS X (201): Meta-analysis
Effectiveness: Extent to which an intervention when used under the usual clinical circumstances does what it is intended to do for a defined population.	CIOMS IX (2014): Risk minimisation
Effectiveness of risk minimisation: Measure of effect of risk minimisation in a setting allowing for meaningful conclusions with regard to the use of a medicinal product.	CIOMS IX (2014): Risk minimisation
Effectiveness threshold: Minimum acceptable level of risk minimisation to be achieved in order for the intervention to be rated a success. The effectiveness threshold is determined subjectively taking into account the impact of risk, the vulnerability of the target population, the drug's benefit in a given indication as well as aspects of practicality and feasibility.	CIOMS IX (2014): Risk minimisation
Efficacy: Efficacy is the ability of a medicine or medical technology to bring about the intended beneficial effect on individuals in a defined population with a given medical problem, under ideal conditions of use.	CIOMS IV (1998) Benefit-risk and CIOMS VI (2005): Clinical trial safety information.
Efficiency: Results achieved in relation to the resources invested.	CIOMS IX (2014): Risk minimisation

Harm: Damage qualified by measures of frequency of occurrence, severity, or duration.	CIOMS IX (2014): Risk minimisation
Hazard: A situation or given factor that under particular circumstances could lead to harm. A source of danger.	CIOMS IX (2014): Risk minimisation
Identified risk: An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples include a.) an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data; b.) an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group, on a parameter of interest suggests a causal relationship; c.) an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions. In a clinical trial, the comparator may be placebo, active substance, or non-exposure.	CIOMS IX (2014): Risk minimisation
Important identified risk and **Important potential risk:** An identified risk or potential risk that could impact on the benefit-risk profile of the product or have implications for public health. What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk, and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important.	CIOMS IX (2014): Risk minimisation
Important missing information: see Missing information.	CIOMS IX (2014): Risk minimisation
Incidence: Number of new cases of an outcome which develop over a defined time period in a defined population at risk. In an epidemiologic sense incidence is a measure where the numerator refers to the number of events (counting only the initial event in each patient) and the denominator often refers to the total person-time at risk during exposure to the study drug.	CIOMS IX (2014): Risk minimisation
Medication guide: Printed document supplied with many prescription medicines that contains U.S. FDA-approved information on particular issues and that can help patients avoid serious adverse events.	CIOMS XI (2022) Patient involvement
Minimal risk: A situation where the probability, and the potential seriousness, of harm or discomfort anticipated in the research are no more than ordinarily encountered in daily life or the performance of routine physical or psychological examinations or tests.	CIOMS XI (2022) Patient involvement
Missing information: Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant.	CIOMS IX (2014): Risk minimisation
Normal/Current clinical practical: Medical care typically used in a particular country, region, or hospital to treat, prevent, or diagnose a disease or a disorder.	CIOMS XI (2022): Patient involvement
Number needed to harm (NNH): The number of individuals needed to be treated for some specified period of time in order that one person out of those treated would have one harmful event (during some specified time period). NNH is the inverse of the absolute risk difference between a treated and a control group. For example, if the rate of a hepatic event is 5% in the treated group as opposed to 1% in a control group over one year of treatment, the difference is 4%. Thus, 25 people would need to be treated for one year to prevent one event (1/25 = 4%).	CIOMS DILI (2020)
Number needed to treat (NNT): The number of individuals needed to be treated for some specified period in order that one person out of those treated should have the desired benefit/outcome, such as the prevention of a medical event under treatment (MI, e.g.). NNT is the reciprocal of the difference in rates of the measured benefit, between a treated and a control group.	CIOMS VI (2005) Clinical trial safety information
Off-label use: Use of a medicine or vaccine in a way that is not in line with its authorised use.	CIOMS XI (2022): Patient involvement
Outcome indicators: Outcome indicators provide an overall measure of the level of risk control that has been achieved with any risk minimisation measure in place. For example, where the objective of an intervention is to reduce the frequency and/or severity of an adverse reaction, the ultimate measure of success will be linked to this objective.	CIOMS IX (2014): Risk minimisation
Package leaflet (= **Patient product information**): A leaflet containing information for the user, which accompanies the medicinal product.	CIOMS XI (2022): Patient involvement
Passive surveillance (of spontaneous reports): A surveillance method that relies on healthcare providers (and consumers in some countries) to take the initiative in communicating suspicions	CIOMS VIII (2010) Signal detection

of adverse drug reactions that may have occurred in individual patients to a spontaneous reporting system.	adopted by CIOMS DILI (2020)
Patient Involvement (=**Patient engagement**): The active, non-tokenistic and collaborative interaction between patients, the patient community, and other stakeholders, where decision making is guided by patients' contributions as partners, recognising their unique experiences, values and expertise.	CIOMS XI (2022): Patient involvement
Patient expert: A person living with a health condition whose knowledge and experience enables the person to take more control over personal health by understanding and managing the health condition. Expert patients may also act as advocates for their condition and help other patients with the same health issue.	CIOMS XI (2022): Patient involvement
Patient information leaflet (PIL) (See Package leaflet)	CIOMS XI (2022): Patient involvement
Patient labelling (See Package leaflet)	CIOMS XI (2022): Patient involvement
Patient organisation (=Patient group): An institution that represents the interests and needs of patients (and their families and caregivers) who have a particular disease, disability or group of diseases and disabilities. Patient organisations may engage in research, education, advocacy and fundraising to further the needs of their patient group.	CIOMS XI (2022): Patient involvement
Patient Package Insert (PPI) (See Package Leaflet).	CIOMS XI (2022): Patient involvement
Patient preference studies: The qualitative or quantitative assessment of the desirability, or acceptability to patients of choices of outcomes or other attributes, that differ among alternative health interventions.	CIOMS XI (2022): Patient involvement
Patient registry: An organised system that collects uniform data on specified outcomes in a population defined by a particular disease, condition, or exposure.	CIOMS XI (2022): Patient involvement
Pharmacoepidemiology: The study of the use and effects of drugs (including biologicals and vaccines) in large numbers of people using methods, analyses and reasoning based on general epidemiology (see also Pharmacology and Epidemiology).	CIOMS XI (2022): Patient involvement
Plain language: Communication that the audience can understand the first time they read or hear it.	CIOMS XI (2022): Patient involvement
Post-authorisation. The stage in the life-cycle of a medicinal product that follows the granting of the marketing authorisation, after which the product may be placed on the market.	CIOMS VIII (2010) Signal detection
Post-authorisation efficacy study (PAES). A study conducted after a medicine is authorised to address scientific uncertainties around how well a medicine works in its authorised indication.	CIOMS XI (2022): Patient involvement
Post-authorisation safety study (PASS): Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures. A post-authorisation safety study may be an interventional clinical trial or may follow an observational, non-interventional study design.	EU DIR 2001/83/EC Art 1(15)] and CIOMS XI (2022): Patient involvement.
Post-marketing surveillance: Monitoring for adverse reactions to marketed products.	CIOMS VIII (2010) Signal detection
Potential risk: An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. Examples include: a.) toxicological findings seen in non-clinical safety studies which have not been observed or resolved in clinical studies: a.) Adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), b.) on a parameter of interest raises a suspicion of, but is not large enough to suggest a causal relationship; c.) a signal arising from a spontaneous adverse reaction reporting system; d.) an event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the medicinal product.	CIOMS IX (2014): Risk minimisation
Power: In statistical terms, a measure or indication of whether an analysis that is conducted is good at detecting differences. A powerful analysis is one that finds differences to be statistically significant. Power largely depends on how many events are observed, which Therefore, depends both on how many individuals are studied (the more studied, the greater the power) and on the rarity of the event (the less there are, the less powerful).	CIOMS VI (2005) Clinical trial safety information
Pragmatic trial: A randomised controlled study designed to evaluate the effectiveness of interventions in real-life routine practice conditions.	CIOMS XI (2022): Patient involvement

