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REVIEW



# Regulatory experience of handling Risk Management Plans (RMPs) for medicinal products in the EU

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**ABSTRACT**

**Introduction**: Risk Management Plans (RMPs) aim to optimize a medicinal product's benefit/risk balance for the individual patient and the target population. Despite differences in regulatory RMP requirements between jurisdictions worldwide, their ultimate aim is to protect public health.

**Areas covered**: The review presents findings of different RMP requirements by different regulatory authorities and additional risk minimization measures (issued between January 2010 and December 2018) indicate how RMPs and additional risk minimization measures translate into actions to protect public health within the European Union (EU) member states and worldwide. Areas covered also include the different International Council for Harmonization (ICH) regional requirements of RMPs by the different regulatory authorities as well as data regarding the number of RMP assessments carried out by the EMA, FDA and Japan, and number of safety communications issued in Malta (taken as an example of a typical small EU member state) and in the United States of America (USA).

**Expert opinion**: The EU legislation adopted in 2010 required RMPs to be included in all new applications for medicinal products in the EU, both for EU centrally authorized and nationally authorized medicinal products. Lessons learnt by EU regulators during this process are discussed in this review.

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Drug safety; pharmacovigilance; risk management plan; risk minimization measures; safety communications

## 1. Introduction

In the European Union (EU), all medicinal products must be authorized before they are made available on the market for patient use. In the EU, an authorization may be granted through national procedures, mutually recognized procedures, and the centralized procedure [1]. A medicinal product is authorized in the EU if at the time of its authorization the benefits outweigh the risks for the target population within the conditions specified in the product labeling [2]. Information related to the safety profile of new medicinal products is based on data obtained during clinical trials; however, at the time of first approval there are uncertainties and the knowledge on its benefit risk profile changes over time as the broader post-marketing use provides additional information [3,4].

The aim of risk management system for medicinal products is to ensure a positive benefit/risk balance by the greatest margin possible for the individual patient and the target population [5]. A Risk Management Plan (RMP) is a stand-alone, multi-part document that is updated by the marketing authorization holder throughout the product lifecycle [4,5]. The RMP reflects the actions needed to increase the knowledge on the safety profile of a medicinal product and describes risk minimization measures (RMMs) [6–8]. The concept of a risk management system was first introduced into EU legislation in 2005 by means of the European Commission (EC) Regulation No 726/2004 and Article 8(3) (iaa) of Directive 2001/83/EC [3]. An EU-RMP was required with an application for a new active substance, similar biological medicinal products and generic/hybrid medicinal products where safety concerns requiring additional RMMs have been identified with the reference product [9]. The EU pharmacovigilance legislation, which came into effect in 2012, required RMPs to be included in all the new applications for a marketing authorization [3].

We aimed to study how these RMPs translate in protecting public health from the perspective of EU member states. This study provides data regarding RMPs assessed at an EU level as well as quantitative data regarding safety communications (aRMMs and DHPCs) assessed and approved at national level using a small EU member state as an example where challenges of resources are associated with its size. We provide key points learnt from the experience gained as national regulators operating in the EU during RMP assessment and management of safety information at national level. Such lessons are of interest to both the industry and other regulatory bodies including EMA. This study also identifies the different RMP requirements of various world regions and countries, and challenges that this presents.

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**Article highlights**

- Regulatory RMP requirements vary across the different world regions or authorities and there is not one set of requirements that is applicable for all the regions worldwide.
- Despite the different RMP format being used, risk minimization measures (RMMs) are always required to optimize the safe and effective use of a medicinal product throughout its lifecycle.
- In the EU, additional RMMs appear to be a more frequently utilized risk management tool when compared to direct healthcare professional communications (DHPCs) and overall, antineoplastic and immunomodulating agents required additional RMMs most frequently.
- In the EU, national competent authorities have a key role in ensuring that RMPs serve as a tool to protect public health through the managed implementation of RMMs and DHPCs adapted nationally according to the needs of local healthcare systems at the member state level.
- The amendments made to the EU pharmacovigilance legislation in 2010 impacted the requirements for a marketing authorization and over time, national regulators have gained considerable experience with RMP assessment and compilation, review, approval and dissemination of safety information at national level. Key lessons learnt from our experience as EU regulators handling RMPs, RMMs and DHPCs are summarized and presentedt from our experience

This box summarizes key points contained in the article.

## 2. Methods

### 2.1. Review of worldwide RMP requirements, structure, and assessment

A literature review of RMP requirements, RMP structure and RMP assessments was conducted to retrieve country-specific regulations, policies, and reports. Literature published between 2005 and 2020 was considered. The following search engines and tools were accessed: Google Web, Google Scholar, PubMed, the EMA website, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) website and different countries' medicines authorities' websites. Sources of information in English, French, Spanish and Japanese were considered.

### 2.2. Review of Risk Minimization Measures and safety communications

RMM assessments in the USA, Japan and the EU were reviewed. In order to understand how aRMM in the EU translates into protecting patient and public health in an EU member state, we reviewed safety communications approved and issued by a small EU member state medicinal product regulatory authority 'the Malta Medicines Authority (MMA)'. Reasons why the output of the MMA is an appropriate for this study are as follows: 1) Malta is an EU member state; 2) the MMA is a small regulatory agency with resources challenges associated with it; 3) the MMA has the legal obligation to implement all RMMs approved by the EMA; 4) English is the official language of Malta and all MMA material is online as well as in English. Safety communications reviewed included DHPCs and aRMMs. DHPCs are sometimes used as risk minimization measures in order to communicate particular safety issues to medical practitioners and these need to be included in the study. aRMMs and DHPCs (compiled and disseminated for products marketed in Malta) were reviewed for the period of January 2010 and December 2018 for aRMMs and January 2012 and December 2018 for DHPCs. The active substances involved were codified using the 5th level of the Anatomical Therapeutic Chemical (ATC) Classification of the World Health Organization (WHO) [10]. The DHPCs issued by the US Food and Drug Administration (FDA) were reviewed for the same period (2012 to 2018) in order to identify any similarities or differences.

