# CMDh-Project for Harmonisation of RMPs (HaRP): Aims and results

## Survey analysis of the project for risk management plan (HaRP) harmonisation

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CMDh-Project for Harmonisation of RMPs (HaRP): Aims and results

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*Last but not least, I would like to dedicate this work to my family*.

# Contents

## List of abbreviations

| Abbreviation | Full Text |
|---|---|
| aRMMs | additional Risk Minimisation Measures |
| Ars | Assessment Reports |
| BADI | Bulgarian Association for Drug Information |
| BG | Bulgaria |
| CAP | Centrally Authorised Product |
| CMDh | Co-ordination Group for Mutual Recognition and Decentralised Procedure – Human |
| DCP | Decentralised Procedure |
| Dir | Directive |
| DSUR | Development Safety Update Report |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| eCTD | electronic Common Technical Document |
| EU | European Union |
| GVP | Good Pharmacovigilance Practice |
| HaRP ARs | Harmonisation of RMP Project Assessment Reports |
| HaRP | Harmonisation of RMP Project |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| INR | International Normalised Ratio |
| IR | Implementing Regulation |
| LoSCs | List of Safety Concerns |
| MA | Marketing Authorisation |
| MAA | Marketing Authorisation Application |
| MAH | Marketing Authorisation Holder |
| MRP | Mutual Recognition Procedure |
| MSs | Member States |
| NAPs | Nationally Authorised Products |

| | |
|---|---|
| NCA | National Competent Authority |
| PAES | Post-Authorisation Efficacy Study |
| PAM | Post Authorisation Measures |
| PAR | Public Assessment Report |
| PBRER | Periodic Benefit Risk Evaluation Report |
| PDF | Portable Document Format |
| PhV WSP Working Party | Pharmacovigilance Work Sharing Procedures Working Party |
| PI | Product Information |
| PIL | Patient Information Leaflet |
| PL | Package Leaflet |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PSMF | Pharmacovigilance Safety Master File |
| PSUR | Periodic Safety Update Report |
| PSUSA | Periodic Safety Update Single Assessment |
| PV | Pharmacovigilance |
| QPPV | Qualified Person Pharmacovigilance |
| REG | Regulation |
| rRMM | routine Risk Minimisation Measure |
| RMP | Risk Management Plan |
| RMS | Risk Management System |
| RMS | Reference Member States |
| RND | Research and Development |
| SmPC | Summary of Product Characteristics |
| SOP | Standard Operating Procedure |
| TC | Teleconference |
| XML | extensible markup language |

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# 1. Introduction

## 1.1. Status quo and the goals of this thesis

The drug regulatory field is a multidisciplinary one which apart from its complexity, is constantly growing and improving. It is achieved by updating existing legislation, regulations, and by developing new guidelines toward enhancing the safety, efficacy, quality, and accessibility of medicines, medical devices, and food supplements. Consequently, regulatory experts must constantly and continuously keep track of the changes in the legal framework to be up-to date and be able to advise on the legal and scientific restrictions that apply to products across all the areas in which companies wish to distribute their products, collect, analyse, and evaluate scientific data.

The main objective of this thesis is to identify the challenges and problems associated with the harmonisation of risk management plans. Due to its product-specific nature, it is sometimes difficult to harmonise the plan itself. These difficulties arise from specific constraints, context, historic reasons, and dependencies with former practices and regulations.

The approval of a drug is granted by the respective authorities, if the benefits of using the medicine outweigh the risks. Consequently, for medicine for which the risks are greater than the benefits for its target patents, is neither recommended nor approved for marketing. Evaluating this is a complex and expensive process, which on one hand side needs to ensure a full understanding of the benefits, but also requires to identify/recognise the risk by evaluating the medical indications and by reviewing a large amount of data. Additionally, there is always some uncertainty and assumptions surrounding the potential benefits as well as the risks of medicine because they can only be determined based on the information available at the time of the study. The European Commission grants such authorisations after the European Medicines Agency has conducted a scientific evaluation of the application for centralised authorised medicines or the respective national competent authorities for nationally authorised medicines.

At the moment of an approval decision, not all properties or potential application risks (mid-term and long-term) are fully recorded and properly understood. At that time of market approval, a new drug had only been tested over a certain time and only on a comparatively small number of patients. A certain number of side effects can occur, for example, among elderly patients under certain circumstances if concomitant medications are taken or if they have certain genetic predispositions. It is, therefore, crucial to continue monitoring drug use after approval. The main purpose of the risk management plan is to describe potential risk aspects known and suspected at the time of the approval of the drug and to define strategies as to how these can be countered in a risk-reducing manner. The RMPs are regularly updated in line with the latest scientific findings. The principal aim of an RMP is to detail the risk management system for a medicinal product, which is necessary

to identify important risks, characterize them, and minimize them by means of suitable mitigation measures.

The RMP format was developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, which is defined in the ICH E2E guidelines.[1]

*"The ICH-E2E is intended to facilitate the preparation of pharmacovigilance during the pre-authorisation assessment stage, as well as ensuring a proactive approach is maintained following authorisation. Although the ICH-E2E is not a summary of risk reduction tools to be used, a pharmacovigilance plan may refer to them, since the safety specifications may be based on the risk reduction protocols around prescribing, dispensing, and other health services. Methods for collecting data will also depend on the health care systems and the risk minimisation tools that link them.[2]"*

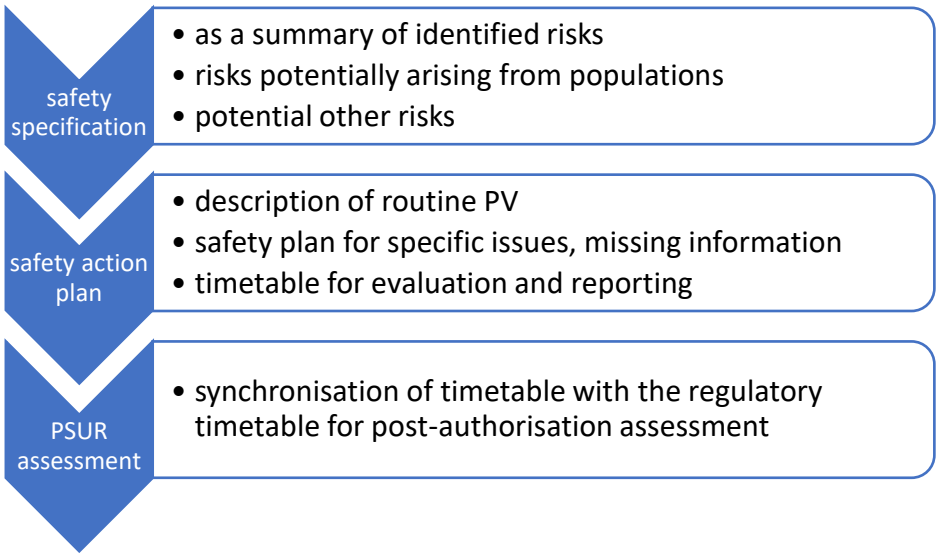


*Figure1: The ICH-E2E guidelines main points:(Own representation based on ICH-E2E)*

The main points of the ICH-E2E guidelines:

- Elements for the safety specification
- The report of routine pharmacovigilance as minimum and inclusion of a safety action plan for specific issues, missing information as needed
- Safety action plan (pharmacovigilance plan), with the description of the rationale for action and timetable for evaluation and reporting milestones
- Possible synchronisation of timetable with the regulatory timetable for post-authorisation assessment, such as PSUR[3] assessment or marketing authorisation renewal assessment
- A general review of methods for data collection to investigate the known or unknown risks and references

[1] Pharmacovigilanz und maintenance von Arzneimittelzulassungen – B. Sickmüller, B. Thurisch, S. Wallik
[2] The pharmacovigilance-related ICH topics - http://www.pharmacy180.com/article/the-pharmacovigilance-related-ich-topics-3050/ Accessed 15.09.2021
[3] PSUR - Periodic Safety Update Report

### 1.2. Structure of thesis

This work starts with an introduction and historical overview of the Risk Management Plan (RMP), its role, building blocks, importance, and objectives. Next, I will perform an overview of the harmonisation process as such:

- Harmonisation with other risk management plans in particular.
- The risk management process to mitigate impact and/or the occurrence of serious adverse reactions in patients taking a drug
- The actively monitoring for the risk evolution and response to managing the risks associated with it.

To obtain a comprehensive picture of the work done currently by the CMDh I have also established contact with the chair of the HaRP group. Where I was provided with an overview of the future plans and challenges ahead of the harmonisation process at the EU level.
Lastly, I will present the outcome of a dedicated survey I performed for the purpose of this thesis among Bulgarian pharmaceutical companies. Notably, elaborate further on the issues, implications, and concerns that hinder the harmonisation process and via the survey pinpoint the problem areas, and identify the future development direction.
It is the objective of the thesis to conduct a study that will evaluate and take into consideration the weaknesses in harmonisation of risk management plans, propose solutions to the problems involved, analyse the current situation, and provide recommendations for future development in line with the process of harmonisation. The survey depicts interesting conclusions, as to the current status quo whereas an analysis of key findings. Moreover, along with some proposed measures a comprehensive assessment of the relationship between the risk management plan process and the national authority's role is elaborated.
It is important not to neglect the risk management plan. The COVID-19 pandemic and the end of the economic expansion have caused many companies to change their priorities from growth and maximizing profits to securing and stabilizing their business in preparation for the "new normal" in covid life in the coming days, weeks, months, and years.[4]
The EMA has issued guidelines on how marketing authorisation applicants for COVID-19 vaccines should prepare their RMPs for COVID-19 vaccines together with Good pharmacovigilance practices after the pandemic outbreak. The guidance examines several

[4] Six business threats in 2020 and how to face them using risk management - https://www.easyproject.com/about-us/project-management-made-easy-blog-tips-resources/1011-6-business-threats-in-2020-and-how-to-face-them-using-risk-management

aspects of the RMP that pertain to COVID-19 vaccine safety monitoring by providing considerations and requirements for each section.[5]

### 1.3. History

Before 2012, the impact of safety concerns on the writing and management of pharmacovigilance documents was fairly low. Nevertheless, a noticeable change was made in 2011 with the introduction of the Development Safety Update Report (DSUR) and the implementation of the GVP modules on the Risk Management Plan (RMP) and the Periodic Safety Update Report (PSUR, also: Periodic Benefit Risk Evaluation Report, PBRER) in 2012. Since 21 July 2012, the risk management plan has been mandated for all new marketing authorisation applications (MAs) regardless of their basis, with the implementation of the *Article 104 Directive 2001/83/EC* of the European Parliament and of the Council dated 6 November 2001 on the Community code for medicinal products. However, some products that were approved prior to July 2012 may not have an approved RMP because the requirement was not mandatory before this date, so there are still some MAs without an RMP for some centrally authorised products.

In 2017 with revision 2 of GVP Module V, an introduction to a new RMP template was made and the definitions for safety concerns were updated. This revision was aimed at decreasing the pending items and commitments to address safety concerns. The revision was targeted to focus on the particular risks that affect the risk-to-benefit balance of the products and would require further evaluation as part of the PV plan or as additional measures for mitigating the risk. The use of the revised RMP format became mandatory for all RMP submissions. The guidance on the format was updated in November 2018.
These products without an RMP may be required to submit an RMP when certain situations arise, such as new safety concerns, or significant changes to the MA. There may need to be submitted a new RMP at any point during a product's lifecycle, or an update of the RMP if needed. The period of time between the research and development stage and between its launch and the loss of the exclusivity (for instance, the patent expiry date) and the period following the loss of exclusivity when generic drugs can appear[6].

Updates to RMPs that relate to a regulatory application should be included with that application if they are consequential to the data provided. The RMP must be submitted as a stand-alone variation if it needs to be updated outside of any regulatory process.

[5] EMA - https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management/risk-management-plans#risk-management-plans-for-covid-19-vaccines-section

[6] European Medicines Agency post-authorisation procedural advice for users of the centralised procedure - https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf

The Agency may request a stand-alone variation for updates of the RMP if any of the following situations occur:

- Following the PSUR procedure or signal procedure. Unless the Periodic Safety Update Single Assessment (PSUSA) procedure covers only CAPs that are part of the same global MA (e.g., duplicate MAs), RMP updates cannot be accepted together with PSURs (centrally and/or nationally authorised medicines) subject to PSUR European single assessment (PSUSA). The MAHs should update their RMP as part of another upcoming process affecting RMPs or through a separate variation submitted after PSUSA has been finalized.
- A modification of the safety specifications may be necessary if changes to the safety concerns occur outside of another procedure; for instance, if interim results from a study assessed as a post-authorisation measure (PAM) result in adding, deleting or reclassifying safety issues.
- When proposing changes to previously agreed category 3 studies in RMP Part III.4.3. As a result, MAHs who provide updated or amended protocols for assessment will also have to submit a PAM procedure, as it may impact the description of the study in Part III.4.3.[7]

## 2. The risk management plan's importance and role

Through active monitoring and management of risks, risk management plans aim to reduce the likelihood that serious safety concerns will occur among patients taking the drug. The RMP has three primary objectives:

- Find out what is known and what is not known about the safety of a drug
- Define how information related to safety can be expanded during the post-approval period on a plan with defined milestones
- To define measures to minimize already known risks related to the use of the drug and to monitor effectiveness of these measures as needed[8]


*Figure 2: Goals of RMPs (own representation based on [2], [6] and [7])*

[7] Risk management plans (RMP) in post-authorisation phase: questions and answers https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/risk-management-plans-rmp-post-authorisation-phase-questions-answers

[8] Translated from Pharmacovigilanz und maintenance von Arzneimittelzulassungen – B. Sickmüller, B. Thurisch, S. Wallik 2. 2020, Editio Cantor Verlag Einführung p.97

According to the Directive 2001/83/EC of the European parliament and of the council on the Community code relating to medicinal products for human use, Current consolidation dated version 26.05.2021:

"*Article 8*

*1. In order to obtain an authorisation to place a medicinal product on the market regardless of the procedure established by Regulation (EEC) No 2309/93, an application shall be made to the competent authority of the Member State concerned."*

It is mandatory that the application is accompanied by specific details and documents, including the risk management plan (*28c, Dir. 2001/83/EC*) that is submitted according to Annex I. The risk management plan with its detailed measures for further monitoring and risk minimization will become part of the approval.

The Risk Management Plan (RMP) is a crucial tool to ensure the safe use of a medicinal product and outlines the medical risks associated with and details the activities and actions it takes to identify, characterize, prevent, or mitigate them.[9]

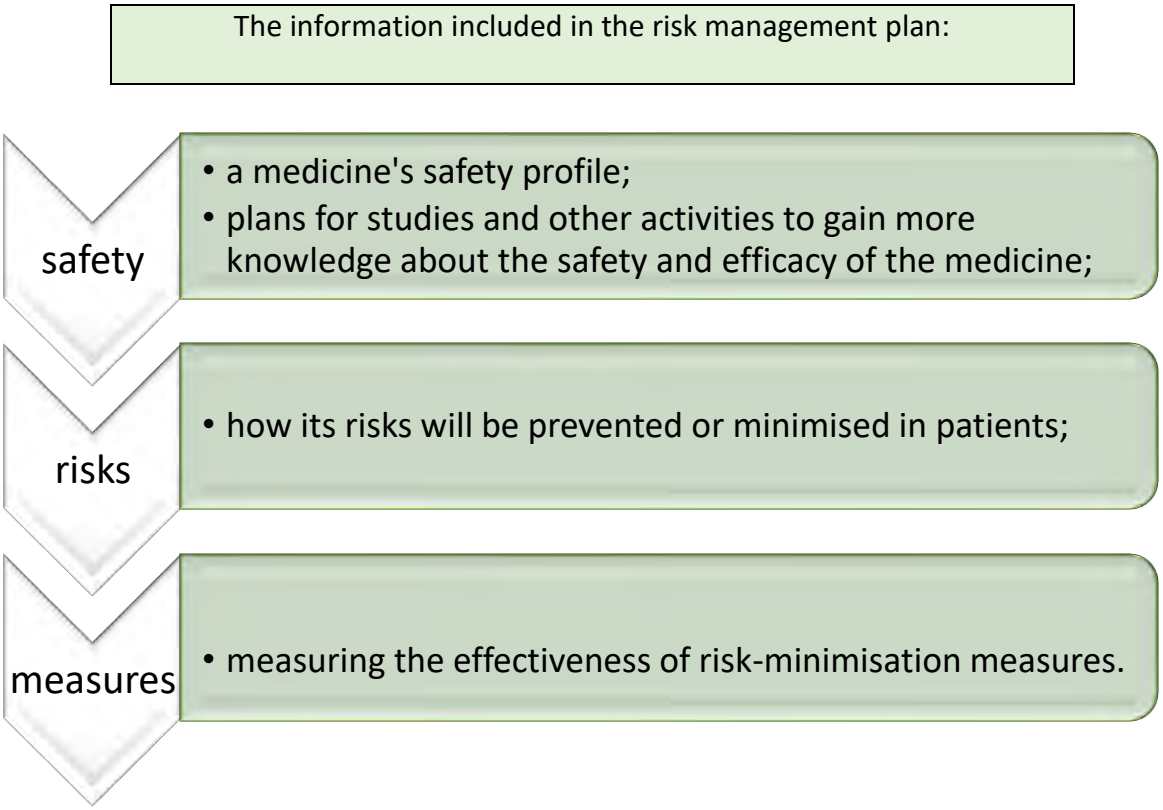


*Figure 3: EMA - Risk management plans - What should it contain (own representation based on [2], [7])*

[9] Directive 2001/83/EC of the European parliament and of the council of 6 November 2001 on the Community code relating to medicinal products for human use - EUR-Lex - 02001L0083-20121116 - EN - EUR-Lex (europa.eu) p.14

In the event of a change in the list of safety concerns or any other significant change to the existing additional pharmacovigilance or additional risk minimization activities, an RMP update is expected to be performed. Such update can be submitted at any time, ad-hoc, when there is a notable change in the safety concerns.