Pre-authorisation (= **Pre-marketing**): The stage in the life-cycle of a medicinal product before the drug has obtained a marketing authorisation.	CIOMS VIII (2010) Signal detection
Prescription Event Monitoring (PEM) or **Cohort Event Monitoring** (CEM): A surveillance method that requests prescribers to report all observed adverse events, regardless of whether or not they are suspected adverse drug reactions, for identified patients receiving a specific drug. Also more accurately named "cohort event monitoring".	CIOMS VIII (2010): Signal detection
Process indicators: Process indicators are measures of the extent of implementation of the original risk minimisation plan, and/or variations in its delivery.	CIOMS IX (2014): Risk minimisation
Product information (PI): Documents proposed by marketing authorisation holders/applicants, amended if required and agreed by regulatory authorities, which provide information to prescribers /HCP or patients on the appropriate and safe use of a medicinal product. As such the product information constitutes the main tool used for routine risk minimisation. For examples regarding terminology used in different regulatory jurisdictions. The EU labelling on the immediate or outer packaging is a part of product information.	CIOMS IX (2014): Risk minimisation adopted by CIOMS DILI (2020)
Registry In Europe: an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition, or exposure. **In the USA**: a patient registry is an organised system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.	EU-GVP Annex I - Definitions (Rev 4). 9 (2017) adopted by CIOMS DILI (2020)
Resource-limited setting (RLS): A country or locale where the capability to provide care for life-threatening illness to most of the population is limited to basic critical care resources, with no or very limited possibility of referral to higher care capability.	CIOMS XI (2022): Patient involvement
Restricted access programme, also known as **Managed/Controlled access** in some jurisdictions: Restricted access programmes aimed at medicinal product risk minimisation consist of interventions seeking to restrict access to a medicine on the market beyond the level of control ensured by routine risk minimisation measures. Examples of interventions that can be linked to restricted access programmes, alone or in combination may include: a.) Documentation of specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria before the patient can receive the medication; b.) Documentation of prescriber, dispenser and/or patient documenting their receipt and understanding of information on the serious risk/s associated with the medicinal product; c.) Explicit procedures for systematic patient follow-up through enrolment in a specific data collection system e.g. patient registry; d.) The medicine being made available for dispensing only through pharmacies or other appropriate distribution channels that are registered and approved to dispense the medicinal product (controlled distribution).	CIOMS IX (2014): Risk minimisation
Risk: The probability of an adverse event, or an outcome, in a defined population over a specified time interval.	CIOMS XI (2022): Patient involvement
Risk: The probability of developing undesirable outcomes relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health or any undesirable outcomes with regard to the environment	CIOMS IX (2014): Risk minimisation
Risk assessment: Risk assessment consists of identifying and characterising the nature, frequency, and severity of the risk associated with the use of a product. Risk assessment occurs throughout a product's lifecycle, from the early identification of a potential product, through the premarketing development process, and after approval during marketing.	CIOMS IX (2014): Risk minimisation
Risk-benefit balance: An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks, *i.e.* any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health.	CIOMS IX (2014): Risk minimisation
Risk communication: Any exchange of information concerning the existence, nature, form, severity or acceptability of health or environmental risks. Effective risk communication involves determining the types of information that interested and affected parties need and want, and presenting this information to them in a useful, accessible, and meaningful way.	CIOMS IX (2014): Risk minimisation
Risk elimination: Absolute or complete prevention of risk, *i.e.* reduction of the frequency of an undesirable outcome to zero.	CIOMS IX (2014): Risk minimisation
Risk evaluation: Risk evaluation is the complex process of determining the significance of value of the identified hazards and estimated risks to those concerned with or affected by the	CIOMS VIII (2010) Signal detection

decision. It therefore includes the study of risk perception and the trade-off between perceived risks and perceived benefits. It is defined as the appraisal of the significance of a given quantitative (or where acceptable, qualitative) measure of risk.	
Risk evaluation and mitigation strategy (REMS): A drug safety program that the U.S. FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS are designed to reinforce medication use behaviours and actions that support the safe use of that medication. While all medications have labelling that informs health care stakeholders about medication risks, only a few medications require a REMS.	CIOMS XI (2022): Patient involvement
Risk factor: Characteristics associated with an increased probability of occurrence of an event or disease.	CIOMS IX (2014): Risk minimisation adopted by CIOMS DILI (2020)
Risk identification: Determining what risks or hazards exist or are anticipated, their characteristics, remoteness in time, duration period, and possible outcomes.	CIOMS IX (2014): Risk minimisation
Risk level / Level of risk: Characterisation of an undesirable outcome by severity and likelihood of occurrence.	CIOMS IX (2014): Risk minimisation
Risk management: Reiterative activities or interventions associated with the identification, characterisation, prevention or mitigation of risks and the measurement of the effectiveness of the risk minimisation measures.	CIOMS IX (2014): Risk minimisation
Risk management plan (RMP): In the European Community, a detailed description of the risk management system. The risk management plan established by the marketing authorisation holder shall contain the following elements: (a) an identification or characterisation of the safety profile of the medicinal product(s) concerned; (b) an indication of how to characterise further the safety profile of the medicinal product(s) concerned; (c) a documentation of measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions; (d) a documentation of post-authorisation obligations that have been imposed as a condition of the marketing authorisation.	EU Directive 2001/83/EC Art 1(28c) and CIOMS DILI (2020)
Risk management plan (RMP): A detailed description of the risk management system [Directive 2001/83/EC Art 1(28c)]. To this end, it must identify or characterise the safety profile of the medicinal product(s) concerned, indicate how to characterise further the safety profile of the medicinal product(s) concerned, document measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions and document post-authorisation obligations that have been imposed as a condition of the marketing authorisation.	CIOMS IX (2014): Risk minimisation
Risk management system: A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent, or minimise risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions [Directive 2001/83/EC Art 1(28b)].	CIOMS IX (2014): Risk minimisation
Risk minimisation: In a broader sense the term risk minimisation is used as an umbrella term for prevention or reduction of the frequency of occurrence of an undesirable outcome (see risk prevention) and reduction of its severity should it occur (see risk mitigation).	CIOMS IX (2014): Risk minimisation adopted by CIOMS DILI (2020)
Risk minimisation action plans (RiskMAPs): FDA approved strategic safety programme designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits. RiskMAPs were developed for products that had risks that required additional risk management strategies beyond describing the risks and benefits of the product in labelling and performing required safety reporting. Prior to REMS being introduced through the Food and Drug Administration Amendments Act of 2007, in 2005, FDA had issued a guidance for industry on Development and use of risk minimisation action plans (the RiskMAPs guidance), that described how to develop RiskMAPs, select tools to minimise risks, evaluate and monitor RiskMAPs and monitoring tools, and communicate with FDA about RiskMAPs.	CIOMS IX (2014): Risk minimisation
Risk minimisation-burden balance: A measure of the effectiveness of risk minimisation relative to the burden it imposes.	CIOMS IX (2014): Risk minimisation
Risk minimisation exposure: One of several measures of the fidelity of implementing a risk minimisation intervention. It describes the amount of risk minimisation delivered to the risk minimisation target (e.g. healthcare professional, patient) in terms of content, frequency, and duration of an intervention.	CIOMS IX (2014): Risk minimisation