## 3. Results

### 3.1. World ICH regions

The requirements of RMPs and their structure for the following regions/ICH countries: EU, USA, Japan, Argentina, Australia, Canada, India, Malaysia, the Republic of the Philippines, Singapore and Switzerland are presented as follows.

#### 3.1.1. Requirement of an RMP by regulatory authorities

In some countries, there is no specific legislative basis for the government to require a pharmaceutical company to provide an RMP. Instead, health regulatory authorities take action based on broader, less specific authorities within existing regulations. Other countries have adopted a legislative approach where laws require an RMP, with appropriate risk minimization activities, to be implemented for certain medicinal products. RMPs have usually been required for new chemical entities or where there is an extension to the indication of the product, especially in pediatric populations or new indications. In these cases, there are usually additional legislative powers that allow regulatory authorities to require pharmaceutical companies to develop RMPs if any safety issues are identified post-marketing [11]. The EU, Japan and the USA have introduced specific requirements as approaches to risk minimization activities [11].

Since July 2012, the EU requires an RMP for all new applications, including biologics and similar biologics, generic, hybrid and fixed combination medicinal products. Additionally, RMPs are required for medicinal products marketed in accordance with Article 10(c) under informed consent and in well-established use, in accordance with Article 10(a) of Directive 2001/83/EC [2,12]. For medicines marketed prior to this date an RMP is not mandatory; however, safety concerns may trigger the need for an RMP. RMPs must be continuously updated.

In the USA, the Food and Drug Administration Amendments Act (FDAAA), enacted in 2007, gave the FDA additional responsibilities to enhance drug safety [13,14]. One of the provisions gave the authority to the FDA to require a Risk Evaluation and Mitigation Strategy (REMS). Provisions that became effective in 2008 authorize the FDA to require application holders to develop and comply with REMS if specific statutory criteria are met. The new regulations and requirements apply to prescription products that are approved under New Drug Applications (NDAs) and

Abbreviated New Drug Applications (ANDAs) and products approved under Biologics License Applications (BLAs) [11]. The determination of whether an REMS is needed is based on the consideration of certain factors namely the estimated size of the population likely to use the drug, the seriousness of the condition that is to be treated, the expected benefit of the drug, the duration of treatment, the seriousness of any known or potential adverse reactions and background rates of disease incidence and whether the drug is a new chemical entity [11].

In Japan, an RMP was not required until 2013. The current RMP guidance applies to new drugs and biosimilar products for which manufacturing, or marketing approval application after April 2013 and for generic drugs on, or after 26 August 2014 [15]. The requirement of an RMP may be determined in consultation with the Japanese Ministry of Health, Labor and Welfare, that occurs at the pre-marketing stage [11]. If the authorities deem the risks associated with a particular medicinal product high, a robust RMP must be developed by the industry and submitted at the time of registration [11].

With the growing use of formal RMPs in the ICH countries of US, Japan and Europe, other countries have started to request or require submission of either a local RMP or for copies of REMS or RMP that pharmaceutical manufacturers have submitted to other regulatory authorities [11]. Argentina, Australia, Canada, India, Malaysia, Singapore and Switzerland all require RMPs for new active substances and biologics. Australia, Canada, Malaysia, Singapore and Switzerland require RMPs, or its update, when there is a significant change in the indications of the medicinal product. Canada requests an RMP for any drug that was previously withdrawn from the market due to a serious safety issue and is being re-introduced onto the market [11] Malaysia does not generally require an RMP for those substances classified as a generic scheduled poison, a generic nonscheduled poison, health supplements and natural products but it is expected that their safety is monitored. Switzerland require an RMP or RMP update if the authorization extension requires changes to the RMP concerning PhV activities and risk minimization measures [16].

Australia is an example of a country whose regulatory authority has adopted guidelines from another international regulator, the EMA [11]. Australia may require an RMP if the biosimilar does not have the same indications (i.e there is omission of any indications of the originator product) and presentations as the reference product. An RMP is not required for a biosimilar if there is an RMP for the reference product and there are no additional PhV activities or additional RMMs and the biosimilar has identical indications, dosage forms and routes administration to the reference product. Generally, RMPs are not required for generic products unless there is: (1) an RMP for the reference product but there are safety concerns which require RMMS; (2) no RMP for the reference product and safety concerns that require specific RMMs have been identified with the reference product [17].

In Brazil, the National Health Surveillance Agency has published a regulatory guide to PhV plans and risk minimization plans since 2009. This guidance was developed based on the ICH E2E, EU Volume 9A and FDA Risk Minimization Action Plans (MAP) guidelines, as well as the relevant legal requirements. A Pharmacovigilance Plan (PVP) and an RMP form the risk management system of the MAH. A PVP is required for all new synthetic, semi-synthetic molecules, new vaccines and biotechnology-derived products. Significant changes to the marketing authorization, when unexpected damage is identified or when requested by the authorities a PVP must be compiled. If measures proposed in the PVP are not enough to address identified, potential or unknown risks, an RMP is required to supplement the PVP. The safety specification includes clinical and non-clinical data. The PVP includes routine PhV practices, action plans for safety issues and an evaluation of the need to elaborate on the risk minimization plan. The RMP includes risk minimization activities, their effectiveness and an RMP for safety concerns [18].