In addition to the circumstances when the RMPs need to be reviewed, a change in the population, study objectives, due date of final results, protocol submission for an imposed study, or addition of a new safety concern to the educational materials may also trigger such actions.

The Guideline for good pharmacovigilance practices (GVP) Module V - Risk management systems define this trigger the following way:

"*The significant changes of existing additional pharmacovigilance and risk minimisation activities may require them to be removed from the RMP. The RMP may also need to be updated when results or issues in the procedure result in changes in routine pharmacovigilance activities beyond reporting adverse reactions and detecting signals, or mandate risk minimisation activities recommending specific clinical measures to reduce the risk. In the Special warnings and precautions for use subsection 4.4 of the SmPC (routine risk minimisation activity), for example, a RMP update might be required when plans for annual enhanced safety surveillance (routine pharmacovigilance activity) are significantly changed."*

A RMP is routinely updated and changed throughout the lifecycle of the medicine as new data becomes available. It is important that the holder of the marketing authorisation submits an updated new RMP.

- This is required by the NCA or EMA, depending on which authorisation procedure it falls under.
- When the RMS is updated, especially when it is prompted by new information that may lead to a significant change in the benefit-risk profile or to the achievement of an important risk-minimization or pharmacovigilance milestone.

It is also possible for EMA or NCA (the competent authority) to specify the date of the next RMP as a condition of granting a marketing authorisation in exceptional cases and whenever risk justifies that requirement.

The following diagram demonstrates the importance which risk management plays, within the critical path of the authorisation.

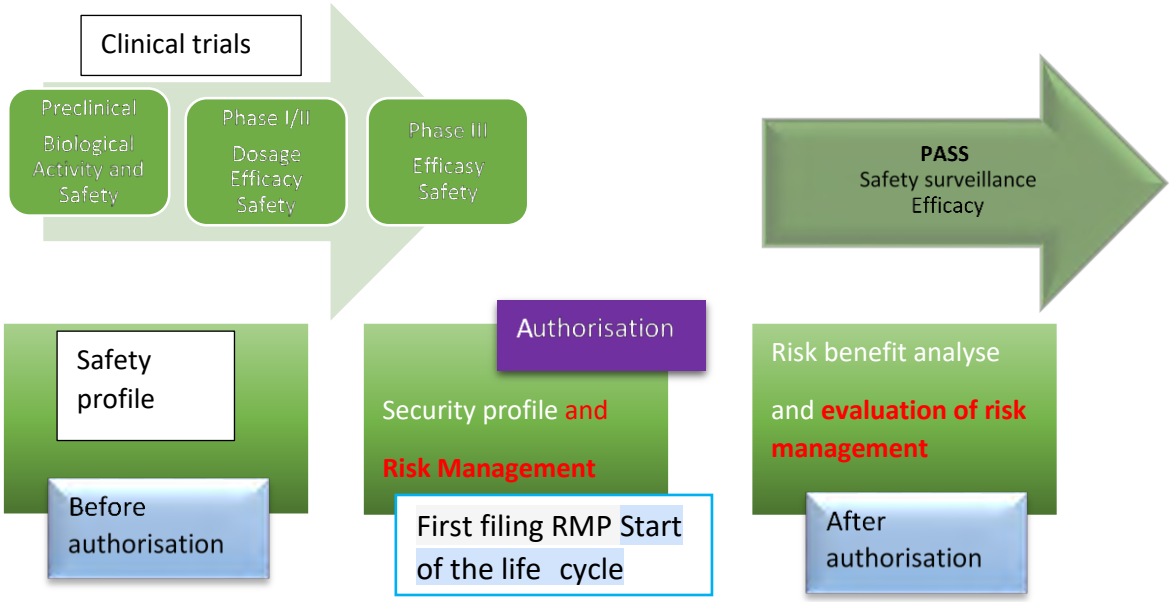


Figure 4: Throughout the life cycle of a drug, the importance of risk management
*(Aktuelles zum RMP, Dr. Walburga Lütkehermölle, MBA Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM, p.6)*[10]

To conclude the main objective of the Risk Management plan is:

- Assuring that the benefits from the use of the substance outweigh the risks
- Grant authorisation by limiting the maximum risk that can be accepted
- The RMPs is reflecting and mitigating on those risks relevant to the risk management activities for an authorised medicinal product
- Continuous risk management, rather than one time effort - the management of risk does not end with the authorisation. The RMP is in fact a dynamic document which requires constant and continuous updates during the life cycle of the drug to reflect on "safety concerns". Upon approval, other RMMs are constantly modified as needed.

[10]Aktuelles zum RMP, Dr. Walburga Lütkehermölle, MBA Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM- https://www.bfarm.de/SharedDocs/Downloads/DE/Service/Termine-und-Veranstaltungen/dialogveranstaltungen/dialog_2019/191108/12-L%C3%BCtkeherm%C3%B6lle.pdf?__blob=publicationFile&v=3 p. 6

# 3. What should RMP address?

The RMP should address:

## 3.1. Identified risks

These are the risks which were recognised and deemed relevant for the medicinal product. Those risks that are associated with the medicinal product, which adverse clinical outcomes have been linked to it, and for which there is enough scientific evidence that they are caused by its use.

A variety of sources, including nonclinical findings followed by clinical data, clinical trials, epidemiological studies, spontaneous reports, and published literature, can identify the risks of adverse effects. Generally, adverse reactions exceeding the placebo comparator in a well-designed randomised clinical trial are considered an identified risk as long as the clinical outcome criteria meet also; Identifying the risk is sometimes associated with measuring the clinical outcome of the adverse reaction (e.g., with laboratory abnormalities). This can result in bleeding due to abnormal International Normalised Ratio (INR) ranges/thrombocytopenia, infection due to neutropenia, and hypotension/ lipothrombosis or renal failure caused by adverse reactions such as dehydration from vomiting or diarrhoea., or Arrhythmia caused by prolonged QTc or Torsade de Pointes because of coronary vasospasm. The risk may be associated with situations such as off-label usage, improper use of medications or drug interactions. In all therapeutic contexts, not all reported adverse reactions are relevant to the risks associated with a given product.

**Important identified risks** – it is a list of risks identified that are expected to affect the risk-benefit balance of the product.

In the Risk Management Plan, the company should focus on important identified risks that may impact the product's balance between risk and benefit.

When a risk is considered to be important, it would usually be accompanied by the following strategies:

- Additional assessment in the context of the pharmacovigilance plan (e.g., the frequency, severity, seriousness, and outcome of such adverse events for these populations under normal conditions of use);
- Activities for reducing risk: product information advising exactly what clinical activities are necessary to minimize risk, or other risk reduction techniques.

### 3.2. Potential risks

The Potential risks are risks which at the time of the assessment cannot be clearly determined or quantified. This can be due to insufficient data or none-conclusive outcomes of tests instances (e.g. with no clear indication of manifestation within the analysed population of the data for the medicinal product). In particular for *medicinal product risks concerning undesirable clinical outcomes and for which there is scientific evidence of the possibility of a causal relationship between this medicine and this outcome, however insufficient evidence currently exists to determine causality.*[11]

It may include signals where there is more than a theoretical basis for the supposition the results of which do not seem to be definitive (i.e., are not disputed nor refuted nor confirmed). In clinical trials and epidemiological studies, there is little evidence to support a causal relationship (for instance, the low number of events or unexpected incidence rates in clinical trials and epidemiological studies). If unwanted clinical outcomes are detected in these studies, no evidence for a causal relationship is available.

**Important potential risks** are those, when they are characterised and if declared, would have an impact on the risk-benefit balance of the medicinal product.

The information should also include an investigation of the frequency, severity, seriousness and outcome of these risks under normal conditions of use, the groups who are at the greatest risk, as well as any recommendations on clinical instructions to reduce the risk or to further reduce it through risk minimization activities.

In general, important potential risks identified in the RMP require further evaluation as part of the pharmacovigilance plan.

### 3.3. Missing information

Considering the target population of the trial and the relevant assumption, we need also to account for potential risks that could be hidden in missing information (e.g., the representative sample). They can be pertinent to risk management planning as to knowledge about the safety of certain anticipated uses such as long-term use or for use with certain specific patient populations for which there is insufficient information to determine whether the safety profile differs from prior user experiences.[9]

There shall be gaps in information necessary to implement risk management planning for a medicinal product when certain anticipated therapeutic uses (e.g. long-term use) or special patient populations have not yet been characterized, despite considerable evidence

[11] Guideline on good pharmacovigilance practices (GVP) – Module V (Rev 2), 28 March 2017, EMA/838713/2011 Rev 2* - https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf access 13.08.2021 online version

that safety profiles differ from those described so far. A population being excluded from clinical studies (e.g., lacking data) does not automatically imply safety concerns. In contrast, risk management planning should focus on addressing situations that differ from the known safety profile. RMP needs to include that population as missing information based on scientific justification.

## 4. Legal basis / guidelines

The documents listed below underline the legal basis for the Risk Management Plan and Harmonisation of RMPs.:

- Dir 2001/83/EC [5] article 1, article 8(3)(iaa), article 22c, article 104 (3) & (e), article 104a, article 106 (c), article 107j (3), article 107k, AMG [10] paragraph 4 (36) & (37), paragraph 62 and paragraph 63b
- Reg 726/2004 [6] article 6(1), article 9(4)(c), (ca), (cb), (cc), article 10a(1), article 14a, article 15, article 21, article 26 and article 28a and IR 520/2010 [7] chapter V and Annex I.
- GVP Module V [17] addresses this topic and provides clear instructions on how to handle this process
- GVP V and RMP Template Rev2 in March 2017
- Guidance on the format of the risk management plan (RMP) in the EU – in an integrated format
- RMP template since 10/2013 RMP for all new authorisation applications [Dir. 2001 83 Art
- Regulation (EU) No 1235/2010 of the European parliament and of the council of 15 December 2010
- Commission implementing regulation (IR) (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council.
- Regulation (EC) No 1901/2006 Article 34(2)
- Regulation (EC) No 1394/2007 Article 14(2)
- Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- GVP Module XVI and GVP Module XVI Addendum I in conjunction with educational materials.
- Europe – Annex 2: HaRP (Harmonisation of RMP Project) – methodology of harmonising RMPs, April 2021 CMDh/402/2019, Rev. 1

## 5. Structure of RMPs

GVP, Module V provides a basic structure for an RMP. Each chapter and revision are developed by a team of experts from the European Administration and the EU Member States. An RMP template can be downloaded from the EMA website, either the full version or the abbreviated version for generic products or products imported in parallel with an RMP.

In principle, the currently available templates from the EMA are more user-friendly than in the first edition, as explanations and examples of what is required can be found in the individual chapters.

As already flagged, throughout the life cycle of the product(s), the RMP should be updated based on the defined triggers. This can include adding safety concerns whenever necessary, but it can also involve removing or reclassifying safety concerns as the safety profile is further characterised. As part of monitoring pharmacovigilance data, the marketing authorisation holder should identify any changes to the risk-benefit balance of medicinal products *[Dir Art 104(3)(e)]* and update the risk management system and the Responsible Management Program accordingly. Critical evaluation of the product's safety profile takes place continuously and is documented in periodic safety update reports (PSURs) (see GVP Module VII), for products where an RMP may or may not be required.

The following two specific milestones should also be taken into account by the marketing authorisation holders of products approved after full initial marketing authorisation applications when reviewing the list of safety concerns and their plans and ongoing pharmacovigilance and risk minimisation activities: within the process of renewal of the five-year period when the first provisional statement of use will be due after the renewal of the first five-year period. A PSUR submission is expected to occur about eight to nine years after a marketing authorisation is granted, at the exact time when the initial applications for generic products containing the active substance will be assessed. As a result, the product's safety profile will be sufficiently well characterised to allow its listing of safety concerns to be updated and reviewed critically.

It may be possible to reduce the list of safety concerns contained in the RMP during the life cycle of the product by following the guidance on risk classification. It can be done in the following situations:

- The safety profile may be removed from some products where important identified risks have been characterized and appropriately managed. In case of products marketed for a long period of time with no additional pharmacovigilance activities and/or risk minimisation activities that have been integrated fully into standard clinical practice, such as participation in treatment protocols or clinical guidelines).

- The safety specification in the RMP may have to be rewritten to remove important potential risks (e.g. in cases where scientific and clinical data do not support the original hypothesis, the impact on the individual is less than expected, resulting in less concern about the risk, or the risk cannot be further characterised by pharmacovigilance), or to redefine as an "important identified risk" (e.g., if strong scientific and clinical data are consistent with a risk-product relationship).
- The pre-authorisation phase is aimed at gathering information regarding the risk-benefit balance in certain excluded populations. It is expected that this classification may become incorrect as the product matures, when new data become available, or if the pharmacovigilance activities currently conducted or proposed in the future would not adequately elucidate the risks associated with the product in the areas that are lacking in information.

It is expected that over time, except for a few patient registries, most of the additional pharmacovigilance activities will be completed and subsequently removed from the RMP. Further risk minimisation activities may no longer be necessary if the recommendations for specific clinical measures to address risks are included in standard treatment protocols in the EU or if risk minimisation evaluations conclude that more effective approaches will need to be adopted. For programs like pregnancy prevention, it could be necessary to maintain some risk minimization activities for the duration of the life of the product.

### 5.1. Structure, format, and content of RMP

The RMP also contains an overview of studies currently being conducted or planned, as well as patient exposure data provided by the PV department (indirect, as prepared by the medical department).

The RMP consists of seven parts (from Part I to Part VII). Following the RMP template [IR Annex I] is required. Part II of the RMP - Safety specification is subdivided into modules [IR Annex I], so the content can be tailored to the specifics of the medicinal product. RMP part II modules generally follow the section titles in the ICH-E2E safety specification (see GVP Annex IV).

By implementing a modular design, the RMP is made more easily updatable, and in certain circumstances content requirements may be reduced. However, the RMP document is expected to be submitted as a single document that includes all modules and annexes, as applicable.

| RMP parts and modules | |
|---|---|
| **Part I** | Product(s) overview |
| **Part II** | Safety specification |
| **Module SI** | Epidemiology of the indication(s) and target population (s) |
| **Module SII** | Non-clinical part of the safety specification |
| **Module SIII** | Clinical trial exposure |
| **Module SIV** | Populations not studied in clinical trials |
| **Module SV** | Post-authorisation experience |
| **Module SVI** | Additional EU requirements for the safety specification |
| **Module SVII** | Identified and potential risks |
| **Module SVIII** | Summary of the safety concerns |
| **Part III** | Pharmacovigilance plan (including post-authorisation safety studies) |
| **Part IV** | Plans for post-authorisation efficacy studies |
| **Part V** | Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) |
| **Part VI** | Summary of the risk management plan |
| **Part VII** | Annexes |

*Table 1: RMP parts and modules overview (GVP Module V – Risk management systems (Rev 2)) [9].*

The relevant RMP documents should include all relevant medicinal products that contain the same active substance(s) from the same applicant/market authorisation holder. This is an active substance-based document) [IR Art 30(2)].

RMP documents should avoid unnecessary and duplicated text, which can be confusing and inaccurate. A sufficient amount of detail should be included.

Whenever possible, the information in the RMP should provide an integrated overview/discussion that highlights the most significant risks, which have been identified or are anticipated based on the pre-clinical, clinical, and post-marketing data presented in other modules of the eCTD. There should be consistency in any data included in the RMP with the other sections of the dossier. Embedding links and references to the relevant sections of the nonclinical and clinical overviews and summaries should be added to the RMP. In the case of new RMP submissions for products with limited safety data in the dossier, the RMP may contain relevant safety data and discussion, which will assist the discussion on risk identification.

### 5.2. RMP part I “Product(s) overview”

A comprehensive overview of information on the RMP. The information should be current and accurate with respect to the ongoing application, as it will appear in the marketing authorisation.

### 5.3. RMP part II “Safety specification”

It consists of a summary of the important identified risk of a medicinal product, important potential risks, and missing information, with a focus on those that need further risk

management activities. The cornerstone of a pharmacovigilance plan and a risk minimisation plan is the safety specification.