Risk minimisation measure or **Risk minimisation activity**: An intervention (or series of interventions) intended to prevent, reduce the occurrence, or reduce the severity, of an undesirable outcome associated with the use of a medicine (adverse reaction). Risk minimisation measures may be routine or additional. (See also Additional risk minimisation and Routine risk minimisation)	CIOMS XI (2022): Patient involvement
Risk minimisation plan: Part of the risk management plan which details the risk minimisation activities which will be taken to reduce the risks associated with an individual safety concern. It includes both routine and additional risk minimisation activities.	CIOMS IX (2014): Risk minimisation
Risk minimisation programme: A system of risk minimisation action(s) that are described and derived from a risk minimisation plan.	CIOMS IX (2014): Risk minimisation
Risk minimisation strategy: Direction and scope of planned risk minimisation as specified by objective(s) and target(s) to reach defined goal(s).	CIOMS IX (2014): Risk minimisation
Risk minimisation target: Recipient or audience for a risk minimisation intervention instrumental to its implementation, e.g. healthcare providers.	CIOMS IX (2014): Risk minimisation
Risk minimisation tool: A risk minimisation tool is a method for delivering an intervention intended to minimise specific/specified risks.	CIOMS IX (2014): Risk minimisation
Risk mitigation: Reduction of the severity of an undesirable outcome should it occur.	CIOMS IX (2014): Risk minimisation adopted by CIOMS DILI (2020)
Risk prevention: Reduction of the frequency of occurrence of an undesirable outcome in a population, population subset or an individual patient.	CIOMS IX (2014): Risk minimisation adopted by CIOMS DILI (2020)
Risks related to use of a medicinal product: Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment.	EU Directive 2001/83/EC Art 1(28)]. CIOMS IX (2014): Risk minimisation.
Routine pharmacovigilance: The set of pharmacovigilance activities required by a regulatory authority for every medicinal product they authorise. In many regions, these minimum requirements are laid down in law or regulations.	CIOMS XI (2022): Patient involvement
Routine risk minimisation measure or **Routine risk minimisation activity** (See also Additional risk minimisation measure and Risk minimisation measure): A risk minimisation measure which is mandatory for all medicinal products in a particular region or territory. Routine risk minimisation measures typically include standard activities such as product labelling, limitations on drug pack size and the legal status of the product.	CIOMS XI (2022): Patient involvement
Safety concern: An important identified risk, important potential risk, or missing information.	CIOMS IX (2014): Risk minimisation
Safety-related outcome of interest (see also Outcome indicators): Clinical outcome indicator closely linked to the goal(s) of a risk minimisation programme which has been selected as suitable indicator of relevance for measuring its effectiveness.	CIOMS IX (2014): Risk minimisation
Special populations: See also Vulnerable populations: Populations to be considered should include (but might not be limited to): a) Children; b) The elderly; c) Pregnant or lactating women; d) Patients with relevant co-morbidity such as hepatic or renal disorders; e) Patients with disease severity different from that studied in clinical trials; f) Sub-populations carrying known and relevant genetic polymorphism; g) Patients of different racial and/or ethnic origins.	CIOMS XI (2022): Patient involvement
Stakeholder: Individuals or organisations involved in the development, regulation, and safe use of a medicine during its life cycle. These may include a) Medicine developers (pharmaceutical and healthcare industry and academia); b) Patients, patient organisations and patient advocates; c) Regulators; d) Health Technology Assessment bodies; e) Payers; and Healthcare professionals.	CIOMS XI (2022): Patient involvement
Standard of care (see also Current Practice and Normal Clinical Practice)**:** Medical care that is the customary treatment, diagnosis or prevention of a disease or disorder in a particular region or setting. This may be as defined in guidelines issued by a relevant medical body, mandated by regulatory and/or medical authorities, or as routinely performed by a reasonable proportion of healthcare professionals.	CIOMS XI (2022): Patient involvement

Summary of product characteristics (SmPC): Part of the marketing authorisation of a medicinal product in the EU setting out the agreed position of the product as distilled during the course of the assessment. It is the basis of information for healthcare professionals on how to use the product safely and effectively.	CIOMS IX (2014): Risk minimisation
Survey: Patient or healthcare professional surveys are designed to gather information to assess a safety signal, knowledge about a labelled adverse event, use of a product as labelled, particularly when the indicated use is for a restricted population or numerous contraindications exist, or confusion in the practicing community over sound-alike or look-alike trade (or proprietary) names. A written protocol should include objectives for the survey and a detailed description of the research methods.	CIOMS IX (2014): Risk minimisation
Target population: While generally referring to the patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorised product information or specifically to populations as defined in epidemiologic studies, in the context of risk minimisation in this book target population refers to the patients targeted by a risk minimisation activity which may be a subset of or overlap with the former.	CIOMS IX (2014): Risk minimisation
Targeted follow-up questionnaire: A questionnaire used to capture specific follow-up/further information from a reporter for an adverse event of special interest. It is part of routine pharmacovigilance.	CIOMS IX (2014): Risk minimisation
Targeted medical event (TME): An adverse event of special interest for a particular medicinal product.	CIOMS VIII (2010) Signal detection
Unmet medical need: An unmet medical need is a condition whose prevention, treatment or diagnosis is not addressed adequately by what is available.	CIOMS XI (2022): Patient involvement
Vulnerable populations: Persons who are relatively or absolutely incapable of protecting their own interests. This may occur when persons have relative or absolute impairments in decisional capacity, education, resources, strength, or other attributes needed to protect their own interests. In other cases, persons can also be vulnerable because some feature of the circumstances (temporary or permanent) in which they live makes it less likely that others will be vigilant about, or sensitive to, their interests.	CIOMS XI (2022): Patient involvement

VACCINE-SPECIFIC TERMS	
Absolute risk: Probability that a specified event will occur in a specified population, in contrast to the relative risk of the event	CIOMS (2017) Vaccine safety surveillance
Active vaccine safety surveillance: A data collection system that seeks to ascertain as completely as possible the number of adverse events following immunization (AEFIs) in a given population via a continuous organized process.	CIOMS (2017) Vaccine safety surveillance
Knowledge gap: Refers to lack of available or easily accessible information on vaccines in countries which need the respective information in contexts like vaccine introduction, new safety issue, change in the nature of the vaccination program, or which have an inadequate passive surveillance system. This lack of information equals a research gap or question which has not been answered sufficiently. Proposed by the CIOMS Working Group on Vaccine Safety.	CIOMS (2017) Vaccine safety surveillance
Passive vaccine safety surveillance: The spontaneous reporting of adverse events following immunization (AEFI) by immunization service providers, hospitals, and patients to the administrative level appropriate in each country depending on its national surveillance system. From there, reports are sent to the next reporting level(s), ending at the international institutions responsible for global AEFI surveillance. Modified for this context from:	CIOMS (2017) Vaccine safety surveillance
Significant knowledge gap: If the knowledge gap has the potential to negatively influence the benefit-risk profile of the vaccine to such a degree that it could significantly affect the safety of those receiving vaccinations, it can be described as a significant knowledge gap (SKG).	CIOMS (2017) Vaccine safety surveillance
Surveillance: The continuing, systematic collection of data that are analysed and disseminated to enable decision- making and action to protect the health of populations.	WHO Global manual on surveillance of AEFIs (2014) adopted by CIOMS Vaccine safety surveillance (2017)

Vaccine pharmacovigilance: Vaccine pharmacovigilance has been defined as the science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.	CIOMS (2018) WG on Vaccine safety communication and CIOMS/WHO WG on Vaccine PV
Vaccine safety communication: Communication about potential risks, demonstrated safety and measures to minimize risks, and programmes to support safe and effective use of vaccines. Vaccine pharmacovigilance has been defined as the science and activities relating to the detection, assessment, understanding and communication of adverse events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization. Vaccine safety communication is therefore a recognized part of pharmacovigilance. Proposed by: CIOMS Working Group on Vaccine Safety.	CIOMS (2018) WG on Vaccine safety communication.
Vaccine safety communication plans (VacSCPs) at country level: "Individual vaccine safety communication plans that are specific to vaccine types and the local situation". *Proposed by Topic group 3 of the CIOMS Working Group on Vaccine Safety.*	CIOMS (2018) WG on Vaccine safety communication.
Vaccine safety communication systems: Generally, systems are understood as consisting of structures and processes to fulfil certain objectives; and in order to enable preparing and implementing planned communication, a vaccine safety communication system consists of certain key functions (Refer to Checklist 5.1): a.) Development of strategic vaccine-type and situation-specific vaccine safety communication plans (VacSCPs); b.) Establishment and maintenance of multistakeholder networks, c.) Collaboration at local, country, regional and international level, d.) Monitoring of vaccine knowledge, attitudes, practices (KAP) and related concerns, rumours and information needs, e.) Interaction with the media through a dedicated spokesperson, f.) Development of communication messages and materials, g.) Implementation of communication interventions, h.) Evaluation of communication interventions, i.) Management of vaccine safety crisis.	CIOMS (2018) WG on Vaccine safety communication.