Within The Republic of The Philippines, Administrative Order 2014–0034 states that no drug establishment shall manufacture, import, export or perform any other activity that involves a drug product without first obtaining a License to Operate (LTO) from the Food and Drug Administration of The Philippines. The development and implementation of an RMP is a requirement for the issuance of a LTO [19].

Generally, updates to existing RMP are requested by the respective authorities usually in response to new safety concerns which may require additional PhV or risk minimization activities.

### 3.1.2. Structure of a risk management plan

The review of the requirements governing the approved structure of RMPs, across different world ICH regions and for different institutions, shows that the structure of an RMP does not follow a clearly defined format that is common for all world regions and countries reviewed. This finding has been previously acknowledged by Trivedi et al., (2006), James et al. (2014), Lis et al., (2015) and Haque et al., (2017) [18,20–22].

In the EU, the concept of an RMP was formally laid down in an amendment to the Directive 2001/83/EC by Directive 2004/27/EC. The structure of the EU-RMP consists of 7 parts. Part I is the product overview. It includes the administrative information on the RMP and an overview of the medicinal product. Part II, the safety specification, is a summary of the safety profile of the medicinal product including what is known and not known, important identified and potential risks and missing information. The PhV plan in Part III describes the structured approach for monitoring the safety concerns of the product. The aim is to better characterize risks and improve on any missing information. The activities described are routine and additional PhV activities. Part IV consists of any plans for post-authorization efficacy studies (PAES). Part V is dedicated to risk minimization measures. It includes detailed information about reducing risks associated with each individual safety concern. Part VI is the summary of the RMP and is publicly available. Annexes are included in Part VII [5].

In the USA, REMS is a required risk management strategy that may include different elements to ensure that the benefits of the drugs outweigh the risks [23]. Each REMS has specific safety measures which target the serious risks

associated with the drug or class of drugs. Compliance to the REMS program is required if it is necessary to ensure that the benefits outweigh the risks. This applies to new drug applications, license applications for biologics and abbreviated new drug applications. A REMS can be required pre- or post-approval [24].

The estimated size of the population likely to use the drug involved, the seriousness of the disease or condition that is to be treated, expected benefits of the drug with respect to its indication, the expected or actual duration of treatment, the seriousness of any known or potential adverse events that may be related to the drug are all taken into consideration when determining whether the REMS is necessary. Additionally, the background incidence of such events in the population likely to use the drug, and whether the drug is a new molecular entity also play an important factor [24].

The REMS contains specific sections and provides a standardized language, developed by the FDA, to describe common REMS requirements [23]. All REMS should include one or more goals, which describe the safety-related health outcomes that the REMS is designed to achieve, including the relevant measurable objective. If the REMS requires elements to assure safe use (ETASU) the document must include one or more goals to mitigate a specific serious risk listed in the labeling of the drug [23]. REMS requirements establish the requirements for both the applicant and the participant. This section is to be subdivided into REMS Participant requirements and REMS applicant requirements. The REMS assessment timetable guides the submission of assessment of the REMS typically by dates 18 months and 3 years after it is initially approved and another on in the 7th year. REMS materials are a comprehensive list of all the materials that are required for the REMS. The list is to be organized by the REMS participant.

An RMP in Japan should follow the structure and templates provided in the national guidelines, based on ICH E2E Guideline. The format of an RMP consists of a (1) Summary of Risk Management Plan, including safety specification and concerns for efficacy, (2) Summary of Pharmacovigilance Plan, (3) Summary of plans for surveillance and studies for efficacy, (4) Summary of risk minimization activities, (5) Lists of pharmacovigilance plan, surveillance and studies for efficacy and risk minimization plan, (6) Organizational structure for Risk management plan and (7) Background information [15,25,26].

In Singapore, an RMP may follow either the EU-RMP or the REMS [27]. Health Canada accepts the EU-RMP format or the REMS format as long as the essential elements are covered. These include safety specification, PhV activities, risk minimization activities and the evaluation of RMMs [4]. Australia only accepts a risk management plan in the EU-RMP format [17].

The content and format of the RMP, in Switzerland, is based on the ICH E2E Guideline entitled Pharmacovigilance Planning and the EMA Guideline on Good Pharmacovigilance Practices (GVP): Module V. The Swissmedic (Swiss Agency for Therapeutic Products) Guidance document on RMP submission refers to the EMA template for the structure of the RMP [16].

Worldwide, the other countries reviewed have different RMP requirements. The RMP structure for Argentina, Brazil, India, Malaysia, Nigeria and The Republic of The Philippines must contain specific sections as specified in their respective regulations and guidelines [18,28–31]. Despite its different structure across different countries, RMMs form part of the RMP in every country reviewed. The PhV plan and safety specification sections are required by the majority of the countries, with the exception of Brazil for the safety specification and The Philippines for the PhV plan.

Australia, Canada and Singapore require a country-specific annex as an additional section in the RMP, irrespective of the format used. The country-specific annex includes information of the epidemiology of certain medical conditions, risk factors, indications, genetics or extrinsic factors applicable to the country's population. PhV activities including risk minimization measures and their evaluation, milestones and timelines are to be discussed in a context pertaining to a specific country [4,17,27]. Table 1 summarizes the structure of RMPs for the different world regions and institutions reviewed.

#### 3.1.3. Review of regulatory RMP Assessments

Discussions between regulators and MAHs at the early stages of drug development are recommended for the development of the RMP and any additional PhV activities and risk minimization measures. It is in the interest of industry and regulators that the least harm and the maximum benefit results from using a medicine, and to avoid unnecessary, inefficient measures or activities.