As part of the post-authorisation process, it should also address the populations susceptible to risk (for both authorised and off-label use), along with any outstanding safety concerns that warrant further investigation to refine the understanding of the risk-benefit balance.

**The considerations that apply to generic products and advanced therapy medicines:**

**Generics**

It is believed that the safety specification for generic medicinal products is the same as that for the reference product or for other generic products for which an RMP is in place.

According to the GVP Module V:

"*The submitting company must propose and justify the most appropriate safety specifications for their product if there are discrepancies between the approved RMPs for such products. The applicant may if this is justified, add, or remove safety concerns compared to the reference product's safety profile for a new generic medicinal product.*

*(For example, when new information is available regarding the current safety profile or when different characteristics exist between the product and the reference product, e.g., there is a risk associated with an excipient only evident in some products with the same active ingredient)."*

**Advanced therapy medicinal products**

Advanced therapy medicinal products (ATMs) are medicines for human use that are based on genes, tissues, or cells. These new treatments open new opportunities for treating diseases and injuries. In Europe, regulation (EC) No 1394/2007 applies to these products. This structure makes these products susceptible to risks that are not normally encountered with other medicinal products, such as germ line transformation, risks to living donors, or vector transmission. Developing ATMP safety specifications should take these risks into account. (Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products).

**Part II of the Risk Management Plan consists of eight modules that are:**

- **Module SI "Epidemiology of the indication(s) and target population(s)" -** In it, incidence and prevalence should be included, as well as outcome of the target disease (indication) as well as relevant co-morbidities, as adequate for assessing safety and risk management.

- **Module SII "Non-clinical part of the safety specification" –** A brief discussion of possible non-clinical studies should be given here if they are deemed necessary and considered for inclusion in the pharmacovigilance plan because of the assessment of non-clinical or clinical data.
- **Module SIII "Clinical trial exposure" -** As part of this RMP module, in order to assess the limitations of the human safety database, a summary report will be prepared. It should provide information on the patients studied in clinical trials in a format appropriate to their study at the time of the submission of the initial RMP or when there are major updates as a result of new information gathered from clinical studies (for example in a new indication). The relevance of this section should be assessed over time, and, if there have not been any significant changes to exposure data from recent clinical trials, this section does not need to be updated.
- **Module SIV "Populations not studied in clinical trials" -** Describe the groups considered to be lacking information in this RMP module. When available and appropriate, specific information should also be provided concerning special populations with lower exposure, or no exposure (e.g. pregnant women, breast-feeding mothers, renal impairment patients, hepatic impairment patients, immune-compromised patients, and populations of different ethnic origins).
- **Module SV "Post-authorisation experience"-** If there are already authorised products that contain the same active ingredient and the post-marketing data are available from post-authorisation experience in other regions outside the EU, the data should be discussed in this module.
- **Module SVI "Additional EU requirements for the safety specification"-** Furthermore, the EU-RMP should cover the following topics in addition to the safety topics required by ICH-E2E: the potential for misuse for illegal purposes, and measures to reduce risks, such as restricted pack sizes, controlled access programs, or special prescriptions.
- **Module SVII "Identified and potential risks" -** An important goal of the RMP module consists of providing a discussion of the identified and important potential risks, along with missing information (i.e., safety concerns).
- **Module SVII sections "Risk considered important for inclusion in the list of safety concerns" and "Risk not considered important for inclusion in the list of safety concerns"-** Risk seriousness, risk frequency, risk-benefit impact of risks must be summarized and discussed in the risk management plan section. Risks that are not taken forward as safety concerns can be grouped according to the reasons for not including them.

- **Module SVII section "New safety concerns and reclassification with a submission of an updated RMP"-** New identified risks of a product are expected to be presented in the safety section of the dossier (with e.g., signals evaluation, periodic benefit-risk analysis, and safety variation assessments) together with information regarding whether the risks should be considered important and explained using the safety specification in the RMP.

A justification should be provided in this section of the RMP whenever an important identified or potential risk or missing information is re-classified or removed, along with appropriate references to the safety data. Here a statement may be included describing prior regulatory requests, as well as a reference to the process where the request came about.

- **Module SVII section "Details of important identified risks, important potential risks, and missing information" -** If an RMP contains multiple products, if there are substantial differences among them (e.g., fixed dose combinations), it is important to state which safety concerns relate to each one.

- **Module SVIII "Summary of the safety concerns"-** Upon completion of the RMP module, the following safety concerns should be listed: important identified risks, important potential risks, and missing information.

### 5.4. RMP part III Pharmacovigilance plan (incl. post-authorisation safety studies)

It is essential that the pharmacovigilance plan focuses on the safety concerns summarized in RMP module SVIII of the safety specifications and adheres to a proportionate balance between benefits and risks. In part III of the RMP, the applicant/authorisation holder discusses how they plan to further characterise the safety concerns raised in the safety specification through the pharmacovigilance plan. Incorporates a structured plan for determining whether an identified risk or potential risk has been confirmed; Identifying and characterizing the severity, frequency, and risk factors of safety concerns; determining where missing information can be found; identifying the extent to which risk mitigation measures are working. Actions aimed at reducing, preventing, or mitigating risk are discussed in RMP part V.

- **Section "Routine pharmacovigilance activities" -** For all medicinal products, routine pharmacovigilance is an essential set of activities as outlined in DIR and REG. As part of routine pharmacovigilance, signal detection is vital for the identification of new risks associated with the product.
- **Section "Additional pharmacovigilance activities" -** An additional pharmacovigilance activity is only required when there is any doubt about the need for it. Consultation with the competent authority is advised in such cases. Non-

clinical studies, clinical trials, or non-interventional studies may be conducted as additional pharmacovigilance activities that are not considered routine. Patients from clinical trial populations may be followed for a long time or a cohort study is performed to characterise the long-term safety of the medicinal product.

- **Section "Summary table of additional pharmacovigilance activities" -** In this section of the RMP, pharmacovigilance activities are outlined in order to identify and characterize risks associated with the use of a medicinal product.

### 5.5. RMP part IV "Plans for post-authorisation efficacy studies"

Post-authorisation efficacy studies (PAES) should be included in this RMP part when they are imposed as conditions for the marketing authorisation or when they are included as specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional conditions. RMP Part IV can be left empty if these studies are not required.

### 5.6. RMP part V "Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)"

Risk minimisation measures should be outlined in Part V of the RMP to enable the risks associated with safety concerns to be reduced. In order for continuing risk minimisation measures to be effective, the effectiveness of these measures needs to be evaluated on a regular basis.

Every medicinal product is subject to **routine risk minimisation activities**. They include the summary of product characteristics, the package leaflet, the package size(s), the labelling on the outer and inner cartons, and the legal status of the product. If necessary for the safe and effective use of a medicinal product, **additional risk minimization activities** should be suggested. They should be explained and justified to support their necessity. This type of measure should be reviewed periodically to determine whether it is necessary to continue. In cases where the need for additional risk minimisation varies across Member States for non-centrally approved medicinal products, the RMP can indicate that this need is agreed at the national level. In the risk minimisation plan, additional risk minimisation activities must be discussed when the Risk Management Plan is updated. Where appropriate, such information should be presented by region within the European Union.

Alternative activities need to be evaluated and undertaken, when implementing a risk minimisation strategy or mitigation actions are not feasible and the method proves ineffective for group of patients. Furthermore, this needs to be considered in cases where the healthcare system as a whole is overburdened excessive or undue degree to accommodate such measures. During the marketing authorisation process, the marketing authorisation holder should comment whether additional or different risk

minimisation activities are necessary for each safety concern, or whether (additional) risk minimisation measures may be removed (for example when risk minimisation measures already form part of standard clinical practice). When a study is required or imposed by a competent authority, it should be included in part III of the RMP, which describes the pharmacovigilance plan.

- **Section "Risk minimisation plan" -** In this section part V of the RMP "Risk minimisation plan" the safety specification should address each of the following safety concerns: routine risk minimisation activities, including details of whether only inclusion in the SmPC and PL is envisaged, or if other routine risk minimisation activities are proposed (if any), with individual objectives and justifications of why needed, and how their effectiveness is evaluated, should be reported.
- **Section "Summary of risk minimisation measures" –** The EMA Guideline on the Format of the Risk Management Plan outlines how additional pharmacovigilance activities should be included. Within this section, a list should be provided of the routine and additional risk minimisation activities by safety concern. (For example, the SmPC section number in which the risk is specified, or the list of educational materials).

### 5.7. RMP part VI "Summary of the risk management plan"

Regardless of whether a medicinal product is centrally or nationally authorised in the EU, part VI of the RMP must be submitted by the marketing authorisation applicant/holder. For each authorised medicinal product, a summary of the RMP shall be made available to the public and shall include the key points of the plan [REG Art 26(1)(c), DIR Art 106(c), IR Art 31(1)]. In accordance with the information contained in part VI of the RMP, the EMA should post the RMP summary on the EMA website together with the other documents the EPAR of the medicinal product, when a decision is made by the European Commission. The national competent authorities should make the RMP summary publicly available on their websites for nationally authorised medicinal products.

When there are important updates to the RMP, the summary should be updated as well. Such an important update can be a change to a safety measure or routine risk minimisation activity if it relates to a new or additional risk identified or potential or if it is altered or removed from a safety concern, specific clinical measures to address the risk, major changes to the pharmacovigilance plan (e.g., addition of new studies or completion of current studies).

RMP part VI should be in alignment with the information presented in RMP part II module SVII and SVIII as well as RMP parts III, IV and V. There should be information regarding the medicinal product and what it is authorised for, a summary of safety concerns and missing

information, risk minimization measures both routine and additional, and pharmacovigilance activities.

### 5.8. RMP part VII "Annexes to the risk management plan"

The RMP should contain the following annexes (if applicable). The annexes, usually, are applicable to all medicinal products if the RMP pertains to more than one medical product.

- **Annex 1 RMP -** A structured electronic representation of the EU risk management plan is found in Annex 1 of the RMP. In response to the Coronavirus outbreak (COVID-19), companies no longer have to submit the RMP to EMA in structured electronic format (EU-RMP Annex 1) since EMA has suspended its maintenance of the database for these files[12].

- **Annex 2 RMP -** Tabulated summary of planned, on-going, and completed pharmacovigilance study programme. As part of this annex, a table should be included summarizing the studies involved in the pharmacovigilance plan, respectively study plans and results, including objectives, safety concerns addressed, and the submission deadline for final results and submitting complete studies, including objectives, safety concerns addressed, and the date of submission to the competent authority (effective, planned, or the reason for not submitting).

- **Annex 3 RMP: Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan**

  Instead of the full protocol of study documents, this annex should include electronic links or references to another module of the eCTD dossier where the protocols are included.

- **Annex 4 RMP: Specific adverse event follow-up forms**

  A follow-up form may be included in this annex by the marketing authority holder to collect additional data on specific safety concerns. Detailed pharmacovigilance activities should be detailed in the pharmacovigilance plan in the RMP for follow-up forms included in this annex**.**

- **Annex 5 RMP: Protocols for proposed and on-going studies in RMP**

  This annex should provide links to other parts of the eCTD dossier, with protocols for studies included in Part IV of the RMP, where protocols for imposed efficacy studies are already included.

[12] Risk management - https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management Access 07.11.2021

- **Annex 6 RMP: Details of proposed additional risk minimisation activities**

  In case it applies, this annex should include key messages of additional risk minimisation activities that are proposed drafts (and, if necessary, approved).

- **Annex 7 RMP: Other supporting data (including referenced material)**

  For the purpose of avoiding duplication of reference materials in the annex, eCTD links or references to other documents should be provided when appropriate.

- **Annex 8 RMP: "Summary of changes to the risk management plan over time**

  This annex should provide a chronological list of all meaningful changes made to the RMP. An explanation of the changes should be included, as well as the date and version number of the revised RMPs.

  When safety concerns were added, removed, or reclassified, specific clinical measures or additional risk minimisation activities may be recommended as part of the risk minimisation plan. Early consultations between marketing authority holders/applicants and regulatory authorities are essential for identifying whether and which additional pharmacovigilance activities are needed. Milestones should then be agreed upon.

The following table provides a summary of the minimum requirements for initial marketing authorisation applications (Guideline on good pharmacovigilance practices (GVP).

| Product | Part I | Part II | | | | | | | | Part III | Part IV | Part V | Part VI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | SI | SII | SIII | SIV | SV | SVI | SVII | SVIII | | | | |
| 0. Full MA application | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| 1. Generic product | √ | | | | | | | ‡ | √ | √ | * | ∫ | √ |
| 2. Informed consent product | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| 3. Hybrid product | √ | † | | † | | | | † | √ | √ | √ | ∫ | √ |
| 4.a. Fixed combination product – new active substance | √ | ∓ | ∓ | ∓ | ∓ | ∓ | ∓ | √ | √ | √ | √ | √ | √ |
| 4.b. Fixed combination product – no new active substance | √ | | † | † | | | | ‡ | √ | √ | * | ∫ | √ |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **5. Well established medicinal use product** | √ | | | | | | | √ | √ | √ | √ | √ | √ |
| **6. Biosimilar product** | √ | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |

√ - relevant/applicable
‡ - relevant only if "originator" product does not have an RMP and its safety profile is not published on CMDh website
* - relevant only when PAES was imposed for the "originator" product
∫ - statement of alignment of safety information in PI is sufficient
† - requirements based on risk proportionality principle, addressing new data generated or differences with the "originator" product
∓ - focus on the new active substance

***Table 2*** *Summary of the minimum RMP requirements for initial marketing authorisation applications (Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) p. 30).*

An RMP or update will require that a notice of change (variation) be submitted, since it is part of the approval process. This also means that RMPs are approval specific. It is possible for RMPs to differ, for example, if approvals have been granted for different indications or dosage forms of the same active ingredient. The RMP submitted with the approval documents contain data and facts on the benefit-risk profile of a drug on the basis of the individual - and not harmonised - studies carried out by the individual holders or applicants for a drug approval to prove efficacy and safety. If a drug has several strengths of the same or similar dosage form, one RMP is usually enough to submit, possibly with a corresponding differentiation of significant risks. It is recommended that applicants for generic approvals adhere as closely as possible to the RMP of the original approval. In some situations, safety concerns can be attributed to the dosage form and maybe also to auxiliary ingredients. The RMP should be submitted as a standalone variation.

In accordance with GVP module V, a RMP must be submitted as PDF files in the electronic Common Technical Document (eCTD) format when it relates to centrally approved drugs (e.g., initial marketing authorisation applications and major variations). Following a Commission decision, the authorisation holders will submit XML versions of RMP Annex 1 within a certain time frame. Information on the RMP is presented in a structured electronic format at Annex 1 of the RMP. Once validated by the EMA, the RMP is uploaded to a database that can be accessed and searched by the EMA as well as the national competent authorities. In each Member State, the process of authorising a medicinal product is different, so it is crucial to comply with national requirements.

| RMP | eCTD |
|---|---|
| Part 1 Product(s) overview | Module 2.3 Quality overall summary<br>Module 3 Quality |
| Module SI Epidemiology of the indication(s) and target population(s) | Module 2.5 Clinical overview |
| Module SII Non-clinical part of the safety specification | Module 2.4 Non-clinical overview<br>Module 2.6 Non-clinical written and tabulated summaries<br>Module 4 Non-clinical study reports |
| Module SIII Clinical trial exposure | Module 2.7 Clinical summary<br>Module 5 Clinical Study reports |

| | |
|---|---|
| Module SIV Populations not studied in clinical trials | Module 2.5 Clinical overview |
| Module SV Post-authorisation experience | Module 2.5 Clinical overview |
| Module SVI "Additional EU requirements for the safety specification" | Data not presented elsewhere in eCTD |
| Module SVII Identified and potential risks | Module 2.5 Clinical overview (including benefit-risk conclusion)<br>Module 2.7 Clinical summary (SPC) |
| Module SVIII Summary of the safety concerns | Module 2.5 Clinical overview<br>Module 2.7 Clinical summary |
| Part III Pharmacovigilance plan (including post-authorisation safety studies) | Module 2.5 Clinical overview<br>Module 2.7 Clinical summary |
| Part IV Plans for post-authorisation efficacy studies | Module 2.5 Clinical overview<br>Module 2.7 Clinical summary |
| Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) | Module 2.5 Clinical overview<br>Module 2.7 Clinical summary |

*Table 3: The mapping of RMP modules to eCTD information [9]*

A RMP may be required for products that do not have one (for example, if significant changes are made to the MA or if there are new safety concerns) and / or when an extension of the approval is requested after 5 years, through the appropriate post-authorisation procedure. The changes in final results, population, or objectives of the study, or the emergence of a new safety concern should all be reflected in the RMP - an updated RMP with appropriate steps.

Each RMP update should be accompanied by an RMP in track change format, which enables the evaluating official body to identify the changes quickly and easily since the last version and compare them with the currently approved version.