ANNEX 2 REFERENCES

References used in this GUIDELINE and other reference of interest	
WHO	
2024	WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory system of medical products: manual for benchmarking and formulation of institutional development plans. https://www.who.int/publications/i/item/9789240087637
2023	Operational guidance for evaluating and publicly designating regulatory authorities as WHO-listed authorities. https://www.who.int/publications/i/item/9789240074767
2023	Manual for the performance evaluation of regulatory authorities seeking the designation as WHO-listed authorities. https://www.who.int/publications/i/item/9789240076969
2021	TRS 1033 - Annex 10: Good reliance practices in the regulation of medical products: high level principles and considerations. https://www.who.int/publications/m/item/annex-10-trs-1033
2021	WHO Global Benchmarking Tool (GBT) for Evaluation of National Regulatory System of Medical Products - Revision VI. https://www.who.int/publications/i/item/9789240020245
CIOMS	
2023	CIOMS Cumulative Glossary with a focus on Pharmacovigilance (Version 2.1) https://cioms.ch/wp-content/uploads/2023/04/CIOMSGlossary_v2.1_1stMay2023.pdf
EMA	
2024	EU-GVP Module XVI – Risk minimisation measures (Rev 3). https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-rev-3_en.pdf
2024	Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum II – Methods for evaluating effectiveness of risk minimisation measures. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-addendum-ii-methods-evaluating-effectiveness-risk-minimisation-measures_en.pdf
2024	EU-RMP Guidance. https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/pharmacovigilance-marketing-authorisation/risk-management/risk-management-plans
2017	Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev 4) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4-superseded_en.pdf
2017	EU-GVP Module V – Risk management systems (Rev 2) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf
2015	Defining the strategic vision for the EMA 'Article 58' process. https://www.ema.europa.eu/system/files/documents/other/wc500205356_en.pdf
2013	Article 58 Strategic Review – Summary https://www.ema.europa.eu/system/files/documents/other/wc500205357_en.pdf
US-FDA	

2024	Risk Evaluation and Mitigation Strategy Logic Model: A Framework to Link Program Design With Assessment; Draft Guidance for Industry. https://www.regulations.gov/document/FDA-2024-D-1032-0002
	Japan PMDA
2012	Risk Management Plan Guidance https://www.pmda.go.jp/files/000153333.pdf
2012	Risk Management Plan templates and instructions for authors https://www.pmda.go.jp/files/000153692.pdf
	HSA
2024	Health Science Authority of Singapore. Guidance for Industry. Postmarketing vigilance requirements for therapeutic products and cell, tissue and gene therapy products. https://www.hsa.gov.sg/docs/default-source/hprg-vcb/guidance-document/guidance-for-industry_post-marketing-vigilance-requirements-for-therapeutic-products-and-ctgtp_v5_07-oct-2024.pdf?sfvrsn=48deb30c_4
2024	Health Science Authority of Singapore. Risk Management Plan. Guidance and templates. https://www.hsa.gov.sg/rmp/overview
2024	Singapore-Specific Annex Template (version 1.0) https://www.hsa.gov.sg/docs/default-source/hprg-vcb/ssa.pdf?sfvrsn=6decdcd_5
2019	Introduction to risk management plans in the Singapore context. https://pmc.ncbi.nlm.nih.gov/articles/PMC7911080/pdf/SMJ-60-483.pdf
	ICH
2024	Glossary of ICH terms and definitions https://doi.org/10.56759/eftb6868
2004	ICH-E2E Guideline on Pharmacovigilance Planning https://database.ich.org/sites/default/files/E2E_Guideline.pdf
	Publications
2022	WHO collaborative registration procedure using stringent regulatory authorities, Expert Review in Clinical Pharmacology. Openly accessible from https://doi.org/10.1080/17512433.2022.2037419

ANNEX 3 USEFUL WEBSITES

Available website links to RMP-relevant documents
Public Assessment Reports and other Public RMP-relevant documents
EU | EMA | European Public Assessment Reports (EUPAR). PFD accessible via : https://www.ema.europa.eu/en/search?f%5B0%5D=ema_medicine_bundle%3Aema_medicine&f%5B1%5D=ema_search_categories%3A83
EU | EMA | Referral Procedures accessible via: https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/referral-procedures-human-medicines.
EU | EMA | Download medicine data portal accessible via: https://www.ema.europa.eu/en/medicines/download-medicine-data#post-authorisation-procedures-for-medicines-69048. Provides access to the list of referral procedures, EURD list for PSUR submission, list of orphan-designated medicines, list of medicines under post-authorization procedures etc.
UK | MHRA | Public Assessment Reports (UKPAR). PDF accessible via: https://www.gov.uk/guidance/safety-public-assessment-reports#section;
Singapore | HSA | Summary Report of Benefit-Risk Assessment. HTML page accessible via: https://www.hsa.gov.sg/therapeutic-products/register/summary-reports-of-benefit-risk-assessment;
Switzerland | Swissmedic Public Assessment Reports (SwissPAR). PDF accessible via: https://www.swissmedic.ch/swissmedic/en/home/about-us/publications/public-summary-swiss-par.html
Australia | Australian Public Assessment Reports (AusPAR). PDF and .docx accessible via: https://www.tga.gov.au/resources/auspar
Canada | Health Canada Safety Reviews HTML page accessible via: https://dhpp.hpfb-dgpsa.ca/review-documents?f%5B0%5D=content_type%3Assr
Canada | Health Canada Product Monographs PDF accessible via: https://health-products.canada.ca/dpd-bdpp/
Japan | Japan Pharmaceuticals and Medical Devices Agency RMP and RMP list via: https://www.pmda.go.jp/safety/info-services/drugs/items-information/rmp/0001.html?utm https://www.pmda.go.jp/english/safety/info-services/drugs/rmp/0001.html

ANNEX 4 PRACTICAL GUIDANCE on *Reliance*

Practical guidance for NRAs in different scenarios of *Reliance*

1.1. Situation A: Assessing a RMP in the context of a PQ-CRP for NDA

1.1.1. Documents under scope

Relying on a RMP produced in the context of WHO Prequalification (PQ) is ideal, enabling simpler RMP assessment process. Henceforth, such RMPs will be referred to as "PQ-RMP". Although PQ-RMPs are designed to fit with the healthcare systems of LMICs, country-specific aspects may need to be considered in addition.

To obtain the "PQ-RMP", the NRA Officer coordinating the MA process may reach out to the WHO-PQ contact person directly or via a WHO contact person at the country level. The signature of a non-disclosure agreement may be required.

1.1.2. Safety Specification

The Safety Specification section of a PQ-RMP is likely to be relevant for LMICs. It should be remarked that the categorisation of the risk may differ from those stated in the RMP used as reference for PQ application. For example, *Anaphylaxis* may be an Important Identified Risk in the "PQ-RMP" but an Important Potential Risk in the RMP for PQ application. Country-specific safety concerns may need to be considered in addition to those addressed in the "PQ-RMP".

1.1.3. Pharmacovigilance Plan

The Pharmacovigilance Plan of a PQ-RMP is likely to be relevant for LMICs. However, in case of a country-specific safety concern, specific pharmacovigilance methods may need to be considered. A lack of ethnicity data in the global NDA may justify a specific safety data collection program. Collaboration across NRAs of countries with similar ethnicity and Health Care System is advisable.

1.1.4. Risk Minimization Plan

The Risk Minimization Plan of a PQ-RMP is likely to be relevant for LMICs. However, country-specific challenges or country-specific features may justify considering alternative risk minimization approaches. Collaboration across NRAs dealing with comparable healthcare system is advisable.

1.1.5. Benefit vs Risk in the context of the local healthcare system

Whenever the pharmacovigilance and risk minimization methods intended to be implemented locally do not differ from those recommended in the "PQ-RMP", the local assessment of the Benefit vs Risk may be skipped. On the other hand, if different risk minimisation methods are intended, it is recommended to perform a Benefit vs Risk assessment in the conditions of the local healthcare system.

1.2. Situation B: Assessing a RMP approved by a recognized reference authority such as a WLA

This situation applies whenever a RMP endorsed by a recognized reference authority such as a WLA is accessible (e.g. EMA-approved EU-RMP). However, the Assessor should bear in mind that EU-RMPs are designed to fit with a healthcare system of the EU. Hence, the RMP assessment process should include performing a critical analysis of the Safety Specifications, Pharmacovigilance Plan, risk minimization plan and Benefit vs Risk evaluation in the context of the healthcare system of the country under scope.

1.2.1. Documents under scope

1.2.1.1. Exemplar: RMP according to EU-GVP Format

As previously emphasized and shown in Table 1 (below), it is of utmost importance to recognize the types of RMP submitted, bearing in mind that so-called "Core (company) RMPs" according to the EU-RMP format reflect solely the opinion of the MAH, lacking endorsement by a recognized reference authority such as a WLA. For this reason, the request to submit the latest version of the EMA-approved EU-RMP should be explicitly stated in the regulation and guidance for MAHs.

Table 1. Different types of RMPs according to EU-GVP Module V	
1. **EU-RMP** According to EU-GVP Module V (Rev.1) from 2017.	▪ In principle, includes all Important identified risks, Important potential risks, and missing information, whether or not those risks are addressed by additional pharmacovigilance or additional risk minimization interventions.
2. **EU-RMP** According to EU-GVP Module V (Rev.2) until 2017	▪ May include only the risks addressed by an additional pharmacovigilance or risk minimization intervention or Post Authorization Study, lacking other Important risks or missing information. ▪ The Warning & Precaution section of the SmPC should be checked to ensure a comprehensive awareness of the safety concerns.
3. **Core RMP** According to EU-RMP format	▪ Looks like EU-RMP but lacks EMA endorsement. Reflects solely the opinion of the MAH. Contents possibly tainted by conflict of interest. Unsuitable in a Reliance perspective. Avoid and request latest EMA-endorsed RMP to be submitted.