For generic medicinal products, the safety specification, where an adequate discussion of the safety profile of the medicinal product is discussed, is expected to be the same as the reference product or other generic products for which an RMP is already in place [5]. Any discrepancies should be justified based on either differences in the products' characteristics (e.g. excipients) or on compelling data generated with this generic product that would warrant a difference in the list of safety concerns in the RMP [11].

Each new RMP, or RMP update, must be assessed. The EMA issued a report on PhV tasks from EU member states covering a period between 2015 and 2018. Each year EMA Pharmacovigilance Risk Assessment Committee (PRAC) assessed at least 500 new or updated RMPs, 649 RMPs in 2015, 570 in 2016, 561 in 2017 and 543 in 2018 [32]. Many RMPs, especially those pertaining to generic medicines, are assessed at national level. More than 36,000 RMPs were submitted to National Competent Authorities (NCAs) the study period, and approximately 7000 RMPs were assessed [32] and as a result, national regulators have gained extensive experience in this regard.

### 3.2. Review of Risk Minimization Measures

Risk minimization measures are public health interventions that aim to optimize the safe and effective use of a medicinal product throughout its lifecycle. They must be included within an RMP. RMMs broadly categorized into those that are routine and those that are additional. The results obtained show that despite the RMP format being used, RMMS are always required.

Table 1. The required structure of a risk management plan for Europe, USA, Japan, Argentina, Australia, Brazil, Canada, India, Malaysia, The Republic of The Philippines, Singapore and Switzerland.

| | | Countries | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Europe | | North America | | South America | | Asia | | | | | |
| | | Europe | Switzerland | USA | Canada* | Argentina | Brazil | India | Japan | Malaysia | Philippines | Singapore* | Australia |
| RMP Structure | Product Overview | ✓ | ✓ | | ✓ | | | ✓ | | ✓ | | ✓ | ✓ |
| | Safety Specification | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Pharmacovigilance Plan | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ |
| | Plan for PAES | ✓ | ✓ | | ✓ | | | | | ✓ | | ✓ | ✓ |
| | RMMs | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Summary of RMP | ✓ | ✓ | | ✓ | ✓ | | | ✓ | ✓ | | ✓ | ✓ |
| | Annexes | ✓ | ✓ | | ✓ | ✓ | | | ✓ | ✓ | | ✓ | ✓ |
| | Administrative information | | | ✓ | ✓ | | | | | | | ✓ | |
| | Goal | | | ✓ | ✓ | | | | | | | ✓ | |
| | Medication guide | | | ✓ | ✓ | | | | | | | ✓ | |
| | Communication Plan | | | ✓ | ✓ | | | | | | | ✓ | |
| | Elements to assure safe use | | | ✓ | ✓ | | | | | | | ✓ | |
| | Implementation system | | | ✓ | ✓ | | | | | | | ✓ | |
| | Timetable for submission of assessments | | | ✓ | ✓ | | | | | | | ✓ | |
| | Surveillance and studies for efficacy | | | | | | | | ✓ | | | | |
| | Background information | | | | | | | | ✓ | | | | |
| | Organization structure for RMP | | | | | | | | ✓ | | | | |
| | Country-specific annex | | | | ✓ | | | | | | | ✓ | ✓ |
| | Evaluating effectiveness of RMMs | | | | | | ✓ | | | | | | |
| | Milestones and timelines | | | | | | ✓ | | | | | | |

* The structure of the RMP accepted is either the EU-RMP format or REMS.

### 3.2.1. RMMs in the USA and Japan

Since 2007 the Food and Drug Administration Amendments Act authorized the FDA to require risk evaluation and mitigation strategies (REMS) as part of the authorization documents in the US [33,34]. A REMS can include the following elements: a Medication Guide, a Communication Plan, Elements To Assure Safe Use (ETASU), an Implementation System and a Timetable for Submission of Assessments [23]. A REMS is only required for some drugs and it can be limited to a few years after the product is launched onto the market. The REMS is only focused on specific serious risks, the communication and elements required to assure safe use. The REMS are rapidly evolving, only managed by a single agency and most REMS are available in one single language. The drugs that require a REMS are drugs which provide major benefit but have associated side-effects that can be devastating. It is a safety strategy to manage known or potential serious risks associated with a medicine and to enable patients to have continued access to such medicines by managing their safe use. The REMS' main concern is the communication of risk.

The FDA has 61 approved, current, active REMS. Fifty-one REMS (84%) include ETASU. These types of REMS require the certification of clinicians or healthcare settings prior to prescribing and participating in additional REMS activities such as training, patient counseling and monitoring [35]. Seven REMS (11%) include a communication plan. The communication plans are an informal means of disseminating information and include letters, websites and fact sheets describing the safety risks identified in the REMS. Three REMS (5%) only include a medication guide [35].

Since 2008, the FDA has approved another 201 REMS documents that are no longer in effect. The number of years during which a REMS document remains active varies from a few months to a decade. Seventy-one REMS (35%) were active for 2 years. Thirty-four (17%) were active for 3 years and 30 (15%) were active for 1 years. Seventeen (8%) were active for less than one year, with REMS for products such as gabapentin and clopidogrel only active for 3 months. Twenty-four percent of the REMS for medicinal products were active for more than 3 years. The REMS that was active for the longest period of time pertained to testosterone-containing products, where the REMS was active for 10 and 11 years according to the product. The REMS for these products was released, i.e. no longer active, in May of 2019 [35].

In Japan, the requirement of RMMs is determined based on whether the identified risks, potential risks and missing information are mentioned in the package leaflet. Since April 2013 a total of 2079 identified risks, 1095 potential risks and 357 missing information have been registered in the 407 approved RMPs. One thousand seven hundred ninety-four (86%) identified risks, were mentioned in the package leaflet as risk minimization activities. In contrast, only 198 (18%) of the potential risks and 4 (1%) of the missing information were included in the package leaflet [36,37].