### 5.9 Pharmacovigilance Risk Assessment Committee evaluation in the EU

Within the EU, the Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for regulatory oversight of centrally authorised drugs. In assessing a RMP, if necessary, the EMA may consult with health professionals or patients to obtain information about proposed risk mitigation measures.

It is the national competent authorities' responsibility to assess RMPs for national approved medicinal products.

## 6. Why do we need a harmonisation of risk management plan?

A key objective of harmonisation is to unify activities and interventions related to identifying and assessing medicine-related risks and reducing them. This will allow us to better understand the problem and come to a more informed decision. By harmonising risk

management plans, we aim to bring together certain criteria that make certain decisions easier to make.

Following the publication of the CMDh's list of safety concerns, it has become apparent that significant inconsistencies exist when looking at the list of safety concerns for products containing the same active ingredient (Including differences from the reference/innovator product).
The Working Party on Pharmacovigilance Procedures Work Sharing introduced a project called the Harmonisation of RMP Project ("HaRP") to improve harmonisation in 2018. Using the same active substances for which marketing authorisations have already been granted, the project seeks to identify safety concerns relating to those same active substances and harmonise them with RMPs already in place.

Project objectives include harmonisation of the RMPs for the same active substances for which MAH have already been granted with more than one RMP.

Aim of the project:

- to harmonise the Risk Management Plans (RMPs)
- of products with the same active substances
- for which marketing authorisations have already been granted
- with different RMPs in place.[13]

HaRP consists of two domains:

***Domain 1*** *– RMPs for which data exclusivity is about to expire. An assessment of the RMP of the reference product will take place in this domain within the framework of revision 2 of GVP Module V, including recent post-marketing experience with the product. In the event that a revised reference RMP is adopted, the List of safety concerns in this document will serve as the reference list that will be used by other MAHs in preparation of their own RMPs after the data exclusivity period expires.*

Domain 1 according to a document from CMDh for the status on the CMDh HaRP project includes developing up to date RMPs for the innovator product for active substances for which the data exclusivity of the reference product will expire soon (prospective approach).[14]

***Domain 2*** *- A list of safety concerns (from approved RMPs of active substances) is posted on the CMDh website (data exclusivity has already expired). In this domain, published lists*

[13] Appendix II: Presentation CMDh - Presentation kindly provided by CMDh "update on HaRP", 29 January 2021
[14] Appendix III: Presentation CMDh – HaRP group with the title "Status on the CMDh HaRP project", 30 January 2019 CMDh

*of safety concerns are reviewed for active substances that are either not innovator products or don't have a comprehensive risk management plan. An initial review is followed by a consultation round in which the pharmaceutical industry and all Member States are asked for feedback. Other RMPs that are not included in the Excel spreadsheet may also be identified during this round, which could provide additional safety issues that should be addressed. It should be noted that the Excel list does not contain all reviewed and approved RMPs. There will be alignment of these lists, resulting in a single harmonised List of safety concerns. This harmonised version of the safety concerns list will serve as a reference list for the preparation and assessment of RMPs by MAHs and National Competent Authorities (NCAs).* [15]

As for both domains, the proposed harmonisation is based on GVP Module V Rev. 2. RMPs can be viewed as old or outdated if a product has already been authorised for a long time (e.g. It is more than 8 years old), and/or the RMP is not yet compliant with GVP Module V, revision 2. An additional method has been developed to harmonise the list of safety concerns for domain 2. For active substances over which there is no innovator, or the innovator has no or old RMP. The same algorithm can be utilized to assess new RMPs submitted in conjunction with marketing authorisation or variation applications for products already authorised for a long period of time (e.g., more than 8 years). In this algorithm, only those safety concerns listed below are eligible for inclusion:

- Conduct additional pharmacovigilance activities, or
- Implement additional risk minimisation measures, or
- Ensure that appropriate targeted questionnaires are in place.

The other safety concerns can be eliminated unless there is an extremely strong and convincing scientific argument against it. Moreover, where no additional pharmacovigilance activities exist, no risk minimisation measures exist, or a targeted questionnaire has not been completed, this risk can be removed from the list of safety concerns (as defined in Annex 2: HaRP (Harmonisation of RMP Project) - methodology of harmonising RMPs).

Rationale algorithm:

- Active substances for which there is no innovator product, or the innovator product has no RMP or an old/outdated (i.e., if a product is already authorised for a long time (e.g., more than 8 years) and/or not yet in line with GVP Module V, rev,

[15] Annex 2: HaRP (Harmonisation of RMP Project) – methodology of harmonising RMPs, April 2021 CMDh/402/2019, Rev. 1 https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Pharmacovigilance_Legislation/RMPs/CMDh_402_2019_Rev.1_2021_04_clean_Annex_2__HaRP_methodology.pdf Accessed 27.09.2021

2) RMP (domain 2) are mostly substances authorised well before 2005, with an established safety profile.

- The safety profile of these substances is well known – important safety concerns are usually already identified, well characterised and/or minimised based on post-marketing experience in the product life cycle.
- When a new active substance is authorised not all risks will have been identified and some will only be discovered in the post-authorisation phase. However, when a substance has been on the market for a considerable time with significant post-marketing exposure there should be few remaining uncertainties.
- Routine pharmacovigilance activities are in place for continuous follow up of the safety profile even if a risk is no longer included in the RMP (e.g., signal detection, PSURs).

For substances with an established safety profile, it is proposed that a risk should only be qualified as important, for the purposes of the RMP, when there are additional activities/measures in place that either characterise the risk further or that are intended to minimise the risk.

It should be noted that the HaRP methodology (HaRP AR) does not apply to the assessment of the need for (ongoing) additional pharmacovigilance activities or additional risk minimisation measures (aRMMs), as this would require a more in-depth assessment. Therefore, it is not allowed to remove existing (ongoing) additional pharmacovigilance activities or aRMMs based on a published harmonised list of safety concerns without providing further data to support this removal.

On the website of CMDh there is a flow chart explaining these steps to adoption by CMDh. The flow chart provides better insight into the complex process of creating a harmonised standard List of Safety Concerns/HaRP assessment report.

Within the HaRP project CAP require no harmonisation. They have published their RMPs on the site of EMA, as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a according to the Dir 2001/83, which is mandatory from 2012; [16].

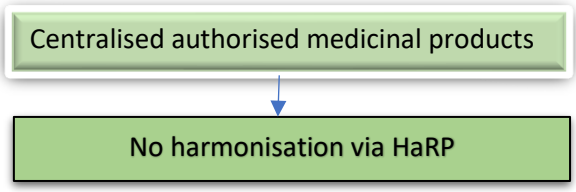


*Figure 5: Flow chart on the assessment and procedure for adoption of HaRP ARs of HaRP Peer Review Group (centralised authorised medicinal product)*[17]

[16] Directive 2001/83/EC of the European parliament and of the council of 6 November 2001 on the Community code relating to medicinal products for human use – EUR-Lex - 02001L0083-20121116 - EN - EUR-Lex (europa.eu) Accessed 12.10.2021

[17] Flow chart on the assessment and procedure for adoption by CMDh of HaRP Assessment reports prepared by the HaRP Peer Review Group CMDh_427_2021_Rev._0_02_2021

The table below introduces exactly the flow chart on the assessment for adoption of HaRP as of HaRP Peer Review Group

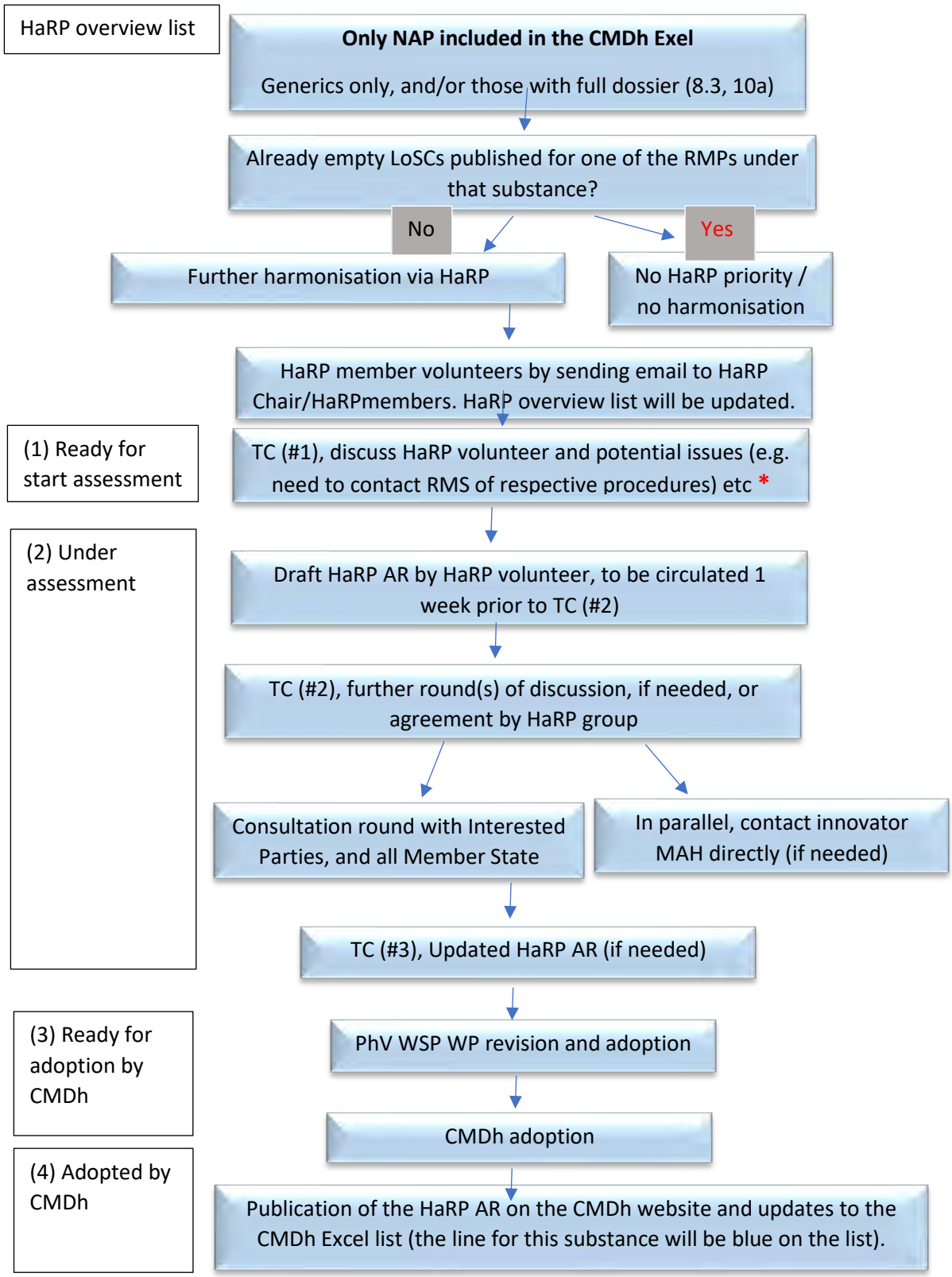


*Figure 6: Flow chart on the assessment and procedure for adoption of HaRP ARs of HaRP Peer Review Group*[18]

[18] Flow chart on the assessment and procedure for adoption by CMDh of HaRP Assessment reports prepared by the HaRP Peer Review Group

TC (#1), discuss HaRP volunteer and potential issues (e.g. need to contact RMS of respective procedures) etc *

* Potential issues:
  - *Could mono substances be combined with double/triple combinations for efficiency reasons?*
  - *In the case of one substance entry, can harmonisation be achieved because of potential differences in indication, formulation, etc. Is it necessary to add more sub-entries?*
  - *Can we identify some NAP innovator products already?*

**AR:** Assessment report
**HaRP**: Harmonisation of Risk Management Plan Project
**NAPs:** nationally authorised products
**RMS:** Reference Member State

This flow chart offers a better understanding of the multiple steps needed for harmonisation List of Safety Concerns/HaRP assessment report. Only NAP products may be selected for further processing harmonisation within the HaRP project. Priority will be given to substances that have been in use for many years.

The HaRP group would not prioritize the substance with 'empty RMP' (i.e., RMP with empty safety concerns) which are already approved "old" but has recently undergone a DCP procedure and has been published on CMDh for further harmonisation especially if the approved empty RMP relates a full-dossier (based on legal basis article 8(3) or 10a of Directive 2001/83/EC) product. A member of the HaRP performs the initial review and harmonisation of the List of Safety Concerns. Those listed in the CMDh Excel file constitute these RMPs.

The pharmaceutical industry and all member states will be asked to respond to the initial review in a follow-up consultation round. There may also be other relevant RMPs, not included in the CMDh excel list, uncovered from other sources during this consultation that could provide safety concerns that need to be considered. The innovator MAH could sometimes be contacted directly (if needed) in parallel with the HaRP AR proposal if an old non-empty RMP exists for the innovator product. The HaRP AR will be adopted by the PhV WSP Working Party and CMDh following agreement by the HaRP group. In addition to publishing the HaRP AR on the CMDh website and updating the CMDh Excel list (the line indicating this substance will be marked blue in the list), the HaRP AR will be published on the CMDh website and officially adopted by CMDh.

CMDh_427_2021_Rev._0_02_2021_ Flow chart HaRP draft for CMDh final version agreed by CMDh new.pdf (hma.eu)

It's well known that pharmaceutical products are authorised for a particular indication and a particular population when the risk-benefit balance is found to be positive. It is generally accepted that no medicine is free of risk or adverse reactions. These consequences may vary greatly depending on severity, likelihood of occurrence, patient impact, and public health implications. Some adverse reactions and risks will only be discovered and defined during the post-authorisation phase, since not all adverse reactions and risks will have been identified at the time of initial marketing authorisation. Risk management plans (RMPs) describe the risk management system necessary to identify, characterise, and minimise the important risks associated with a medicinal product.[19]

**Current developments in generic RMPs**

Preparing and evaluating generic approvals pose special challenges to pharmaceutical companies and national authorities because some RMPs are extremely inconsistent regarding safety issues.

This led to CMDh forming the working group Harmonisation of RMP Project, which has set itself the following main goals:

- by the end of the market exclusivity period, refine and clarify RMPs for originator products so that they could be used as templates for generic products.
- Harmonisation of the list of safety concerns for the same active substances with currently on-hand RMPs, for which marketing authorisation is already in place.

The HaRP working group began its work in the 2nd quarter of 2018.[20]

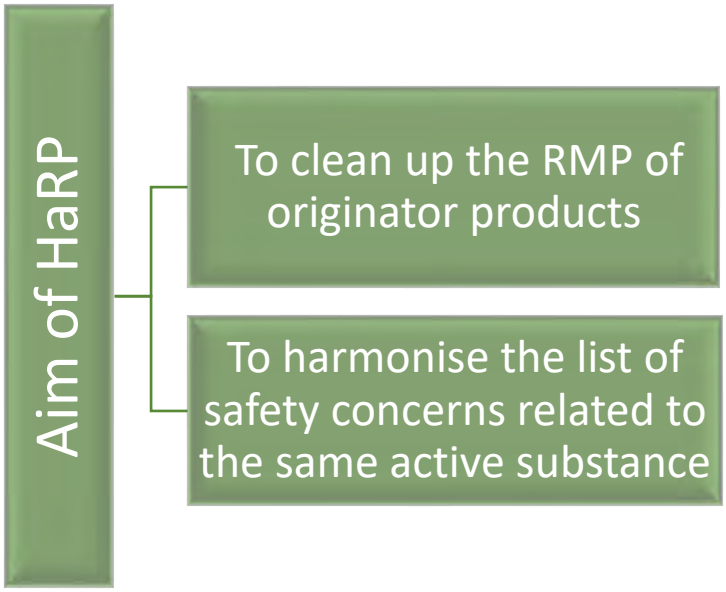


*Figure 7: Aim of the HaRP (Harmonisation of the Risk Management Plan)*

[19] Guideline on good pharmacovigilance practices (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

[20] Pharmacovigilance und Maintenance von Arzneimittelzulassungen – B. Sickmüller, B.Thurisch, S. Wallik (Hrsg.)

Unfortunately, very little information is publicly available about approved RMPs for existing authorised medicinal products. When there is no information available on the safety concerns of the reference product, a generic product's RMP development can be a major challenge. It is possible to submit RMPs for the same active substance to different Reference Member States. This may result in different results from the assessment procedure and ultimately inconsistent RMPs for the same active ingredient. Due to this reason, the Coordination Group for Mutual Recognition and Decentralized Procedure - Human (CMDh) decided in 2014 to publish a list of safety concerns related to approved RMPs for each substance. Moreover, the CMDh agreed to include in the public assessment report (PAR) from January 2014 the safety concerns from concluded Mutual Recognition Procedures (MRP)/Decentralized Procedures (DCP). The CMDh Working Party on Pharmacovigilance Procedures Work Sharing is responsible for updating the list.