For most EU-RMPs, only Part VI (Summary of the Risk Management Plan) is publicly available on the EMA website. However, starting with anti-COVID vaccines and antiviral agents, the EMA is increasingly making full EU-RMP contents available. To ensure access to full RMP contents, signing an agreement with the EMA may be required. Such an agreement should also cover granting access to PBRER Assessment Reports performed by the EMA.

1.2.1.2. EU-RMPs are acceptable by NRAs of all EU Member States. EU-RMPs are also acceptable by NRAs belonging to the ACCESS consortium (that includes UK's MHRA, Australia's TGA, Singapore's HSA, Health Canada and Swissmedic), as well as by many other NRAs globally. *Country-Specific Annex*

Initially created in 2012 by Australia's TGA, the concept of Country-Specific Annex (CSA) was subsequently adopted by Singapore's HSA, the Philippine's FDA, then followed by an increasing number of NRAs. The principle and purpose of the CSA is to describe and justify the differences between the contents, especially the pharmacovigilance and risk minimization interventions

described in the EU-RMP, and the interventions -or lack of intervention- intended in the non-EU country under scope.

The Singapore-Specific Annex (SSA) Template provided in the REFERENCE AND ANNEXES section, or this GUIDANCE is recommended for its convenience. Whilst the HSA requests explicitly the submission of the latest EMA endorsed version of the EU-RMP, the SSA becomes "The Singapore RMP" after endorsement by the HSA. When no EU-RMP exists, that SSA template may be used for creating a RMP applicable in Singapore, which is also the approach recommended by this Guidance.

1.2.2. Safety Specifications

In Situation B, all safety concerns included in the Warnings & Precautions and Contra-Indications of the SmPC should be assessed, not limited to those stated in the Safety Specifications section of the EU-RMP or other WLA-endorsed RMP used as reference.

1.2.3. Pharmacovigilance Plan

In Situation B, the assessment of the Pharmacovigilance Plan consists of evaluating if the methods described in the reference WLA are sufficient, applicable and likely to be effective to collect the targeted safety information in the context of the local healthcare system. In the contrary case, alternative and/or additional methods should be considered. If conducting a post-authorization safety study is considered, its rationale, feasibility and capability to effectively collect the analysable safety information should be carefully assessed. The pharmacovigilance methods proposed by in the Country-Specific Annex (if provided by the MAH) should be considered.

1.2.4. Risk Minimization Plan

The Risk Minimization Plan described in the RMP approved by the recognized reference authority such as a WLA should be evaluated with regard to its relevance, feasibility and capability to address the targeted safety concerns in the context of the local healthcare system. Whenever justified, alternative or additional risk minimization measures should be considered.

~~6~~.4.5 Benefit vs Risk in the context of the local healthcare system

Whenever the safety concerns, pharmacovigilance methods, and the locally suitable risk minimization measures do not differ from those stated in an RMP used as a reference, the local assessment of the Benefit vs Risk may be skipped. If conversely, any of those components differ, a local Benefit vs Risk Assessment should be conducted assuming the intended pharmacovigilance and risk minimization methods are effectively implemented.

1.3. Situation C: Assessing other RMP-relevant documents

The principles and processes described for Situation B apply also to Situation C. The main difference is in the challenges faced in retrieving RMP-relevant documents whenever the RMP of the originator product is not accessible. In such situations, the alternative approach consists of searching for publicly available documents.

1.3.1. Searching for EU-RMP Part VI (RMP Summary)

EU-RMP exists for all products approved by the EMA from 2012 and may also be available for earlier approved products. For such products, Part VI should be retrieved from the EMA website.

As described in Table 2 (below), Part VI of the EU-RMP generally includes a brief description of the Safety Specifications, Pharmacovigilance plan, Risk Minimisation and Post-Authorisation Safety Studies (PASS), however not as detailed as in the corresponding sections of the RMP.

Table 2. Content of Part VI of the EU-RMP (Publicly available)	
I	The medicine and what it is used for
II	Risks associated with the medicine and activities to minimise or further characterise the risks
II.A	List of important risks and missing information
II.B	Summary of important risks (includes description of risk minimization interventions)
II.C	Post-authorisation development plan

Whilst Part VI of the EU-RMP contains the most essential information, it remains a sub-optimal source of information. It is therefore advisable to approach the EMA to establish a non-disclosure agreement granting access to full RMP contents as well as PSUR/PBRERs and their EMA Assessment reports.

1.3.2. Searching for European Public Assessment Reports (EPAR)

The EMA publishes detailed information on the medicines assessed by the CHMP. The main vehicle for this information is known as a European Public Assessment Report (EPAR)**.** An EPAR is not a single document but an information resource containing several components, including a core set of regulatory documents. EPARs are updated periodically. EPARs are displayed on the EMA website using four different sections containing different components of the EPAR, shown in Table 3.

Table 3. Components of European Public Assessment Reports (EPAR)	
Section	Type of information
Overview	Public-friendly overview in question-and-answer format.
Authorisation details	Key details about the product and the marketing authorisation holder
Product information	Package leaflet and summary of product characteristics; labelling; list of all authorised presentations; pharmacotherapeutic group; therapeutic indications.
Assessment history	Public assessment report for the initial authorisation; public assessment report(s) for any variation concerning major changes to the marketing authorisation; withdrawal assessment report; tabulated overview of procedural steps taken before and after authorisation.
Search method	[European Public Assessment Reports] [Non-proprietary name] May be retrieved from EMA or Member State NRA website e.g. HPRA (Ireland)

1.3.3. Searching for EMA procedure under Regulation 726/2004/EC Article 58

Procedure under Regulation 726/2004/EC Article 58 (EU-Medicines for all or EU-M4all) allows the EMA, in cooperation with the WHO, to give opinions on medicines and vaccines for human use intended exclusively for markets outside of the EU.

It aims to help address public health inequities existing in LMICs by providing a mechanism whereby scientific and manufacturing expertise could be provided to manufacturers, the WHO, NRAs, and the broader global health community regarding the development and assessment of products intended to be marketed in LMICs.

EU-M4all Procedures combine EMA's scientific, clinical, and manufacturing review capabilities with local epidemiology and disease expertise of the WHO and LMIC national regulators to provide a unique development and assessment pathway.

1.3.4. Searching for EMA referral procedures

Reports of EMA referral procedures alone do not constitute an alternative for a RMP but may be essential to consider among other RMP-relevant documents, not limited to Situation C.

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the EU.

Table 4. EMA referral procedures	
Directive 2001/83/EC Article 107i referral	Urgent Union procedure for safety issues. Applies where urgent regulatory action is considered on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities of an authorised medicinal product(s).
Regulation 726/2004/EC Article 20 referral	Triggered for medicines that have been authorised via the centralised procedure in case of quality, safety or efficacy issues**.**
Directive 2001/83/EC Article 31 referral	This type of referral is triggered when the interest of the EU is involved, following concerns relating to the quality, safety or efficacy of a medicine or a class of medicines.
Directive 2001/83/EC Article 29 referral	This type of procedure may be triggered by a marketing-authorisation holder when applying for a new indication, new pharmaceutical form or new route of administration for use in children for a product authorised under Directive 2001/83/EC.

1.3.5. Searching for Australian Public Assessment Report (AusPAR)

The TGA is a tWLA and a member of the ACCESS Consortium. TGA makes AusPAR reports available for a large number of products approved in Australia. AusPARs, especially the most recent ones, may include a benefit vs risk assessment discussion, a summary description of the Safety Specification, Pharmacovigilance and Risk Minimisation Plans. However, if the TGA is to be used as a reference authority from a reliance perspective, establishing a non-disclosure agreement is required.

1.3.6. Searching for Health Canada's Product Monographs

The Health Canada (HC) is a WLA and a member of the ACCESS Consortium. For a large number of products approved in Canada, HC makes publicly available comprehensive Product Monographs (Table 4) which constitute an appreciable source of information. However, those monographs do not include a discussion on the benefit vs risk balance nor a summary of the pharmacovigilance and risk minimisation plans.

1.3.7. Searching for MHRA Public Assessment Reports.

The MHRA is a WLA, and a member of the ACCESS Consortium. The MHRA makes available Public Assessment Reports for a limited number of products.