### 3.2.2. RMMs in the EU

In the EU additional RMMs are built onto existing routine RMMs, both of which are integrated into an overall RMP with its PhV plan and effectiveness measures. For centrally authorized products aRMMs that have been recommended by the PRAC and agreed by the Committee for Medicinal Products for

Table 2. Top 20 active substances and the respective therapeutic class for which RMMs were required in Malta.

| ATC Code | Active Substance | Therapeutic Class | No. of RMMs assessed | % of total RMMs |
|---|---|---|---|---|
| L04AC07 | Tocilizumab | Interleukin inhibitors | 58 | 8.7 |
| S01LA04 | Ranibizumab | Antineovascularisation agents | 44 | 6.6 |
| L04AX04 | Lenalidomide | Other immunosuppressants | 34 | 5.1 |
| B01AE07 | Dabigatran etexilate | Direct thrombin inhibitors | 33 | 5.0 |
| L04AA06 | Mycophenolic acid | Selective immunosuppressants | 18 | 2.7 |
| M05BA08 | Zoledronic acid | Bisphosphonates | 18 | 2.7 |
| L04AA27 | Fingolimod | Selective immunosuppressants | 17 | 2.6 |
| L04AB02 | Infliximab | Tumor necrosis factor alpha (TNF-α) inhibitors | 16 | 2.4 |
| L01XC02 | Rituximab | Monoclonal antibodies | 15 | 2.3 |
| L04AC05 | Ustekinumab | Interleukin inhibitors | 15 | 2.3 |
| L01XC11 | Ipilimumab | Monoclonal antibodies | 14 | 2.1 |
| L01XC17 | Nivolumab | Monoclonal antibodies | 14 | 2.1 |
| L04AX06 | Pomalidomide | Other immunosuppressants | 14 | 2.1 |
| S01LA05 | Aflibercept | Antineovascularisation agents | 13 | 2.1 |
| V03AC03 | Deferasirox | Iron chelating agents | 13 | 2.1 |
| L01XE08 | Nilotinib | Protein kinase inhibitors | 12 | 1.8 |
| L04AB04 | Adalimumab | Tumor necrosis factor alpha (TNF-α) inhibitors | 12 | 1.8 |
| B01AF01 | Rivaroxaban | Direct factor Xa inhibitors | 11 | 1.7 |
| L01XX43 | Vismodegib | Other antineoplastic agents | 10 | 1.5 |
| R03AK07 | Formoterol and budesonide | Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics | 9 | 1.4 |

Human use (CHMP) will become conditions for the safe and effective use of a medicinal product once they have been agreed upon by the European Commission through a Commission decision [8]. The CHMP opinion will outline the key elements of any additional RMMs imposed on the applicant or MAH. The EC decision may describe the responsibilities of the NCAs in ensuring that the RMMs are implemented in the MSs in according to the key elements defined [8]. For products authorized via MRP or DCP, aRMMs should be included in the RMP and may also be laid down as conditions of the marketing authorization. The EMA, in collaboration with the MSs and facilitated through PRAC, monitors the outcomes of the RMMs within the RMP. The PRAC evaluates the outcomes of the RMMs, including any aRMMs and makes recommendations as necessary regarding any further regulatory actions.

In all the different scenarios, implementation of the RMMs takes place at a national level and each NCA is responsible for the oversight of the implementation of the RMMs imposed as a condition of marketing authorization irrespective of the route of authorization. The NCAs agree on the final content, format and media of risk minimization tools prior to their distribution and ensure that approved aRMMs are disseminated in line with agreed communication plans in their member state. This allows the different member states to tailor to the required conditions and restrictions to national legal requirements and local healthcare systems. This means that RMMs may need to be assessed by multiple agencies, in many languages and national variations can occur [8]. EU regulators issue national guidance documents for pharmaceutical companies on their PhV obligations with respect to risk management including the procedure on how to submit RMMs for national approval and the national assessment process [38].

Table 3. Top 10 active substances and the respective therapeutic class for which DHPCs were required.

| ATC Code | Active Substance | Therapeutic Class | No. of DHPCs disseminated | % of total DHPCs |
|---|---|---|---|---|
| L04AA27 | Fingolimod | Immunosuppressants | 5 | 3.2 |
| L04AX06 | Pomalidomide | Immunosuppressants | 4 | 2.6 |
| M01AB05 | Diclofenac | Antiinflammatory and antirheumatic products, non-steroids | 4 | 2.6 |
| M05BX04 | Denosumab | Drugs affecting bone structure and mineralization | 4 | 2.6 |
| A10BK02 | Canagliflozin | Blood glucose lowering drugs, excluding insulins | 3 | 1.9 |
| B05BA10 | Combination | I.V. Solutions | 3 | 1.9 |
| L01XX02 | Asparaginase | Other antineoplastic agents | 3 | 1.9 |
| L03AB10 | Peginterferon alfa-2b | Immunostimulants | 3 | 1.9 |
| L04AA06 | Mycophenolic acid | Immunosuppressants | 3 | 1.9 |
| L04AX04 | Lenalidomide | Immunosuppressants | 3 | 1.9 |