Companies can more easily create RMPs when safety concerns associated with approved RMPs are published. Additionally, this approach would ensure a more consistent outcome. Considering the information contained in the list, the Working Party on Pharmacovigilance Procedures Work Sharing will discuss how full harmonisation might be achieved (if applicable) of RMPs for the same active substances. When a national competent authority has concerns about a risk that affects the benefit-risk balance of the medicinal product, that authority can request an RMP for that product.

# 7. Safety concerns updated

## 7.1. Safety concerns with new approved RMPs

MAHs and Member States can provide the list of safety concerns that accompany new approved RMPs. To ensure that MPs' safety concerns are reported to the CMDh secretariat, MAHs are requested to provide a list of concerns for products for which approval has been granted, or an updated RMP has been approved, either through a variation or renewal procedure. There are different cases:

- As part of the new marketing application process or variation and renewal procedures, if any RMP evaluated is not in line with a list of safety concerns on the CMDh website (marked blue on the list), the MAH must provide the list to the CMDh secretariat.
- In case the RMP approved during a new marketing application procedure or variation/renewal procedure is in line with the harmonised list of safety concerns for the substance as published on the CMDh website (marked blue on the list), there is no need to provide the list of safety concerns to the CMDh secretariat.

- Normally, the MAH has to provide the CMDh secretariat with the approved "empty" list of safety concerns if the RMP approved during a new application or variation/renewal procedure doesn't include safety concerns (so called "empty" RMP).

If it is a purely national procedure, the MAH should be reminded by the referent member state or Member State (if applicable) who has approved the RMP, that the list of safety concerns should be sent to CMDh secretariat at the end of the approval process.

MAH may also provide lists of safety concerns of RMPs of active ingredients that are not on the CMDh list, if requested by the Referent Member State (RMS) or MS. In particular, the lists of safety concerns that are approved following a complete dossier (legal basis article 8(3) of Directive 2001/83/EC) are highly welcomed.

## 7.2. Concerns and updates regarding existing RMPs on the published list

Based on the Cover Note to List of safety concerns per approved Risk Management Plan (RMP) of active substances per product:

*"The Member State/Referent Member State(RMS)/MAH should notify the CMDh secretariat as soon as possible if the information previously included in the published list needs to be updated via e-mail address including Active substance(s), Product name in the RMS (in case of a product approved via MRP/DCP) or in the Member State (in case of a strictly nationally authorised product); MRP/DCP procedure number. In case of a product approved via MRP/DCP: the number of the procedure during which the RMP has been assessed and approved. In case of a product authorised via a strictly national procedure, "N/A" should be included in the respective column., Legal basis of the product; Name of the MAH. In case of a product approved via MRP/DCP: the name of Marketing Authorisation Holder in RMS.*

*An authorised product which was approved through a strictly national process should include the Member State which approved the updated RMP and approval date.*

- *Number and date of current version of RMP.*
- *Provide the link to all updates to PAR (if appropriate) or state that existing links to PAR are still appropriate.*
- *Add this information to the template for safety concerns in order to update safety concerns/additional pharmacovigilance activities and/or aRMMs. Any changes to the information to be included in the list should be in red."*[21]

New applications should be based upon a harmonised list of safety concerns (referred to in blue in the published list*). These agreed safety concerns should be included in RMPs during*

[21] Cover Note to List of safety concerns per approved Risk Management Plan (RMP) of active substances per product https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Pharmacovigilance_Legislation/RMPs/CMDh_329_2015_Rev.5_2021_04_clean_-_HaRP_Cover_Notex.pdf Accessed 12.10.2021

*the next review of an existing marketing authorisation. As part of the HaRP project, only safety concerns in the RMP are considered, instead of PSURs.*

There may be some differences between the RMP and PSUR in terms of safety concerns. Moreover, still points to follow up on safety concerns that were not addressed in the RMP (anymore) by means of PSURs for further characterization.

A safety concern is considered within the scope of risk management planning and therefore evaluated based on risk-benefit impact and the need for additional risk minimization controls and /or further evaluation as part of GVP Module V rev.2. This module is used for the current HaRP project. In general, PSURs are expected to address the safety concerns defined in the RMP as a minimum. According to the safety specification in the PSUR, there are likely to be risks and missing information that are critical to the benefit/risk balance of the active substance and could reap benefits from further investigation in the PSUR.

According to a presentation kindly provided by CMDh for the aim of the thesis CMDh makes three important steps:

**Step one:** The List of Safety Concerns published on the CMDh website has also shown:

- first inconsistencies within generic products as well as with the reference product
- second inconsistencies among products containing the same actives

**Step two:** HaRP domains, domain 1 not yet started and domain 2 clean-up (harmonisation) of the Excel List of safety concerns as published on the CMDh website (first step for substances with no reference product or with reference product without an RMP in place).[22]

**Step three:** RMP Peer Review Group (RMP PRG) set up for (initially) especially domain 2:

- Chaired by NL.
- Composed by around 20 members, mainly experienced RMP assessors from MSs.
- Started in April 2018: monthly meetings via TC to date.

[22] Presentation kindly provided by CMDh "update on HaRP", 29 January 2021, Appendix II

# 8. Survey of the RMP experience in the Bulgarian pharmaceutical companies

For the purpose of this thesis a stocktaking survey was performed on harmonising the risk management. The exercise was conducted in the Bulgaria pharmaceutical industry and completed by reputable pharmacovigilance experts from April - May 2021. The outcome and conclusions were presented by me in a seminar organised by Bulgarian Association for Drug Information. The way forward and conclusions were acknowledged and the work on this aspect was very well received. The slides presented by me during this seminar are enclosed as *Appendix I.*

## 8.1. Scope and Objectives of the survey

Since 2007, Bulgaria has been a member of the European Union (EU). Experts from pharmaceutical companies located in Bulgaria and those with affiliates there participated in the survey. The survey was conducted by 12 regulatory experts from 12 different companies: some producing original, innovative medicines and others producing generic medications. In order to ensure that problem points could be expressed freely, it was anonymous. Based on the answers to the questionnaire, a graphical representation was put together to illustrate the problem points.

To receive feedback from various Bulgarian pharmaceutical companies (applicants) regarding the harmonisation of risk management plans, an online questionnaire was created and distributed with the assistance of the **B**ulgarian **A**ssociation for **D**rug **I**nformation (BADI). BADI is a non-government organisation, which objectives are:

- **Objective 1:** To prepare and organise national and international forums for sharing experience, information, and qualification in the field of drugs and regulatory affairs in Bulgaria.
- **Objective 2**. to develop, examinate, and prepare opinions, scientific developments, and publications relating to the activities independently or in collaboration with regulatory authorities, professional and non-governmental establishments, and other associations both in Bulgaria and the European Union.
- **Objective 3**. to participate in the development, discussion, experts' assessment, and analysis of draft legal acts, guidelines, and instructions relating to both in Bulgaria and the European Union.[23]

The survey scope largely focuses on RMP and its harmonisation, whereas the main goals were to:

[23] BADI – Bulgarian Association of Drug Information Activities
https://www.badibg.org/index.php?option=com_content&view=article&id=14&Itemid=13

- ✓ **Stocktaking** - feedback from various Bulgarian pharmaceutical companies (applicants) regarding the harmonisation of risk management plans, an online questionnaire was created and distributed with the assistance of the Bulgarian Association for Drug Information (BADI).
- ✓ **Status quo overview** – Provide an overview of the current state of RMP adoption and use to the November BADI conference. Results of a survey on harmonising risk management plans are included in the thesis, which was conducted in Bulgaria from April to May of 2021.
- ✓ **HaRP group Input** – Provide input to the HaRP group and support the future development of the harmonisation process

Lastly, the outcome of this stocktaking exercise was presented in the BADI conference in November 2021 and was duly shared with the HaRP work group in order to provide feedback for further improvements.

### 8.2. The survey results

**Question 1:** Upon reviewing the risk management guides, do you agree that they are sufficient to implement comprehensive risk management in accordance with regulatory requirements? *

*The regulatory normative documents refer to documents such as guidance on the format for the EU risk management plan (RMP), guidance on the risk management plans for COVID-19 vaccines, guidelines for the development of medicines and other stakeholders GVP, GCP etc. the regulations and directives.

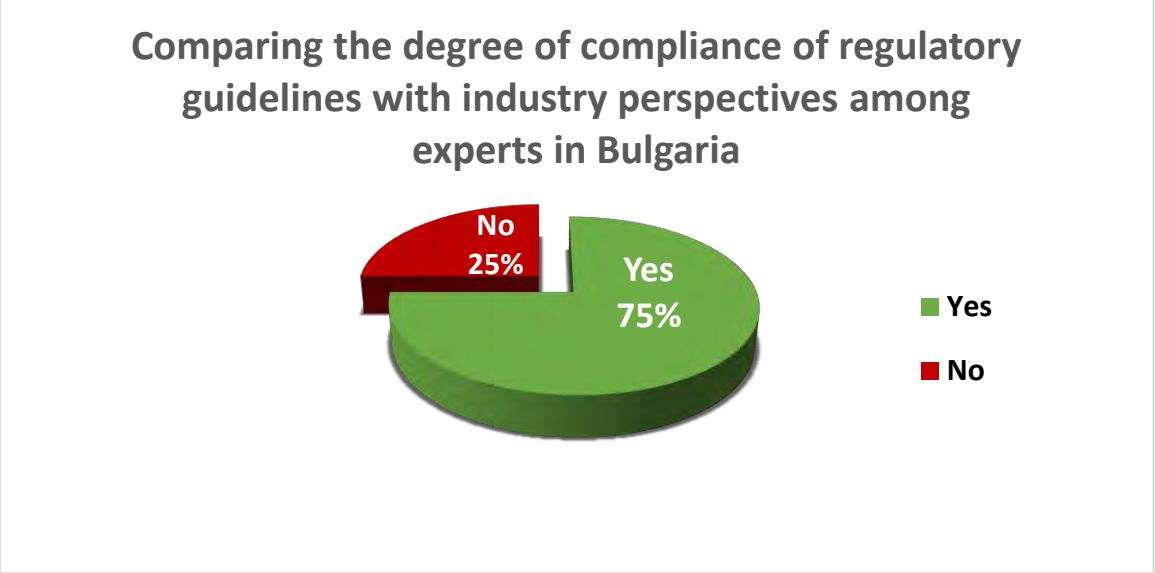


*Figure 8: Shows the degree of adequacy of regulatory guidelines according to industry perspective among experts in Bulgaria*

Most respondents said that there are sufficient documents in compliance with regulatory requirements, while 25% noted that there are not enough.

By regulatory normative documents it is meant the guidelines like Guidance on the format of the risk management plan (RMP) in the EU, Guidance on risk management plans for COVID-19 vaccines, Guidance for medicine developers and other stakeholders on COVID-19, the regulations and directives.

**Question 2:** Regarding Risk Management approach, have you implemented internally developed methodologies/best practices?


*Figure 9: Custom/Internally developed risk management methods/best practices*

In the survey, it appears that more than half of the respondents (8 safety experts) introduced new methodologies and practices, while 33,3 percent of the experts did not introduce any new methodologies.

**Question 3:** In your view, does the identification of potential risks play an important role in the RMP? And if yes, how important do you consider them from 1 to 3?

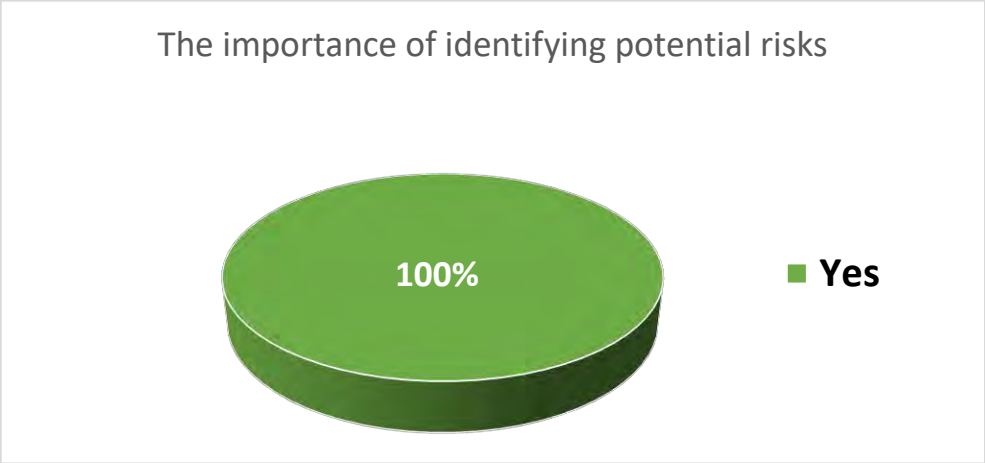


*Figure 10: Experts in BG's regulatory field emphasize the importance of identifying potential risks*

This question focuses on the role of the identification of potential risks, whether they play a significant role in the risk management plan, and for what level the role is critical. The importance of identifying potential risks is emphasized.
In addition, they comment on how important they perceive each point in their importance ranking from 1 to 3, where 3 is the most important.

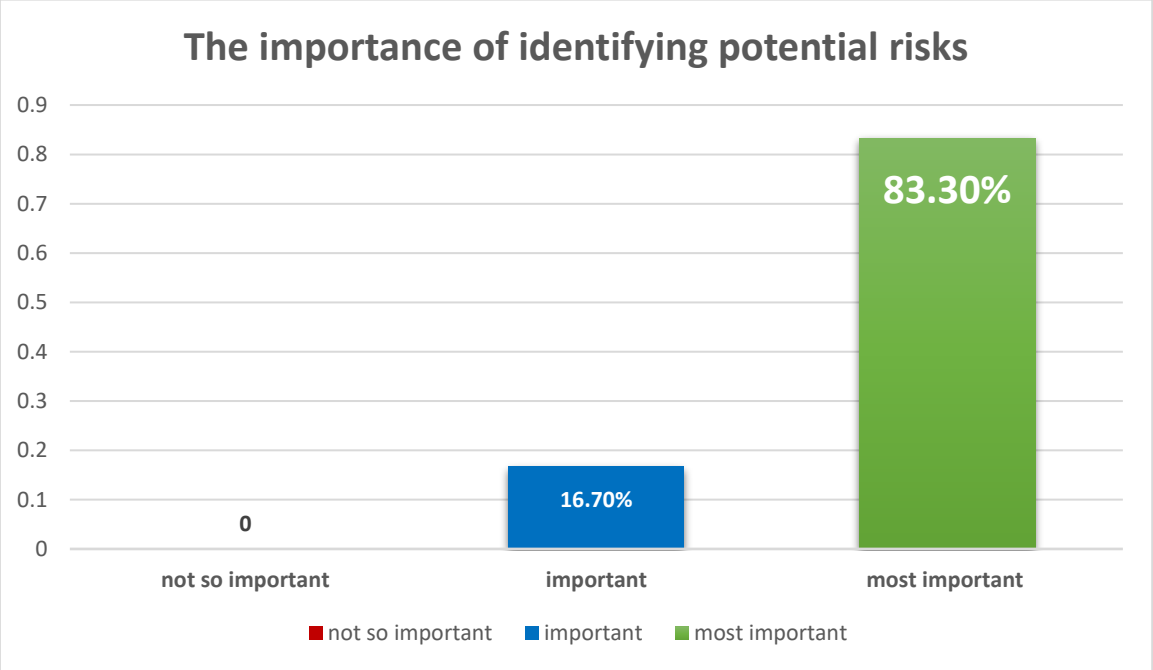


*Figure 11: Classification per importance factor*

**Question 4:** Do you think that the current risk management plan template by EMA and Risk minimisation measures are sufficient to ensure a harmonised approach to your risk management activities? If not please elaborate

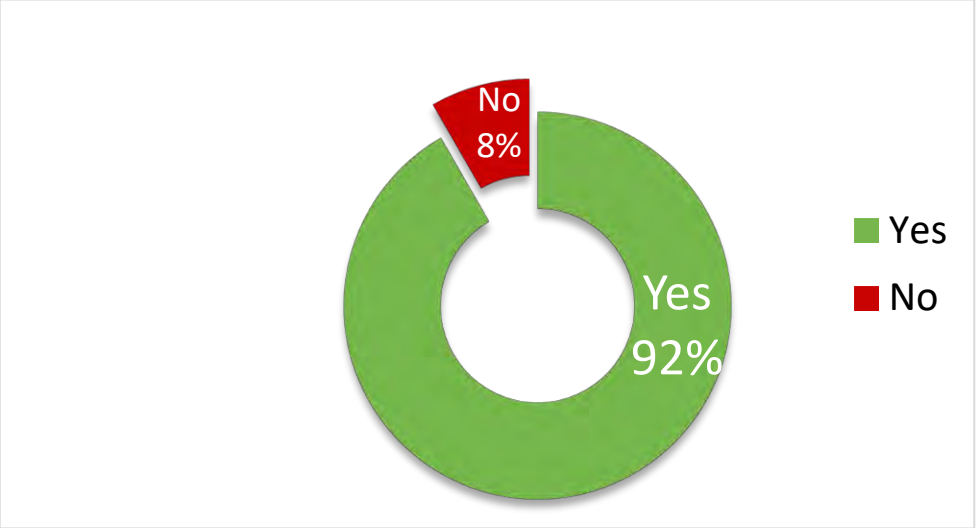


*Figure 12: Overview of the responses regarding the template cover and potential gaps*

According to participants, the rate of harmonisation of the risk management plan is satisfactory. The compelling majority (91,7%) of participants considering that the template is well defined and sufficient to enable the process. However, 8,3% still find gaps that are worth investigating even though difficult to easily frame.