1.3.8. Searching for Swissmedic Public Assessment Reports.

Swissmedic is a WLA and a member of the ACCESS Consortium. A large number of SwissPAR reports are available in English, French, German and Italian, and are searchable by trade names.

ANNEX 5

WHO MODEL RMP ASSESSMENT REPORT TEMPLATE

31 OCTOBER 2025

TABLE OF CONTENTS

Assessor Information	
Assessor's Name	
Date of review submission	

RMP Information	
Active substance(s) (INN or common name):	
Name of MAH or applicant:	
Version of RMP	
Data lock point for this RMP	DD-MM-YYYY

OVERALL SUMMARY

[The overall summary should provide a concise, integrated assessment of the safety profile of the medicinal product and the adequacy of the proposed risk management strategy. It should highlight:

- Safety Specification: The key important identified risks, important potential risks, and areas of missing information. The summary should indicate which safety concerns require proactive management, additional data collection, or further evaluation.
- Pharmacovigilance Plan: The suitability of the proposed pharmacovigilance activities to further characterise and quantify clinically relevant risks, detect new adverse reactions, and address gaps in knowledge.
- Risk Minimisation Plan: The adequacy of the planned risk minimisation measures to reduce the occurrence and/or severity of important risks, and the appropriateness of methods for assessing the effectiveness of these measures in routine practice.

The summary should integrate these elements to provide an overall conclusion on whether the proposed activities are proportionate to the safety concerns, aligned with the benefit–risk profile of the product, and feasible within the local health care system.]

ASSESSMENT

1	Characterization of the RMP

1.1. Nature of the Product	
[_]	Chemical | Pharmaceutical product
[_]	Chemical | Contrast agents for imaging
[_]	Biological | Vaccines and other immunizing products
[_]	Biological | Blood and plasma-derived products for medical use
[_]	Biological | Recombinant products
[_]	Biological | Monoclonal antibodies
[_]	Biological | Cell and tissue therapies
[_]	Biological | Biosimilar
[_]	Herbal and other traditional medicines
[_]	Other categories of medical products (specify)
Remark: more than one category may apply such as “recombinant” and “biosimilar”.	

1.2. Product Information	
Product name	
If not originator, indicate originator	
Active substance	
Product class	
Indication	
Marketing Authorization Holder/Manufacturer	

Storage conditions	**Guiding questions: Storage, distribution and other risk linkage** • Are there risks associated with temperature excursions (e.g. potential impact on vaccine potency)? • Are storage and handling conditions appropriate for the intended healthcare settings (e.g. hospitals versus community settings)? • Are the identified risks and proposed risk minimization measures linked to storage, distribution, or environmental conditions relevant to the local context?
Posology	**Guiding questions:** Scientific and Clinical Justification • Is the proposed dose supported by adequate clinical pharmacology, PK/PD, and efficacy/safety data? • Is the dosing regimen (dose, frequency, duration) scientifically justified and clinically feasible? • Are dose adjustments justified for specific populations (e.g., renal/hepatic impairment, elderly, children)? Dosing and Target Population • Is the posology clearly defined for all relevant age groups, body weights, or clinical subgroups (e.g., infants, pregnant women, immunocompromised) if needed? • Does the dosing regimen consider adherence and feasibility in real-world practice (e.g., pill burden, frequency, route of administration)? Regulatory Consistency • Is the proposed posology aligned with the SmPC and product information? • Is the dosing regimen consistent with that approved in other major regulatory jurisdictions (e.g., EMA, FDA, WHO PQ)? If not, are differences explained and justified? • Are there discrepancies between clinical trial dosing schedules and the proposed marketing authorisation? Risk Management & Pharmacovigilance Considerations • Does the posology increase the risk of medication errors (e.g., complex titration, confusing units, multiple formulations)? • Are there risks of under-dosing (loss of efficacy, resistance development) or overdosing (toxicity, serious adverse events)? • Are additional risk minimisation measures required to support correct dosing (e.g., educational materials, dosing devices, clear labelling)? • Will special pharmacovigilance activities be needed to monitor dosing-related safety concerns (e.g., therapeutic drug monitoring, registries)?

1.3. Categorize the type of RMP-relevant document to be assessed

More than one type of document may be under scope of the assessment such as EMA-endorsed EU-RMP + Country-Specific Annex proposed by the MAH.

	RMP or relevant documents (i.e. Public Assessment Report) issued or endorsed by	*Version*	*Comments/ Link*
[_]	PQ RMP (e.g. WHO Pre-Qualification (PQ) process or WHO Collaborative registration procedure (CRP))		
[_]	WLA-approved RMP [specify]		
[_]	RMP-approved by other NRA [specify]		
[_]	Country/Region specific RMP		

2 Epidemiology, Indications and expected Benefits

Epidemiology of the disease	This may discuss inter-regional (e.g. EU, US, Asia, Africa etc.) variations including local context. If the epidemiology varies across countries, this should be discussed. Incidence and prevalence, demographics of the target population – age, sex, race/ethnic origin, risk factors for the disease, mortality, morbidity and conventional therapy should be discussed. **Guiding questions:** <u>Disease Burden & Epidemiology</u> • What is the incidence and/or prevalence of the disease in the relevant regions or populations? • Is the epidemiological data up to date and referenced properly? • Is the disease burden described (e.g., morbidity, mortality, quality of life)? • Are there regional, ethnic, or demographic differences in disease epidemiology?
Epidemiology of the indication(s) and target population	Complete for each indication. If a medicine has an indication for both prevention and treatment of the same disease (e.g. malaria) or is to treat one disease (e.g. oncology), list the "linked" indications together, including combination therapy. **Guiding questions:** <u>Target population</u> • Who are the intended recipients of this treatment (e.g., age group, sex, special populations)? • Are vulnerable populations included (e.g., paediatrics, elderly, pregnant women, immunocompromised)? • Are genetic or metabolic differences relevant to efficacy or safety in the local population? <u>Risk factors and subgroups</u> • Are there subgroups with a higher baseline risk of adverse events? • Are special subgroups identified that may require tailored safety monitoring? • Does the target population profile raise specific needs for risk minimization (e.g., limited literacy, health system capacity)?
Concomitant medication(s) and important co-morbidities found in the target population	Discuss other medications frequently used with the medicinal product (e.g. to treat the disease or complications of it) and list co-morbidities of the target population, including local context. **Guiding questions:** <u>Concomitant therapies and interactions</u> • What are the most common concomitant therapies used with this product? • Does the drug have known interactions with other medicines? • Could concomitant use increase the risk of AEs (e.g., QT prolongation, bleeding)?
NRA Assessor's comment	
Indications	Detailed description of the indications as detailed in the RMP.

NRA Assessor's comment	
	Discussion about the indications (i.e. endorsed, objections), further comments. **Guiding questions:** Scientific and clinical justification ▪ Is the indication scientifically, clinically, and regulatorily justified? ▪ Is there a clear unmet medical need or advantage over existing therapies? ▪ Does the benefit–risk balance remain positive within the proposed indication? Scope and target population ▪ Does the indication clearly define for each age group the medicine is indicated for? ▪ Who are the intended recipients of this treatment (e.g., age group, sex, special populations)? ▪ Is the indication too broad or too narrow compared to the clinical trial population? ▪ Are any subgroups (e.g., elderly, children, pregnant women) included without sufficient supporting data? ▪ Does the proposed indication include high-risk populations (e.g., immunocompromised, elderly, patients with co-morbidities)? ▪ Does it imply a large or vulnerable target population, increasing exposure and risk? Regulatory Consistency ▪ Should the indication be modified, restricted, or clarified to ensure safe and appropriate use? ▪ Is the proposed indication consistent with the SmPC (Summary of Product Characteristics)? ▪ Is it the same or different from the indication approved in other regulatory jurisdictions (e.g., FDA, EMA)? Risk Management & Pharmacovigilance Considerations ▪ Does the indication suggest off-label use potential (e.g., vague wording or broad population)? ▪ Will the indication require additional risk minimization measures or pharmacovigilance activities? ▪ Is there an intention to include paediatric population, pregnant or breastfeeding women, and patients with renal or hepatic impairment? (e.g. Is a paediatric Investigation Plan in place?) ▪ Does the indication raise population-level concerns, such as herd immunity, resistance, or misuse?
Expected benefits	Description of the expected benefits in target population including local context.
NRA Assessor's comment	
Discussion about the unmet needs and benefits for target population.	