The competent authorities of EU Member States are legally required to established and use quality systems for performing their pharmacovigilance tasks and responsibilities [39,40]. Each national competent authority implements a quality system that is adapted to the respective organization. Quality assured pharmacovigilance systems are documented through written records, policies and standard operating procedures (SOPs). Based on our experience as national regulators we recommend that SOPs define the available triggers for the start of the process as well as adherence to timelines as mandated by the European Commission (if applicable) as key performance indicators (KPI). In the case of a written procedure for managing RMMs, triggers could include incoming RMMs received by e-mail or post from third parties, decisions published on the community register which may contain conditions to the Marketing Authorization as well as internal triggers received from other departments within the NCA. SOPs should cross-link to other processes and other documents such as policies or guidelines as applicable. SOPs should incorporate risk-based thinking and take a pragmatic approach but contain necessary details required to produce outputs of good quality. In line with CIR 520/2012 article 14 Management of human resources – 'The national competent authorities shall have sufficient competent and appropriately qualified and trained

Table 4. The number of DHPCs and RMMs per year that have been reviewed and approved by the MMA.

| Number per year | | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|---|---|---|---|---|
| DHPCs | | - | - | 8 | 41 | 22 | 24 | 20 | 20 | 22 |
| Diverse Additional RMMs | Total | 7 | 24 | 38 | 98 | 93 | 92 | 109 | 108 | 121 |
| | Information for patients | 2 | 6 | 9 | 34 | 31 | 43 | 61 | 39 | 52 |
| | Information for HCP | 1 | 3 | 9 | 19 | 23 | 13 | 19 | 20 | 21 |
| | Information for prescribers | 3 | 4 | 6 | 12 | 12 | 10 | 10 | 15 | 10 |
| | Reminder and Alert Cards | 1 | 9 | 5 | 13 | 13 | 12 | 18 | 20 | 26 |
| | Dosing, administration and reconstitution | 0 | 2 | 7 | 12 | 5 | 7 | 0 | 10 | 3 |
| | Other | 0 | 0 | 2 | 8 | 9 | 7 | 1 | 4 | 9 |
| | Products in PPP | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 2 | 2 |

Abbreviations: HCP = healthcare professional, PPP = pregnancy prevention programme

personnel available for the performance of pharmacovigilance activities' [41] and to this effect PV staff at national agencies are adequately trained to ensure that they can carry out their tasks (which include RMP assessment and processing of RMMs and DHPCs) efficiently, effectively and in a timely manner.

Taking Malta as our example, since 2010, the Malta Medicines Authority (MMA) has received 671 RMMs that have been approved. The top 20 medicinal products that required an assessment of the RMM in Malta are shown in Table 2. When looking at the medicinal products with respect to the therapeutic class, interleukin inhibitors, antineovascularisation agents, other antineoplastic agents and monoclonal antibodies required the most RMMs.

Table 4 shows the number of DHPCs and RMMs per year that have been reviewed and approved by the MMA. The data illustrate the diversity of aRMMs and gives an overview of the amount of educational material directed toward different target audiences. Educational programs are risk minimization tools with a clearly defined scope, related to a specific safety concern, to supplement the information already available in the SmPC and PIL. Educational tools may have several target audiences, address multiple-safety concerns, and be delivered in several ways to ensure they are accessible [8]. Educational tools include leaflets and brochures for prescribers, healthcare professionals, patients and carers. Examples of educational tool include patient alert cards and reminder cards as well as prescribers' checklists and reconstitution, dosage and administration guides targeting different HCPs. Another risk minimization tool is a pregnancy prevention program (PPP), which is a set of interventions aimed at minimizing pregnancy exposure during treatment with a medicinal product known to be teratogenic or with potential teratogenic effect [8]. Educational material, in the form of leaflets, brochures and alert cards, treatment initiation forms, safety advice and brochures for prescribers are issued for products that are under a PPP. In our example, 12 products have been placed under a PPP between 2012 and 2018 in Malta.

Controlling access to a medicinal product beyond that ensured by routine risk minimization measures (i.e beyond the legal status) is the key feature of a controlled access

Table 5. Key lessons learnt from EU regulators experience of handling RMPs, RMMs and DHPCs.

| Lessons Learnt | |
|---|---|
| RMP Assessment | |
| Guidelines | MAHs or applicants benefit from clear guidance on the format of a RMP. This decreases variation in the RMP content. Assessors benefit from having a template for assessment reports. |
| Training Staff | Staff are well trained in order to assess RMPs efficiently and effectively. |
| Human Resources | Assessment can become resource intensive. RMPs assessments involving multiple RMPs may be cumbersome and time-consuming, (especially if RMPs are added during the assessment period which requires the assessor to multiple RMPs in a very short period of time). |
| No RMP previously existing | RMP of the medicinal product must be assessed from first principles. |
| Generic product has RMP while reference product does not | The RMP of the generic medicinal product must be assessed from first principles. |
| RMP updates | Is the RMP assessed completely or are the changes assessed? It is more difficult to single out the changes that have been affected from one version to another. It requires skill thus staff must be appropriately trained. If it is only the changes that are being assessed, it must be clearly stated in the assessment report.<br>RMP updates should not be accepted together with the PSUR or PSUSA. If there are changes to safety concerns requiring update outside a regulatory procedure, RMP should be submitted as a standalone procedure. Discussions with regulators facilitates RMP submission and avoids unnecessary submission and assessments. |
| Parallel RMP submissions | Different MAHs may submit different RMPs in parallel. It has been the case that RMPs are added at a later stage. The number of RMPs that need to be assessed then increases drastically. In these circumstances it is advisable for the assessor to choose the best RMP and advise MAHs to follow the format and information of that RMP.<br>Assessors are trained to find parallelisms. |
| Additional monitoring | Any post-authorization safety studies must be incorporated into the RMP. This contributes to an increased workload. Trained staff and procedure management help overcome these challenges. |
| RMMs and DHPCs | |
| Guidelines | The industry and MAHs benefit from clear guidelines outlining the process involved for submission, review and approval of RMMs. |
| SOPs | Should clearly identify triggers for the start of the process as well as timelines mandated by EMA scientific committees as key performance indicators |
| Training | Adequately training the staff responsible for this procedure ensures that they can carry out their tasks efficiently, effectively and in a timely manner |

Abbreviations: PSUR= Periodic Safety Update Report, PSUSA= Periodic Safety Update Report Single Assessment, SOP= Standard Operating Procedure

program. It is a tool for minimizing an important risk with significant public health or individual impact for a product with clearly demonstrated benefit, which would otherwise not be available without controlled access [8]. A requirement to test or to monitor a patient in a specific way can also be used as a controlled access tool [8]. In a controlled distribution system, it is ensured that the stages of a distribution chain of a medicinal product are tracked up to the prescription or dispensing of the product.