**Question 5:** Do you believe that the process between regulators and pharmaceutical companies is sufficiently harmonised as according to the RMP? If no, why?

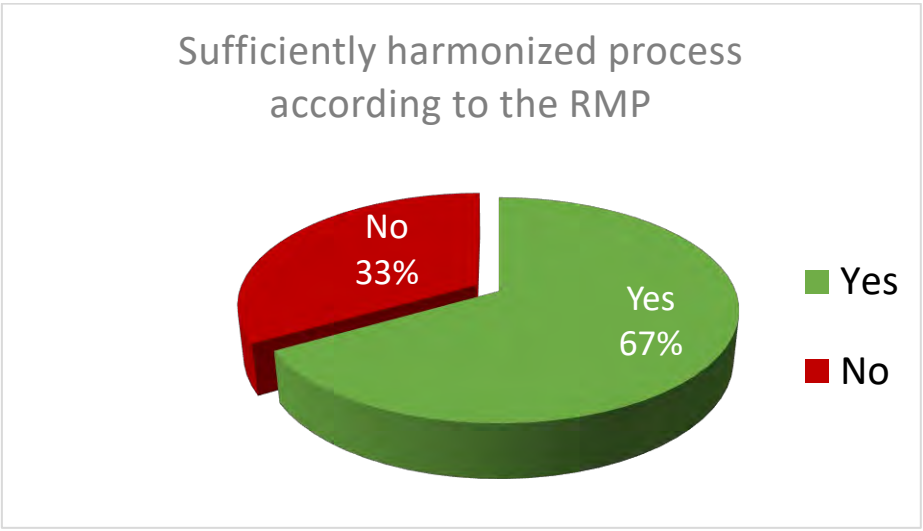


*Figure 13: Satisfaction of the experts regarding state of harmonisation of the RMP*

A solid 67% majority of participants consider the process between the Regulator and the pharma industry to be sufficiently harmonised. While a good 1/3rd (33 %) disagree. Their argument is that identifying the risks depends on the evaluation of the Referent Member State and differs from that of the Concerned Member State(s). There is no guideline at the national level for implementing aRMMs and implementing some of them is nearly impossible due to the passive nature of the organisations (e.g., pregnancy registers).

As a problem, it is noted that the information for RMPs of reference products is not sufficient.

Paper-based work has a higher rate of errors connected with aggregation and structuring errors compared to digitally synchronized work.

## **Question 6:** In your opinion, what are the main challenges or pain points involved in filling out, completing, and harmonising your RMP

According to the experts, the main challenges regarding filling, completing and harmonising RMP are:

- Harmonisation of aRMMs – Additional risk minimisation measures

Assessment of the aRMMs is crucial to determine whether they are effective. If an intervention wasn't successful, explain why and what corrections were necessary. The evaluation should be conducted for each additional risk minimisation tool individually and for the entire program as a whole.

- Not always easy to find the originator's RMP (with regards to the generic products we need to refer to the originator). How to find the originator, the referent medicinal product

A referent medicinal product is a medicinal product for which a marketing authorisation has already been granted either by a MS or by the Commission when a complete dossier has been submitted i.e. following the submission of the data required by Dir 2001/83/EC, art. 8(3), 10a,10b or 10c.

- Collect all relevant information and thoroughly evaluate the risk and benefit profile
- The use of data-driven standart operating procedures (SOPs) and technology
- Harmonisation between a referent and a generic product
- Some reference products are not published their RMPs, and they have stated that they will be available at a later time, due to different reasons.

## **Question 7:** How are you dealing with cases when RMP for a generic medicine is missing / no information is available on the safety concerns of the reference medicinal product?

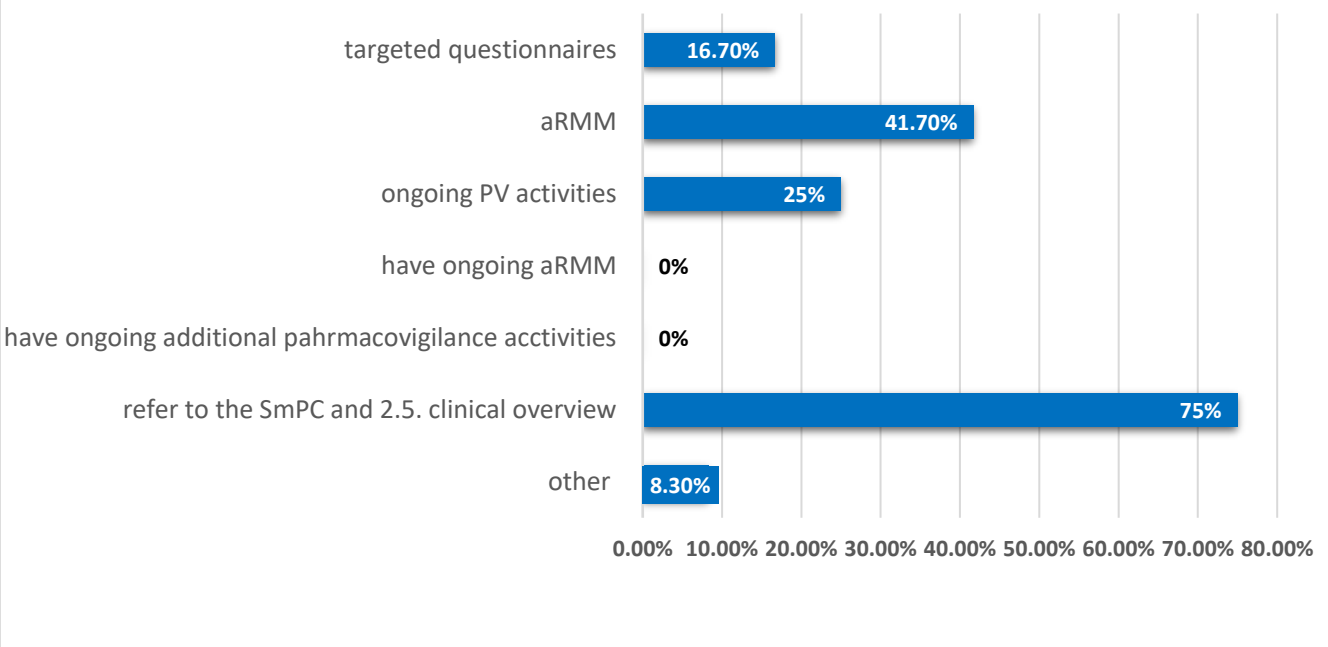


Figure 14: How the experts deal with cases when RMP for a generic medicine is missing, and no information is available on the safety concerns of the reference medicinal product

Seventy-five percent of the safety experts refer to the SmPC as well as the Module 2.5 Clinical Overview (eCTD). Approximately 41,7 % of the experts are taking ongoing measures to keep risks to a minimum - have ongoing additional risk minimisation measure and 25 % of them have ongoing pharmacovigilance activities.

These pharmacovigilance activities are designed to detect, assess, understand, and prevent drug-related adverse events post-marketing. 16,7% of respondents have implemented essential targeted questionnaires. A section of the commentary says that the expert always researches product risks in depth.

**Question 8:** How difficult is it to find information about the reference medicinal product for a generic drug (if there is no information on safety concerns of the reference medicinal product)? How challenging it is?

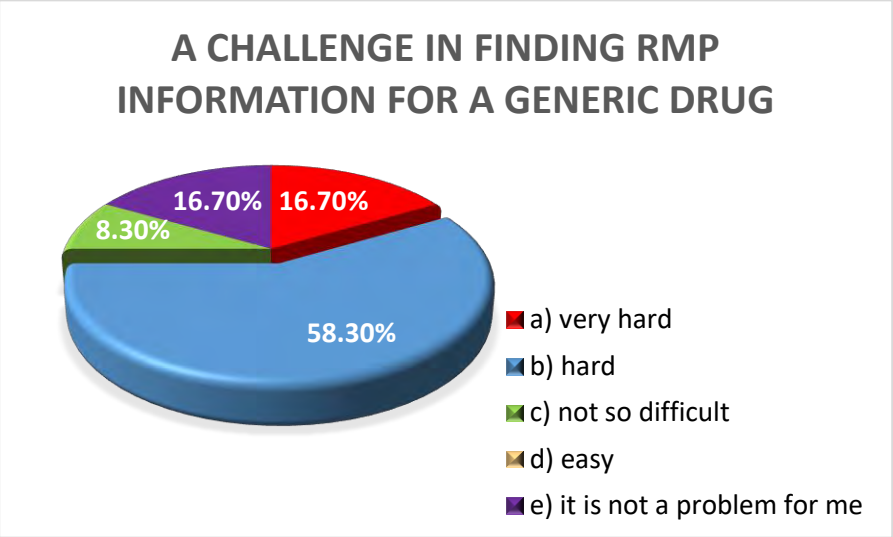


*Figure 15: Difficulties of finding the information or lack of it on the safety concerns*

When submitting marketing authorisation documents, one of the conditions is to provide a summary of the RMP, but very often the companies of the original medicinal products announce that they will provide the information at a later stage and never provide, from which the generic medicines suffer later. This opinion was expressed by a pharmacovigilance expert in the survey.

**Question 9:** According to you how important is the harmonisation of RMP for the same active substance when they are submitted via different Articles of procedure with different risk management systems (RMSs)?

A consideration was made of the importance of harmonising RMP when they are submitted via different articles of procedure, with different RMSs, for the same active substance

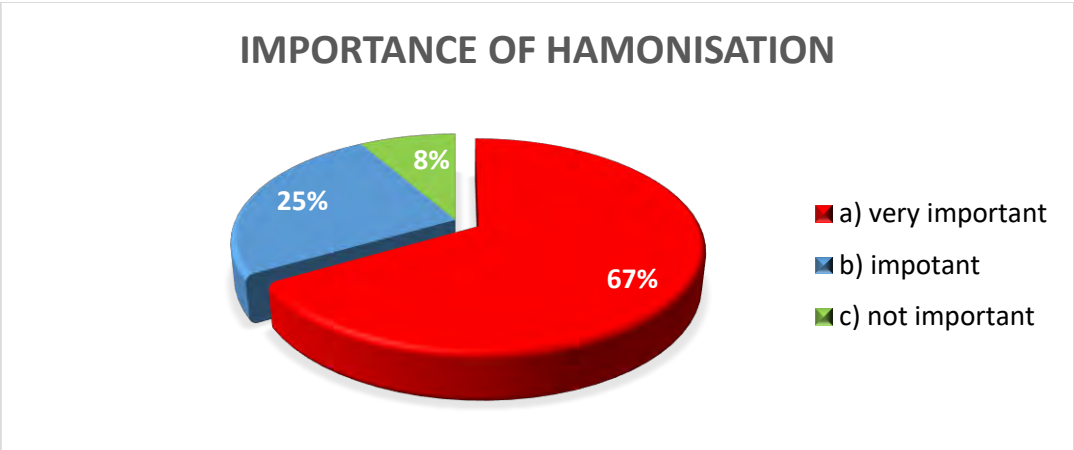


*Figure 16: An overview of the importance of harmonisation*

The fact that RMPs are submitted using different procedures with different approaches to the same active substance leads to different outcomes/disharmonised RMPs for the same active substance. It was commented that these RMPs could not be harmonised.

**Question 10:** There are often different RMPs for the same active substance submitted by different procedures with different RMSs. In this way, outcomes can vary for the same active substance and there can be proliferations of disharmonised RMS (for the same active substance). In your opinion, are inconsistent results of procedures as a result of different RMPs for the same active substance a significant concern? Please elaborate if not.

Often RMPs for the same active substance are submitted via different procedures with different RMSs. This results in outcomes that vary for the same active substance and proliferation of lack of harmonised RMSs (for the same active substance).

A majority of participants emphasize that inconsistent results in procedures stem from lack of harmonised RMPs for a given active substance are a significant concern.

Three participants hold the opinion that it is not a significant concern, but nevertheless it remains a moderate concern and that the inconsistent outcomes of procedures as a result of lack of harmonised RMPs are not a problem, but rather they are quite normal for them.

**Question 11:** What are the main root causes that undermine the harmonisation of the RMP?

Insufficient training and unclear guidance are the main root causes for the lack of RMP harmonisation. It was noted that there wasn't a unified approach because of diverging opinions. There was a strong emphasis on the fact that the original companies themselves are actively resisting this happening.

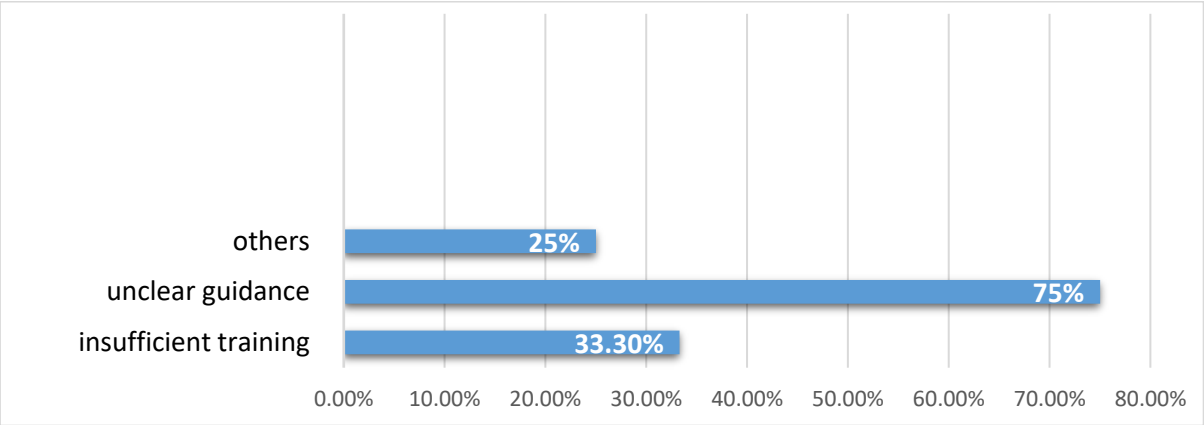


*Figure 17: Issues regarding RMP Harmonisation*

**Question 12:** What are the main benefits that can be achieved by harmonising the RMP, according to you?

As per the experts, harmonisation of RMP can yield the following benefits:

- ✓ Improved patient care and greater confidence in physicians,
- ✓ Standards that are the same across the EU for the same active substance,
- ✓ Improving safety and compliance through transparency,
- ✓ Refrained from providing misleading information, identified some risks, recommended some dosages, followed all safety precautions
- ✓ In order for products that contain the same active ingredients to have the same information,
- ✓ for the same INN the RMP should be identical,
- ✓ Publicly available clear information
- ✓ A streamlined guidance system, common activities, and a common cost. It would improve the assessment of drug-related risks.
- ✓ It will not be necessary to write RMPs, since we will refer to the original RMPs.

# 6. Problem points and suggestions for improvements

## 6.1. Problems and difficulties

**a) Difficulties in finding information, the lack of any RMP -** a decision should be to create a register of RMP on the website of the EMA, another international institution and also on the sites of national health authorities for a national authorised medicinal product.

In addition to RMPs for centrally authorised medicines, EMA provides summaries of RMPs for pharmaceuticals, which are provided to stakeholders as a more comprehensive opportunity to understand the decision-making processes of European regulatory authorities when reviewing medicine safety or active ingredient safety[24].

It is also challenging for medicines with well-established use to find RMP. However, very little information is publicly available of the reference medicinal product.

**b)** the lack of national regulatory mechanisms at the local level regarding the lack of RMP

**c)** a clear register where to trace the harmonisation of the process

**d)** Now, it is a challenge to assess/prepare an RMP if no information is available on the safety concerns of the reference medicinal product, especially for generic products. For generic products in particular, the development of an RMP is sometimes a major

[24] EMA publishes RMP summaries - https://www.ema.europa.eu/en/search/search/type/ema_document/ema_editorial_content/ema_document/field_ema_doc_type%253Aname_field/EPAR%20-%20Risk-management-plan%20summary

challenge if information about safety concerns of the reference drug cannot be accessed.