3 Safety Concerns and methods to address them

Safety Concerns and other risks	
Safety Specification (as stated in RMP)	
Important identified risks	[Indicate all the important identified risks according to the MAH]
Important potential risks	[Indicate all the important potential risks according to the MAH]
Missing information	[Indicate all the missing information according to the MAH]
Other risks (as stated in Product Information)	
Contraindication(s)	[Indicate all contraindications stated in the product information (SmPC)]
Special warnings and precautions for use	[Indicate all risks stated in "Special warnings and Precautions" section of the product information (SmPC)]
Interaction with other medicinal products and other forms of interaction	[Indicate all risks stated in "Special warnings and Precautions" section of the product information (SmPC)]
Fertility, pregnancy and lactation	
Effects on ability to drive and use machines	
Undesirable effects (Adverse reactions)	
Overdose	
Other risks	
NRA Assessor's comment	

Assessment of Pharmacovigilance Plan

Assessment of routine and additional pharmacovigilance plan	
Routine Pharmacovigilance Activities	[Pharmacovigilance method proposed by the MAH]
Additional Pharmacovigilance Activities	[Pharmacovigilance method proposed by the MAH]
NRA Assessor's comment	[Assessor´s comments, endorsement of the methods proposed by the WHO PQ, EMA, WLA or another NRA, additional requests or recommended measures]
Assessment of Risk Minimization Plan (Routine or Additional)	
Routine Risk Minimisation Measures	[Routine Risk Minimization methods proposed by the MAH]
Additional Risk Minimisation Measures	[Additional Risk Minimization methods proposed by the MAH]
NRA Assessor's comment	[Assessor´s comments, endorsement of the methods proposed by the WHO PQ, EMA, WLA or another NRA, additional requests or recommended measures]

4	Important information in pre- and post-marketing authorisation studies

Part 1 | Pre-authorisation phase	
Clinical studies	[Summarise studies and key results from the clinical development phase]
Part 2 | Post-authorisation phase	
Post-authorization safety and efficacy studies (PASS/PAES)	[Describe studies and key results from the PASS/PAES]

5 Assessment of the Benefit vs Risk Balance

Part 1 | New medicine under scope	
Key benefits	[Describe key benefits, clinical relevance, key population for which benefit is anticipated, magnitude of benefit if applicable, duration of benefit, etc.]
Uncertainties regarding benefits	[Describe uncertainties (e.g. limited efficacy data), list sources of the evidence of benefits including limitation of the sources (e.g. small sample size, lack of data in certain populations), indicate populations where uncertainty is especially relevant, etc.]
Safety profile: (Key risks and non-key risks)	[Identified or potential risk, missing information, characterise risks regarding their potential mechanism, frequencies, risk factors, risk groups, preventability, etc.]
Uncertainties regarding risks	[Describe uncertainties (e.g. limited long-term safety data), list sources of the evidence including limitation of the sources (e.g. data quality, generalisability of findings), indicate populations where uncertainty is especially relevant, etc.]
Risk management needs	[Discuss impact of the risk on risk-benefit balance of the product and on public health]
Part 2 | Disease context and current therapeutic offer	
Remaining medical need under current therapeutic options.	[Summarise local epidemiology, standard of care including safety profile. Discuss if new medicine under scope addresses the remaining medical needs in the local context, etc.]
Part 3 | Benefit vs risk assessment summary	
NRA Assessor's comment	
[Compare the benefits and the risk regarding clinical relevance and impact of uncertainties. Highlight if there are significantly different outcomes for subpopulations, e.g. children, pregnant]	
Conclusions	
1. The overall benefit-risk balance considered **remains positive**. No additional Risk Minimization activities are required. 2. The overall benefit-risk balance considered **inadequate**. Additional Risk Minimization activities are required.	

6 Action taken by NRAs and/or MAHs for safety reasons

Actions taken by the MAH	[List any significant regulatory action (including those initiated by the MAH in any market in relation to a safety concern.]
Actions taken by NRAs	[Significant regulatory action would include a restriction to the approved indication, a new contra-indication, a new or strengthened warning in section 4.4 of the SPC (or equivalent) or any action to suspend or revoke a marketing authorisation.]
NRA Assessor's comment	

7 Questions to the MAH and Responses

Queries to the MAH (if any)	[Specify your queries]
MAH Responses	[MAH responses to be provided here]
Assessor´s Conclusions	[Acceptance of the MAH responses or additional queries]
Risk Management Plan Commitments in [Country]	[Describe the details of agreed MAH's commitments in risk management plan including routine and additional pharmacovigilance activities and risk minimisation measures here]

8 RMP Summary and Conclusions

Pharmacovigilance Plan Commitments by MAH in [Country]	
Risk Management Plan Commitments by MAH in [Country]	[Describe the details of agreed MAH's commitments in risk management plan including routine and additional pharmacovigilance activities and risk minimisation measures here]
Required Risk Minimisation activities by NRA	**Routine** (specify)
	Additional (specify)

9 Approval of RMP assessment report

Prepared by (name of assessor) _____Date_____

Approved by (name of approver) _____ Date_____

ANNEX 5

WHO MODEL RMP ASSESSMENT REPORT TEMPLATE

31 OCTOBER 2025

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ASSESSMENT

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1.1. Nature of the Product	
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[_]	Chemical | Contrast agents for imaging
[_]	Biological | Vaccines and other immunizing products
[_]	Biological | Blood and plasma-derived products for medical use
[_]	Biological | Recombinant products
[_]	Biological | Monoclonal antibodies
[_]	Biological | Cell and tissue therapies
[_]	Biological | Biosimilar
[_]	Herbal and other traditional medicines
[_]	Other categories of medical products (specify)
Remark: more than one category may apply such as “recombinant” and “biosimilar”.	

1.2. Product Information	
Product name	
If not originator, indicate originator	
Active substance	
Product class	
Indication	
Marketing Authorization Holder/Manufacturer	

Storage conditions	**Guiding questions: Storage, distribution and other risk linkage** • Are there risks associated with temperature excursions (e.g. potential impact on vaccine potency)? • Are storage and handling conditions appropriate for the intended healthcare settings (e.g. hospitals versus community settings)? • Are the identified risks and proposed risk minimization measures linked to storage, distribution, or environmental conditions relevant to the local context?
Posology	**Guiding questions:** Scientific and Clinical Justification • Is the proposed dose supported by adequate clinical pharmacology, PK/PD, and efficacy/safety data? • Is the dosing regimen (dose, frequency, duration) scientifically justified and clinically feasible? • Are dose adjustments justified for specific populations (e.g., renal/hepatic impairment, elderly, children)? Dosing and Target Population • Is the posology clearly defined for all relevant age groups, body weights, or clinical subgroups (e.g., infants, pregnant women, immunocompromised) if needed? • Does the dosing regimen consider adherence and feasibility in real-world practice (e.g., pill burden, frequency, route of administration)? Regulatory Consistency • Is the proposed posology aligned with the SmPC and product information? • Is the dosing regimen consistent with that approved in other major regulatory jurisdictions (e.g., EMA, FDA, WHO PQ)? If not, are differences explained and justified? • Are there discrepancies between clinical trial dosing schedules and the proposed marketing authorisation? Risk Management & Pharmacovigilance Considerations • Does the posology increase the risk of medication errors (e.g., complex titration, confusing units, multiple formulations)? • Are there risks of under-dosing (loss of efficacy, resistance development) or overdosing (toxicity, serious adverse events)? • Are additional risk minimisation measures required to support correct dosing (e.g., educational materials, dosing devices, clear labelling)? • Will special pharmacovigilance activities be needed to monitor dosing-related safety concerns (e.g., therapeutic drug monitoring, registries)?

1.3. Categorize the type of RMP-relevant document to be assessed

More than one type of document may be under scope of the assessment such as EMA-endorsed EU-RMP + Country-Specific Annex proposed by the MAH.