### 3.3. Review of safety communications

Safety communication is a broad term that encompasses the active dissemination of safety information on medicines to the target audience such as patients and healthcare professionals. The need to communicate safety information is considered throughout the risk management process and is vital to promote the rational, safe and effective use of medicines in line with the objectives of pharmacovigilance.

#### 3.3.1. Review of DHPCs in the USA

In the USA, DHPC letters are used to notify healthcare professionals about important new or updated information about a drug, usually in relation to important safety concerns that could affect the decision to use a drug or change the way the drug is used. Some DHPC letters are written as part of REMS communication programs to inform different target audiences about the implementation of new and modified REMS or to present additional safety information about the medicinal product [42].

Since 2010, the FDA has issued 151 DHPCs. Five DHPCs (3.3%) concern fluoroquinolones. Fingolimod and ponatinib had four DHPCs (2.6%) each that were issued by the FDA. Three DHPCs (2%) concern canagliflozin and another 3 (2%) concern the SGLT2 inhibitors as a class. Codeine, ezogabine, olanzapine and gadolinium-based contrasts each have 3 DHPCs (2%) of the total DHPCs issued.

#### 3.3.2. Review of DHPCs in the EU

In the EU, DHPCs are sometimes used as risk minimization measures within an RMP, where information is delivered by a MAH directly to healthcare professionals, to inform them of the need to take certain actions in relation to a specific medicinal product. There are several publications that reviewed DHPCs in the EU. These include publications by de Vries et al. (2017), Radecka et al. (2018) and Hoeve et al (2021) [43–45].

DHPCs are disseminated by one or a group of MAHs either at the request of the NCA or on the MAH's own initiative [46]. Centrally authorized products, or products subject to a EU procedure, submit the draft DHPC and communication plan to the Agency, which coordinates the review process by its scientific committees, namely the involvement of PRAC and finalization by the CHMP or Co-ordination group for Mutual recognition and Decentralized procedures – human (CMDh), The DHPC is then implemented at a national level [46].

When medicinal products authorized via a decentralized procedure (DCP) or mutual recognition procedure (MRP), the MAH submits a draft DHPC and communication plan to the Reference Member State (RMS). The RMS coordinates the process with the MAH, keeping concerned Member States (CMS) involved in the process [46]. For medicinal products that are authorized on a purely national level, the MAH submits the draft DHPC including the relevant communication plan to the NCA of the Member State where the medicinal product is authorized. In situations where a single DHPC prepared at an EU level is not suitable due to the differences between the Member States, it is proposed that a core EU DHPC is agreed at an EU level, setting out core EU messages, which are then complemented at a national level with additional information to address different national situations [46].

The preparation of DHPCs involves the cooperation between the MAH and the NCA and an agreement between the MAH and NCA should be reached prior to a DHPC being disseminated to the target audiences [8,46]. The MAH and NCA agree on the content of the DHPC as well as its communication plan, the intended recipients, timetables and channels used to disseminate the DHPC [46]. In situation where several MAHs are obligated to send out a DHPC, such as when there are several marketing authorization holders of the same active substance or in cases where a class of products is involved, efforts should be made at the national level to ensure that healthcare professionals in a given Member State receive a single DHPC with a consistent message that coverings all the medicinal products affected by a single safety concern [46].

Taking Malta as our example, since 2012, the MMA has received 156 DHPCs that have been approved and disseminated in Malta. The top 10 medicinal products for which a DHPC was approved and disseminated in Malta are shown in Table 3. When looking at the medicinal products with respect to the therapeutic class immunosuppressants required the largest number of safety information dissemination. The list also includes non-steroidal anti-inflammatory drugs, drugs affecting bone structure and mineralization as well as blood glucose-lowering drugs. For these medicinal products safety concerns include, but are not limited to, new contraindications in pregnant women, contraindications in patients with cardiac conditions or cerebrovascular diseases and advice to minimize risks of serious hepatoxicity. In contrast to the EU, where in our example, the largest amount of DHPCs concerns immunosuppressants, in the USA, the largest amount of DHPCs concern the use of antibiotics although DHPCs on immunosuppressants and antineoplastic agents are also among the most disseminated DHPCs in USA.

Upon comparing the rates of DHPCs and RMMs as communication/educational tools approved at member state level in Malta, the data obtained suggest that RMMs are used much more frequently to communicate safety information (see Table 4). This may reflect the fact that the new medicinal products being authorized (via EU centralized procedure) are more complex and require more elaborate risk mitigation measures than dissemination of a DHPC letter.

## 4. Conclusion

A risk management plan is a tool to protect public health. It describes what is known and unknown about the safety of the medicinal product, further characterize the risk after

authorization and define appropriate measure to minimize the risks associated with the medicinal product. The RMP is a requirement for the authorization of many different types of medicinal products. The developers of a medicinal product must comply with the different requirements of the authority granting the marketing authorization. Typically, the risks to be mitigated are similar across locations. The impact of these risks may, however, differ due to differences within healthcare systems and delivery issues.