**Problems from pharma industry point of view**

- Lack of publicity available RMP of the reference medicinal product
- No register of all RMP of one place
- No clear mechanism of harmonisation of the process
- No national support and register of the RMP of the medicinal products

**Problems from CMDh point of view**

- Time consuming process
- Getting consensus across stakeholders and, ultimately, adoption by CMDh is a difficult process by which the RMPs are cleaned up one by one for each substance.
- As several hundred substances are eligible for harmonisation, it will take years before even a small proportion of these substances is harmonised
- Maintenance of existing HaRP ARs. How to keep harmonised lists up to date?
- List of regulatory procedures that will impact RMPs considered still to be defined how and by whom outcomes of relevant procedures could be monitored in a systematic manner
- Products assessed: possible incomplete picture of existing RMPs not included in CMDh list of safety concerns?
- To consider including also "old" substances in domain 2 where the innovator product has an RMP (which is not harmonised yet): to develop a procedure to enable clean-up of safety concerns of substances for NAPs (where the innovator product has an RMP in place).
- To work on a procedure together with PRAC on RMPs involving CAPs (centrally authorised products): to develop a procedure to enable clean-up of safety concerns of substances with a CAP [either innovator or generic] (involving PRAC and MAHs)
- How to involve/reach all MAHs (i.e., MAHs not part of Trade associations).
- To agree on a procedure for Industry (MAHs) input on assessment reports agreed by the HaRP Group.
- To work further on a procedure to finalise and publish the ARs.
- Once harmonised: to keep the harmonisation reached.

## 6.2. Possible solutions

✓ Clear and well-structured register of reference medicinal products on the website of EMA and national health authorities to improve efficiency of new drug development and registration processes, to promote public health, prevent

duplication of clinical trials in humans and minimize the use of animal testing without compromising safety and effectiveness.

- ✓ The development and implementation of harmonised Guidelines and standards
- ✓ It is necessary to change the current work-up for harmonisation
- ✓ Document reviewing the status of the art of the HaRP project and containing the proposals to speed up the HaRP assessment process
- ✓ 'Regular' process: harmonisation assessment as performed during the pilot waves
- ✓ with some modifications to the process proposed to reduce the need for multiple rounds of assessment in HaRP
- ✓ A new (empty) LoSC can be used for further harmonisation purposes (some HaRP ARs have already been prepared by the HaRP group). Reciprocal assessment of substances with overlapping safety concerns that can be assessed at the same time.
- ✓ Applicability has to be verified.

## 7. Conclusion

With RMP and risk management in general, we trigger number of concurrent measures like routine reporting requirements, but also measures that help to continually assess the risk to benefits profile of the product. As such, the RMP is a paramount to ensure safe, in high quality, and effective medicines. Risk management requires to proactively identify risks, response strategies, and ways to avoid or mitigate risk. For the cases where the risks cannot be prevented or avoided, a development of an emergency plan is needed. In the whole process, risk management plays a vital role to secure one of the most essential characteristics in healthcare - to continuity of care for patients and healthcare professionals, in a consistent and continuously improving[25] manner.

One might wonder, why risk-taking plays such a role within the pharmaceutical industry and in particular why even taking risk is allowed. Alike every other business, the drug development (RND [26] ), manufacturing, production, distribution and ultimately use contributes to the risks that are allocated in each stage of the cycle. As such effective risk management is needed not only because of financial consideration (avoid loses), but most importantly in health care these risks need to be managed in order to minimize the potential impact to patients' safety. For this reason, risk management is so critical in the pharmaceutical industry and to be effective, requires having a suitable risk management plan. The risk management plan allows to anticipate and prepare for the unexpected, minimizing risks and lowering excessive costs before they occur/happen or are incurred. By

[25] Continuously improving – referencing to the risk/benefit ratio

[26] RND – Research and Development in Pharmaceutical industry is notoriously expensive. Therefore, managing risks saves money as well.

considering potential risks or events before they happen and having a risk management plan in place, we can save money and protect our health.

On the website of CMDh, all HaRP Assessment Reports are clearly visible, a number that has grown over time.

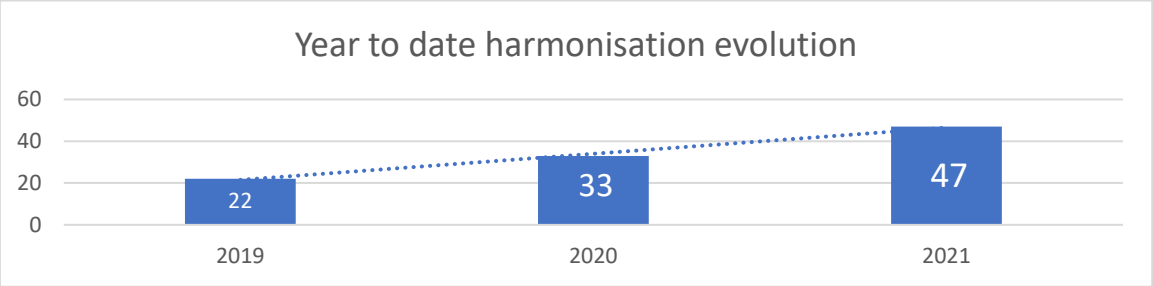


*Figure 18: Trend analysis on Harmonisation progress, source CMDh website*

The aim of the project is to harmonise the Risk Management Plans (RMPs) of products with the same active substances for which marketing authorisations have already been granted with different RMPs in place.

**This has the following positive aspects:**

- **a)** The purpose of harmonisation is to reduce the burden of preparing and assessing RMPs by MAHs and NCAs, respectively.
- **b)** Stakeholders acknowledge the need to eliminate inconsistencies between LoSCs approved for products containing the same substances.
- **c)** This project achieves the major achievement of harmonising and cleaning up RMPs by using GVP V (Rev. 2). The proposed methodology is both feasible and increasingly accepted across stakeholders and NCAs.
- **d)** Intense collaboration among HaRP members (and assessors in NCAs) has resulted in a greater acceptance of an "empty" RMP and can be considered successful.

HaRP project can only be successful if all stakeholders will collaborate and commit - to actively participate in the project - to utilise the final agreed list of safety concerns/ARs both in the building and the assessment of RMPs in EU!
Prior to the introduction of the HaRP, many differences in the risk management plan for the same active substance were identified, which put a heavy burden on the pharmaceutical industry and increased the workload.

The introduction of the project has significantly facilitated consistency and collaboration in the work of pharmaceutical companies. As such, it will increase the quality of the risk management plans and by focusing on continuous improvement in managing the risks in a comprehensive manner. Consequently, it expected to bring greater quality and value of the supplied of medicinal products; enhance transparency, security and safety for the patients;

and by applying consistently risk management practices the HaRP project will reinforce trust across the industry and by the patients.

In certain cases, risk avoidance is not a feasible option - therefore, managing these risks in a consistent and transparent fashion are critical for sustainable success. Harmonising the risk management plan is an essential enabler, which will save time, apply consistency and provide benefits to the efficiency in the overall process. Moreover, by harmonising the risk management plans there would be strong benefits to the quality and adequacy of risk-based decision-making process concerning the drugs in their entre product lifecycle – from the regulators, throughout the industry and ultimately by the patients.

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## Appendix I – Nov. 2021 Presentation BALI

HaRP –
Harmonisation of risk management plan project

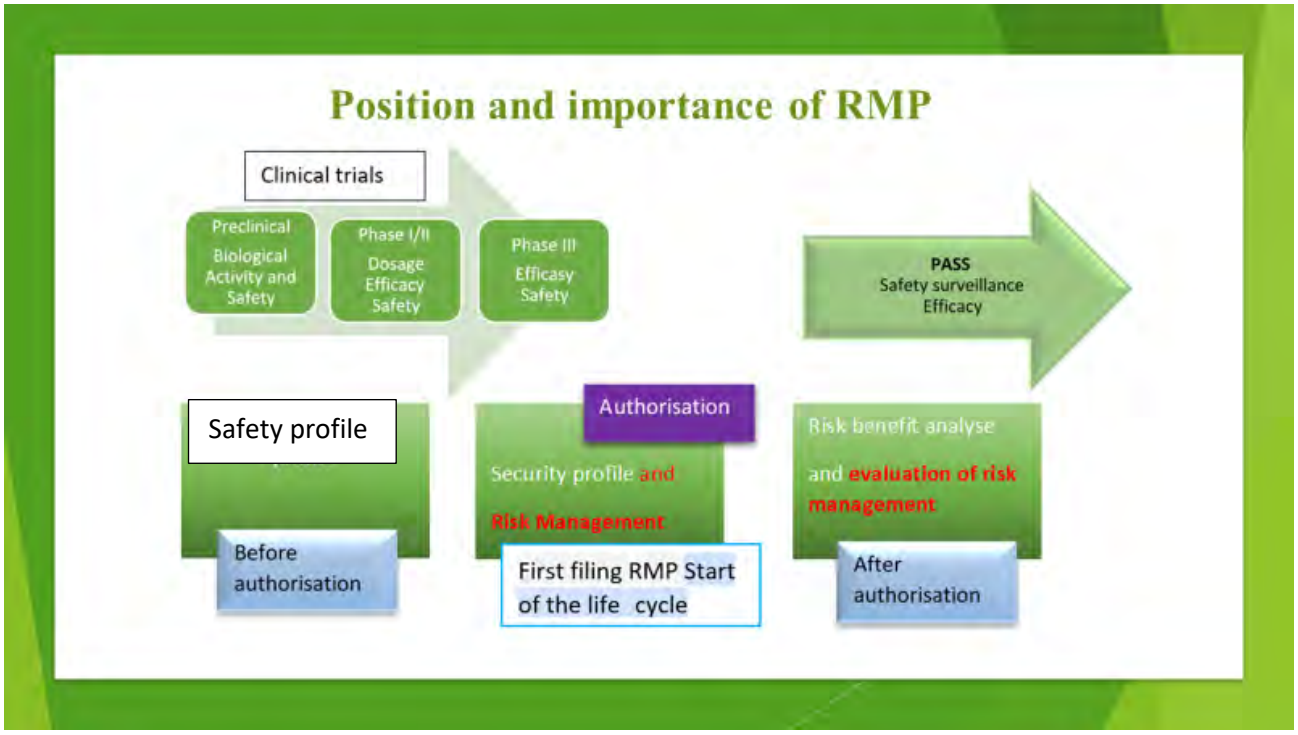
Rumyana Atanasova
MPharm, MBA

Bulgarian Association for Drug Information (BADI)


Agenda

- RMP, RMS, RMM
- HaRP
- Survey
- Pain Points
- The way forward

Bulgarian Association for Drug Information (BADI)


Position and importance of RMP
Clinical trials
Preclinical
Biological Activity and Safety
Phase I/II
Dosage Efficacy Safety
Phase III
Efficasy Safety
PASS
Safety surveillance Efficacy
Safety profile
Before authorisation
Authorisation
Security profile and
Risk Management
First filing RMP Start of the life cycle
Risk benefit analyse
and evaluation of risk management
After authorisation


Risk Management Plan (RMP)- History
Since July 2012 a RMP
still MAs without an RMP
new safety concerns, significant changes to the MA may trigger the need to introduce an RMP.
a dynamic document
EMA post-authorisation procedural advice for users of the centralised procedure
Bulgarian Association for Drug Information (BADI)


| RMP parts and modules | |
|---|---|
| **Part I** | Product(s) overview |
| **Part II** | Safety specification |
| **Module SI** | Epidemiology of the indication(s) and target population (s) |
| **Module SII** | Non-clinical part of the safety specification |
| **Module SIII** | Clinical trial exposure |
| **Module SIV** | Populations not studied in clinical trials |
| **Module SV** | Post-authorisation experience |
| **Module SVI** | Additional EU requirements for the safety specification |
| **Module SVII** | Identified and potential risks |
| **Module SVIII** | Summary of the safety concerns |
| **Part III** | Pharmacovigilance plan (including post-authorisation safety studies) |
| **Part IV** | Plans for post-authorisation efficacy studies |
| **Part V** | Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) |
| **Part VI** | Summary of the risk management plan |
| **Part VII** | Annexes |

## *Summary of the minimum RMP requirements for initial marketing authorization applications*

| Product | Part I | Part II | | | | | | | | Part III | Part IV | Part V | Part VI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | SI | SII | SIII | SIV | SV | SVI | SVII | SVIII | | | | |
| 0. Full MA application | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| 1. Generic product | √ | | | | | | | ‡ | √ | √ | * | ∫ | √ |
| 2. Informed consent product | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| 3. Hybrid product | √ | † | | † | | | | † | √ | √ | √ | ∫ | √ |
| 4.a. Fixed combination product – new active substance | √ | ₸ | ₸ | ₸ | ₸ | ₸ | ₸ | √ | √ | √ | √ | √ | √ |
| 4.b. Fixed combination product – no new active substance | √ | | † | † | | | | ‡ | √ | √ | * | ∫ | √ |
| 5. Well established medicinal use product | √ | | | | | | | √ | √ | √ | √ | √ | √ |
| 6. Biosimilar product | √ | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |

√ - relevant/applicable
‡ - relevant only if "originator" product does not have an RMP and its safety profile is not published on CMDh website
* - relevant only when PAES was imposed for the "originator" product
∫ - statement of alignment of safety information in PI is sufficient
† - requirements based on risk proportionality principle, addressing new data generated or differences with the "originator" product
₸ - focus on the new active substance

Nov. 2021 Implementation of HaRP 05/11/2021 7

▶ *Guideline on good pharmacovigilance practices (GVP) Module V - Risk management systems (Rev 2) p. 30*

## Harmonisation why do we need? Goals and mission


- Mitigate risks

identify risk, characterize it and minimize it through appropriate measures

- Preserve benefits

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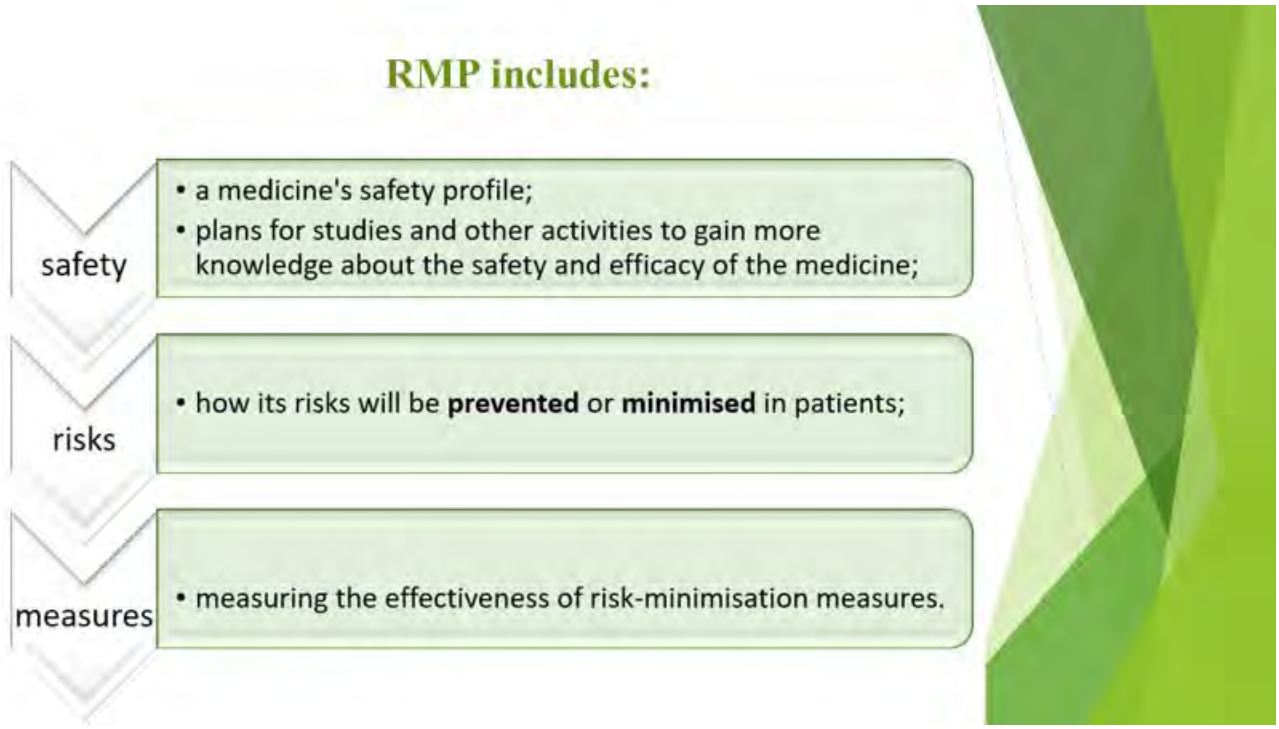
RMP includes:
safety
• a medicine's safety profile;
• plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine;
risks
• how its risks will be prevented or minimised in patients;
measures
• measuring the effectiveness of risk-minimisation measures.