	RMP or relevant documents (i.e. Public Assessment Report) issued or endorsed by	*Version*	*Comments/ Link*
[_]	PQ RMP (e.g. WHO Pre-Qualification (PQ) process or WHO Collaborative registration procedure (CRP))		
[_]	WLA-approved RMP [specify]		
[_]	RMP-approved by other NRA [specify]		
[_]	Country/Region specific RMP		

2 Epidemiology, Indications and expected Benefits

Epidemiology of the disease	This may discuss inter-regional (e.g. EU, US, Asia, Africa etc.) variations including local context. If the epidemiology varies across countries, this should be discussed. Incidence and prevalence, demographics of the target population – age, sex, race/ethnic origin, risk factors for the disease, mortality, morbidity and conventional therapy should be discussed. **Guiding questions:** <u>Disease Burden & Epidemiology</u> • What is the incidence and/or prevalence of the disease in the relevant regions or populations? • Is the epidemiological data up to date and referenced properly? • Is the disease burden described (e.g., morbidity, mortality, quality of life)? • Are there regional, ethnic, or demographic differences in disease epidemiology?
Epidemiology of the indication(s) and target population	Complete for each indication. If a medicine has an indication for both prevention and treatment of the same disease (e.g. malaria) or is to treat one disease (e.g. oncology), list the "linked" indications together, including combination therapy. **Guiding questions:** <u>Target population</u> • Who are the intended recipients of this treatment (e.g., age group, sex, special populations)? • Are vulnerable populations included (e.g., paediatrics, elderly, pregnant women, immunocompromised)? • Are genetic or metabolic differences relevant to efficacy or safety in the local population? <u>Risk factors and subgroups</u> • Are there subgroups with a higher baseline risk of adverse events? • Are special subgroups identified that may require tailored safety monitoring? • Does the target population profile raise specific needs for risk minimization (e.g., limited literacy, health system capacity)?
Concomitant medication(s) and important co-morbidities found in the target population	Discuss other medications frequently used with the medicinal product (e.g. to treat the disease or complications of it) and list co-morbidities of the target population, including local context. **Guiding questions:** <u>Concomitant therapies and interactions</u> • What are the most common concomitant therapies used with this product? • Does the drug have known interactions with other medicines? • Could concomitant use increase the risk of AEs (e.g., QT prolongation, bleeding)?
NRA Assessor's comment	
Indications	Detailed description of the indications as detailed in the RMP.

NRA Assessor's comment	
	Discussion about the indications (i.e. endorsed, objections), further comments. **Guiding questions:** Scientific and clinical justification ▪ Is the indication scientifically, clinically, and regulatorily justified? ▪ Is there a clear unmet medical need or advantage over existing therapies? ▪ Does the benefit–risk balance remain positive within the proposed indication? Scope and target population ▪ Does the indication clearly define for each age group the medicine is indicated for? ▪ Who are the intended recipients of this treatment (e.g., age group, sex, special populations)? ▪ Is the indication too broad or too narrow compared to the clinical trial population? ▪ Are any subgroups (e.g., elderly, children, pregnant women) included without sufficient supporting data? ▪ Does the proposed indication include high-risk populations (e.g., immunocompromised, elderly, patients with co-morbidities)? ▪ Does it imply a large or vulnerable target population, increasing exposure and risk? Regulatory Consistency ▪ Should the indication be modified, restricted, or clarified to ensure safe and appropriate use? ▪ Is the proposed indication consistent with the SmPC (Summary of Product Characteristics)? ▪ Is it the same or different from the indication approved in other regulatory jurisdictions (e.g., FDA, EMA)? Risk Management & Pharmacovigilance Considerations ▪ Does the indication suggest off-label use potential (e.g., vague wording or broad population)? ▪ Will the indication require additional risk minimization measures or pharmacovigilance activities? ▪ Is there an intention to include paediatric population, pregnant or breastfeeding women, and patients with renal or hepatic impairment? (e.g. Is a paediatric Investigation Plan in place?) ▪ Does the indication raise population-level concerns, such as herd immunity, resistance, or misuse?
Expected benefits	Description of the expected benefits in target population including local context.
NRA Assessor's comment	
Discussion about the unmet needs and benefits for target population.	

3 Safety Concerns and methods to address them

Safety Concerns and other risks	
Safety Specification (as stated in RMP)	
Important identified risks	[Indicate all the important identified risks according to the MAH]
Important potential risks	[Indicate all the important potential risks according to the MAH]
Missing information	[Indicate all the missing information according to the MAH]
Other risks (as stated in Product Information)	
Contraindication(s)	[Indicate all contraindications stated in the product information (SmPC)]
Special warnings and precautions for use	[Indicate all risks stated in "Special warnings and Precautions" section of the product information (SmPC)]
Interaction with other medicinal products and other forms of interaction	[Indicate all risks stated in "Special warnings and Precautions" section of the product information (SmPC)]
Fertility, pregnancy and lactation	
Effects on ability to drive and use machines	
Undesirable effects (Adverse reactions)	
Overdose	
Other risks	
NRA Assessor's comment	

Assessment of Pharmacovigilance Plan

Assessment of routine and additional pharmacovigilance plan	
Routine Pharmacovigilance Activities	[Pharmacovigilance method proposed by the MAH]
Additional Pharmacovigilance Activities	[Pharmacovigilance method proposed by the MAH]
NRA Assessor's comment	[Assessor´s comments, endorsement of the methods proposed by the WHO PQ, EMA, WLA or another NRA, additional requests or recommended measures]
Assessment of Risk Minimization Plan (Routine or Additional)	
Routine Risk Minimisation Measures	[Routine Risk Minimization methods proposed by the MAH]
Additional Risk Minimisation Measures	[Additional Risk Minimization methods proposed by the MAH]
NRA Assessor's comment	[Assessor´s comments, endorsement of the methods proposed by the WHO PQ, EMA, WLA or another NRA, additional requests or recommended measures]

4	Important information in pre- and post-marketing authorisation studies

Part 1 | Pre-authorisation phase	
Clinical studies	[Summarise studies and key results from the clinical development phase]
Part 2 | Post-authorisation phase	
Post-authorization safety and efficacy studies (PASS/PAES)	[Describe studies and key results from the PASS/PAES]

5 Assessment of the Benefit vs Risk Balance

Part 1 | New medicine under scope	
Key benefits	[Describe key benefits, clinical relevance, key population for which benefit is anticipated, magnitude of benefit if applicable, duration of benefit, etc.]
Uncertainties regarding benefits	[Describe uncertainties (e.g. limited efficacy data), list sources of the evidence of benefits including limitation of the sources (e.g. small sample size, lack of data in certain populations), indicate populations where uncertainty is especially relevant, etc.]
Safety profile: (Key risks and non-key risks)	[Identified or potential risk, missing information, characterise risks regarding their potential mechanism, frequencies, risk factors, risk groups, preventability, etc.]
Uncertainties regarding risks	[Describe uncertainties (e.g. limited long-term safety data), list sources of the evidence including limitation of the sources (e.g. data quality, generalisability of findings), indicate populations where uncertainty is especially relevant, etc.]
Risk management needs	[Discuss impact of the risk on risk-benefit balance of the product and on public health]
Part 2 | Disease context and current therapeutic offer	
Remaining medical need under current therapeutic options.	[Summarise local epidemiology, standard of care including safety profile. Discuss if new medicine under scope addresses the remaining medical needs in the local context, etc.]
Part 3 | Benefit vs risk assessment summary	
NRA Assessor's comment	
[Compare the benefits and the risk regarding clinical relevance and impact of uncertainties. Highlight if there are significantly different outcomes for subpopulations, e.g. children, pregnant]	
Conclusions	
1. The overall benefit-risk balance considered **remains positive**. No additional Risk Minimization activities are required. 2. The overall benefit-risk balance considered **inadequate**. Additional Risk Minimization activities are required.	

6 Action taken by NRAs and/or MAHs for safety reasons

Actions taken by the MAH	[List any significant regulatory action (including those initiated by the MAH in any market in relation to a safety concern.]
Actions taken by NRAs	[Significant regulatory action would include a restriction to the approved indication, a new contra-indication, a new or strengthened warning in section 4.4 of the SPC (or equivalent) or any action to suspend or revoke a marketing authorisation.]
NRA Assessor's comment	

7 Questions to the MAH and Responses

Queries to the MAH (if any)	[Specify your queries]
MAH Responses	[MAH responses to be provided here]
Assessor´s Conclusions	[Acceptance of the MAH responses or additional queries]
Risk Management Plan Commitments in [Country]	[Describe the details of agreed MAH's commitments in risk management plan including routine and additional pharmacovigilance activities and risk minimisation measures here]

8 RMP Summary and Conclusions

Pharmacovigilance Plan Commitments by MAH in [Country]	
Risk Management Plan Commitments by MAH in [Country]	[Describe the details of agreed MAH's commitments in risk management plan including routine and additional pharmacovigilance activities and risk minimisation measures here]
Required Risk Minimisation activities by NRA	**Routine** (specify)
	Additional (specify)

9 Approval of RMP assessment report

Prepared by (name of assessor) _____Date_____

Approved by (name of approver) _____ Date_____