This review of the regulatory RMP requirements for the different world regions or authorities has shown that there is not one set of requirements that is applicable for all the regions analyzed. This may pose challenges for the industry to develop an RMP that complies with requirements of different countries. Forming part of the ICH or certain world (ICH) region nay influence legislative/RMP requirements. Harmonization initiatives on a world level, such as ICH, are beneficial in this regard. This study also illustrates how RMP components related to ensuring the safe and effective use of medicinal products result in safety information being disseminated at EU member states level for the benefit of patients and safeguard public health. National competent authorities have a key role in this process.

## 5. Expert opinion

The amendments made to the EU pharmacovigilance legislation in 2010 impacted the requirements for a marketing authorization. RMPs are to be included in all new applications [3]. Today, the RMP is also a requirement for innovative medicinal products as well generic medicinal products. The requirement of RMP is independent of the route of authorization as it is required both in centrally authorized as well as nationally authorized medicinal products. The change in legislation has significant implications for applicants, holders of EU marketing authorizations and national competent authorities within MSs. Such changes included; a pharmacovigilance system master file (PSMF) was introduced instead of a detailed description of the PhV system, the RMP became a requirement for all new products, post-authorization measures were enhanced with post-authorization safety studies (PASS) and post-authorization efficacy studies (PAES) became legally binding [3].

The RMP serves as a tool to protect public health only if the information within it somehow reaches the public. Article 26 of Regulation (EC) 1235/2010 and Article 106 of Directive 2010/84/EU instruct EU member states and the European Medicines Agency that a Summary of the RMP for each authorized medicinal product is made available to the public and shall include the key elements of the risk management plan together with other documents of the European public assessment report (EPAR) of that medicinal product [5]. The RMP summary includes a brief overview of the epidemiology of the disease, a summary of the benefits of treatment with the medicinal product and a description of the unknowns of treatment benefits. It also includes a summary of the important risks and how they are managed, an explanation of any missing data that needs to be collected, any additional measures to ensure the safe use of the medicine, any planned studies to be conducted to obtain more information and where applicable, an explanation of any updates that have been made [5]. The EPAR is derived from the assessment of the documentation submitted by the applicant and the scientific decisions taken by the EMA CHMP during the centralized evaluation process and is published on the EMA website [47]. The target audience for these summaries are patients and members of the public with no or very limited knowledge of the disease and treatment in question [48]. Making the summary of RMP available to the public, increases transparency and access to information on medicinal products.

Risk minimization measures are required to mitigate risks, while maintaining a positive benefit–risk ratio. These routine and additional measures are based on the drug safety information available at the time of approval and those resulting from post-authorization studies. Routine RMMs address most of the safety concerns and are required for every medicinal product. The summary of product characteristics (SmPC), package leaflet (PL) and labeling present a controlled and standardized format for ensuring adequate information for healthcare professional and patients about the medicinal product (e.g. contraindications, warnings and precautions and adverse reactions). A medicinal product is authorized with a specific pack size to control the number of maximum dosage units. The legal status of a medicinal product includes information on whether the product is subject to a medical prescription and may also restrict administration of the medicinal product to specific settings or specialists [49].

Additional risk minimization measures should only be considered when essential for the safe and effective use of the medicinal product [8]. The successful implementation of additional RMMs requires all the stakeholders to contribute. It must be ensured that aRMMs do not introduce any undue burden. When an RMP is updated, the impact and effectiveness of additional RMMs is assessed and it is decided whether a specific risk minimization activity should be retained, modified or removed. A robust, multifocal and integrated evaluation of effectiveness of the different elements of the RMMs is needed to allow regulators to take timely and adequate decisions on RMMs [50]. It is interesting to note that the impact of safety warnings and related risk minimization activities on drug use patterns and drug safety may be different between member states [51,52].

An RMP is a highly technical document that is compiled by the MAH, or the industry which is then assessed by highly trained experts. National regulators have experience with RMP assessment and compilation, review, approval and dissemination of safety information. Over time such experience has allowed the competent authorities in member states to develop a workforce with skills and tools to overcome the challenges associated with RMP and RMM assessment and safety communication at member state level. Skills are acquired through training and from various sources such as attending the meetings of the Pharmacovigilance Risk Assessment Committee. During these meetings the members from different member states acquire information that can be adapted and applied to their needs.

Challenges in relation to RMP assessments we have experienced include submissions of RMPs through inappropriate procedures and having to assess multiple RMPs for the same medicinal product. Procedures such as the decentralized procedure, where the product is to be authorized in multiple member MSs at the same time, tend to result in a number of different RMPs. Despite having the same format, different RMPs compiled by each MAH may contain different information, and some RMPs may be of better quality than others. In order to overcome this challenge, the assessor may choose the best RMP in his or her opinion and ask the other MAHs to follow that format.

RMPs are required to be updated throughout the product's lifetime. From one version to the next, an RMP may thus have several changes. There are two approaches that an assessor can take: (1) choose to assess the whole RMP or (2) only assess the changes that have been made. It is cumbersome and time-consuming to assess the RMP from first principles every time, yet it is very challenging to identify the changes that have been made.

Over the years, we national regulators have learned several lessons related to the RMP assessment and compilation, review, approval and dissemination of safety information. Lessons related to the challenges presented were learnt and summarized in Table 5. These lessons may be of considerable use to other regulatory authorities, the industry, and entities involved in such procedures.

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## Disclaimer

The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organizations with which the author(s) is/are employed/affiliated.

## Declaration of interest

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