In BG since 21.12.2012
ЗЛПХМ – Раздел II
Изисквания към документацията за издаване на разрешение за употреба
Чл. 27 (13) (изм. - ДВ, бр. 102 от 2012 г., в сила от 21.12.2012 г.) план за управление на риска с описание на системата за управление на риска, която заявителят ще въведе за съответния лекарствен продукт, заедно с резюме на плана;
Доп. Разпоредби
43а. (нова - ДВ, бр. 102 от 2012 г., в сила от 21.12.2012 г.) "План за управление на риска" е подробно описание на системата за управление на риска.
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Bulgarian Association for Drug Information (BADI)

## HaRP

- Who? The **Working Party on Pharmacovigilance Procedures Work Sharing Group** 2018
- Why? To improve harmonisation
- Mission - to **identify safety concerns** related to those same active substances and harmonize them with RMPs already in place.
- Two domains
  - Domain 1 - data exclusivity is about to expire
  - Domain 2 - data exclusivity has already expired

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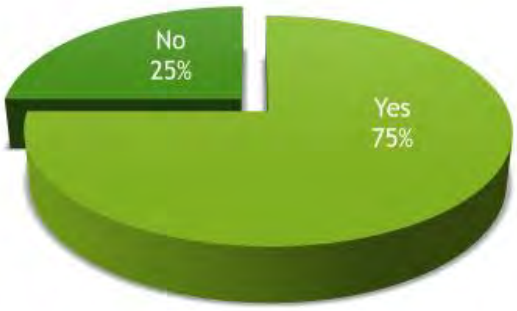
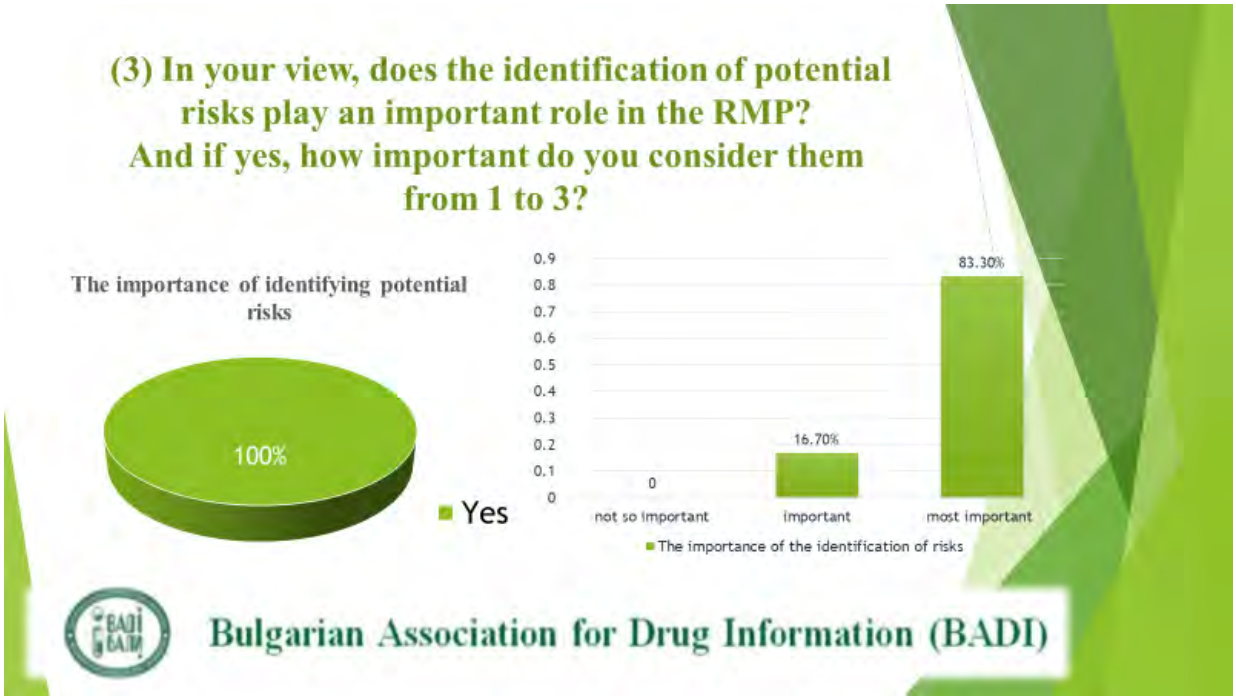
## (1) Upon reviewing the risk management guides, do you agree that they are sufficient to implement comprehensive risk management in accordance with regulatory requirements?




Bulgarian Association for Drug Information (BADI)


(2) Regarding risk management approach, have you implemented internally developed methodologies/best practices?
No
33.30%
Yes
66.70%
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%
70.00%


(3) In your view, does the identification of potential risks play an important role in the RMP? And if yes, how important do you consider them from 1 to 3?
The importance of identifying potential risks
100%
Yes
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
16.70%
83.30%
not so important
important
most important
The importance of the identification of risks
Bulgarian Association for Drug Information (BADI)

**(4) Do you think that the current risk management plan template by EMA and risk minimisation measures are sufficient to ensure a harmonized approach to your risk management activities?**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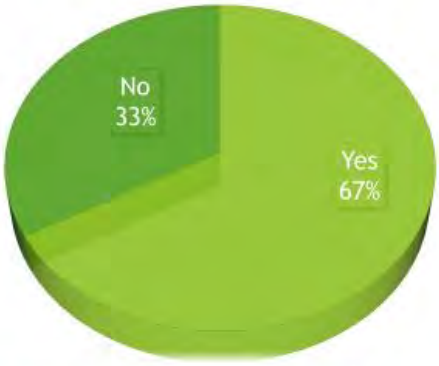
**(5) Do you believe that the process between regulators and pharmaceutical companies is sufficiently harmonized as according to the RMP? If no, why?**

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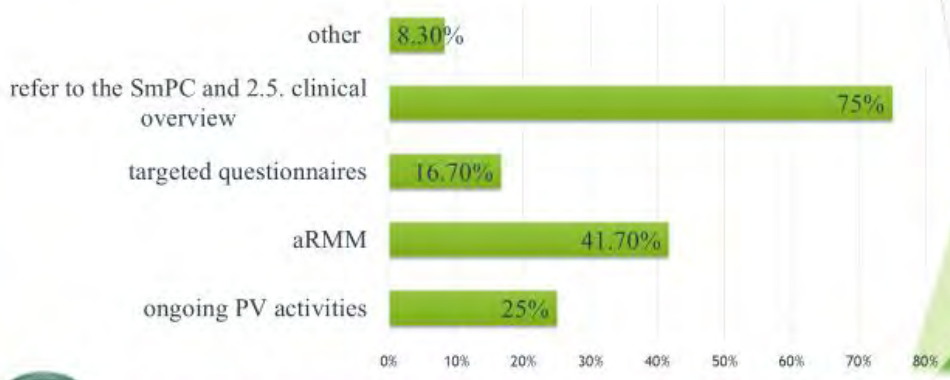
## (6) In your opinion, what are the main challenges or pain points involved in filling out, completing, and harmonizing your RMP

- Harmonization of aRMMs
- Not always easy to find the originator's one
- Collect all relevant information and thoroughly evaluate the risk and benefit profile
- Clear guidance
- Information for RMPs of reference product not publicly available

Bulgarian Association for Drug Information (BADI)

## (7) How are you dealing with cases when RMP for a generic medicine is missing / no information is available on the safety concerns of the reference medicinal product?

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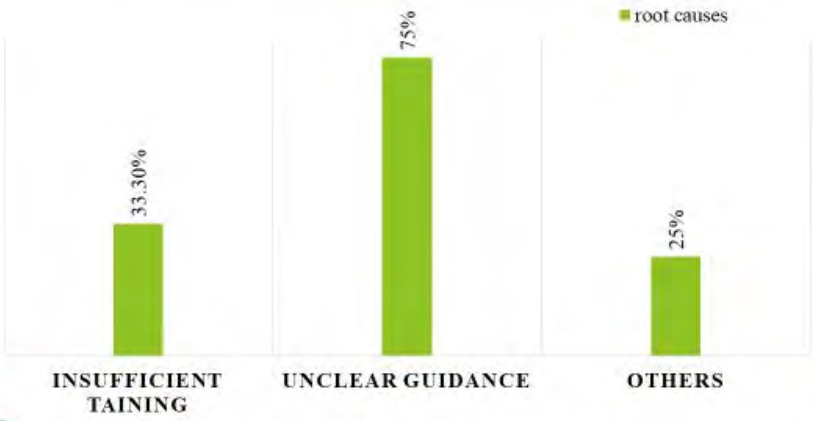
**(8) There are often different RMPs for the same active substance submitted by different procedures with different RMPs. Outcomes can vary for the same active substance and there can be proliferations of disharmonized RMS. In your opinion, is this a significant concern?**

**a significant concern**

- it is a concern, but they are rather normal for them

**Bulgarian Association for Drug Information (BADI)**

**(9) What are the main root causes that undermine the harmonization of the RMP?**




**Bulgarian Association for Drug Information (BADI)**

## (10) What are the main benefits that can be achieved by harmonizing the RMP?

- Improved patient care and greater confidence in threatening physicians
- Standards that are the same across the EU for the same active substance
- Improving safety and compliance through transparency
- Refrained from providing misleading information, identified some risks, recommended some dosages, followed all safety precautions
- for the same INN the RMP should be identical
- Publicly available clear information
- A streamlined guidance system, common activities, and a common cost - improve the assessment of drug-related risks.
- It will not be necessary to write RMPs, since we will refer to the original RMPs

Bulgarian Association for Drug Information (BADI)

## Problem points and suggestions for improvements

**Problems**

- Lack of publicity available RMP of the reference medicinal product
- No register of all RMP of one place
- No clear mechanism of harmonisation of the process
- No national support and register of the RMP of the medicinal products

**Possible solution**

- **Clear and well-structured register of reference medicinal products on the website of EMA and national health authorities** to improve efficiency of new drug development and registration processes, to promote public health, prevent duplication of clinical trials in humans and minimize the use of animal testing without compromising safety and effectiveness
- **The development and implementation of harmonized guidelines and standards**

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## Legal basis / guidelines

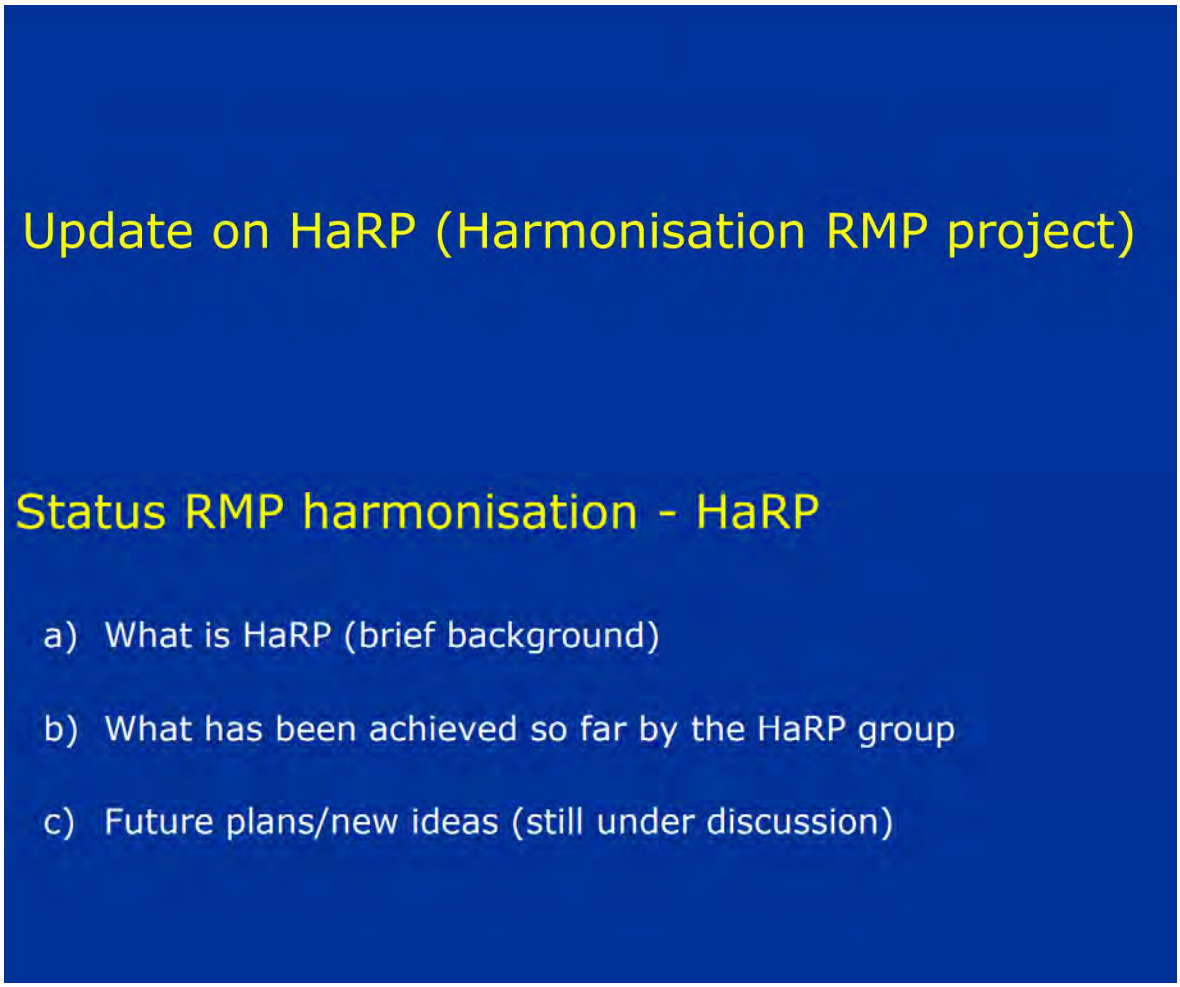
- Dir 2001/83/EC [5] article 1, article 8(3)(iaa), article 22c, article 104 (3) & (e), article 104a, article 106 (c), article 107j (3), article 107k, AMC (1) [illegible] & (37), paragraph 62 and paragraph 63b
- Reg 726/2004 [6] article 6(1), article 9(4)(c), (ca), (cb), (cc), article 10a(1), article 14a, article 15, article 21, article 26 and article 28a and IR 520 [illegible] and Annex I.
- GVP Module V [17] addresses this topic and provides clear instructions how to handle this process
- Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness [illegible] 2)
- GVP V and RMP Template Rev2 in March 2017
- Guidance on the format of the risk management plan (RMP) in the EU – in integrated format
- RMP template since 10/2013 RMP for all new authorization applications [Dir. 2001 83 Art
- Regulation (EU) No 1235/2010 of the European parliament and of the council of 15 December 2010
- Commission implementing regulation (IR) (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation [illegible] No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council:
- Regulation (EC) No 1901/2006 Article 34(2):
- Regulation (EC) No 1394/2007 Article 14(2)
- Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for [illegible] products for human use and veterinary medicinal products
- GVP Module XVI and GVP Module XVI Addendum I in conjunction with educational materials.
- Europe – Annex 2: HaRP (Harmonisation of RMP Project) – methodology of harmonising RMPs, April 2021 CMDh/402/2019, Rev. 1

## Thank you for your attention !!!

## Appendix II – CMDh presentation (1) update on HaRP, January 2021


update on HaRP

29 January 2021



## a) What is HaRP

Legislation requirements on RMPs:
burden both for Marketing Authorisation Holders and National Competent Authorities!


HaRP = Harmonisation of RMPs Project

Aim of the project:

- to harmonise the Risk Management Plans (RMPs)*
- of products with the same active substances
- for which marketing authorisations have already been granted
- with different RMPs in place

## Step one: CMDh List of safety concerns published on CMDh website

- The List of Safety Concerns published on the CMDh website has also shown:

⇨ inconsistencies within generic products as well as with the reference product

⇨ inconsistencies among products containing the same actives

## Step two: 2 HaRP domains

**Domain 1**

Developing up-to-date RMPs of the innovator product for active substances for which the data exclusivity of the reference product will expire soon (prospective approach)

(Domain 1 not yet started)

**Domain 2**

- Clean-up (harmonisation) of the Excel List of safety concerns as published on the CMDh website (first step for substances with no reference product or with reference product without an RMP in place)

## Step three: RMP PeerReview Group (RMP PRG)

- RMP PRG set up for (initially) especially domain 2
- Chaired by NL
- Composed by around 20 members, mainly experienced RMP assessors from MSs
- Started in April 2018: monthly meetings via TC to date

# b) What has been achieved so far by the HaRP group

## What has been done so far by the RMP PRG

- 2 pilots/ waves of preparing HaRP ARs haven been finalised and ARs have been published in July 2019 and May 2020
- Evaluation of 2 pilots/waves plus suggestions how to proceed
- Several HaRP ARs finalised which still need to be sent out to stakeholders for input

## Assessment reports finalised and published IN JULY 2019 (cover note also updated)

Almotriptan
Alprazolam
Amlodipine
Bemiparin sodium
Bisoprolol
Calcium carbonate
Cetirizine
Colchicine
Donepezil
Etoposide
Fluorouracil
Haloperidol
Hyoscine butylbromide
Macrogol 3350, Sodium Chloride, Sodium Hydrogen Carbonate, Potassium Chloride
Melphalan
Menotrophin
Methylphenidate*
Montelukast
Pantoprazole
Rupatadine Fumarate
Testosterone
Vinorelbine

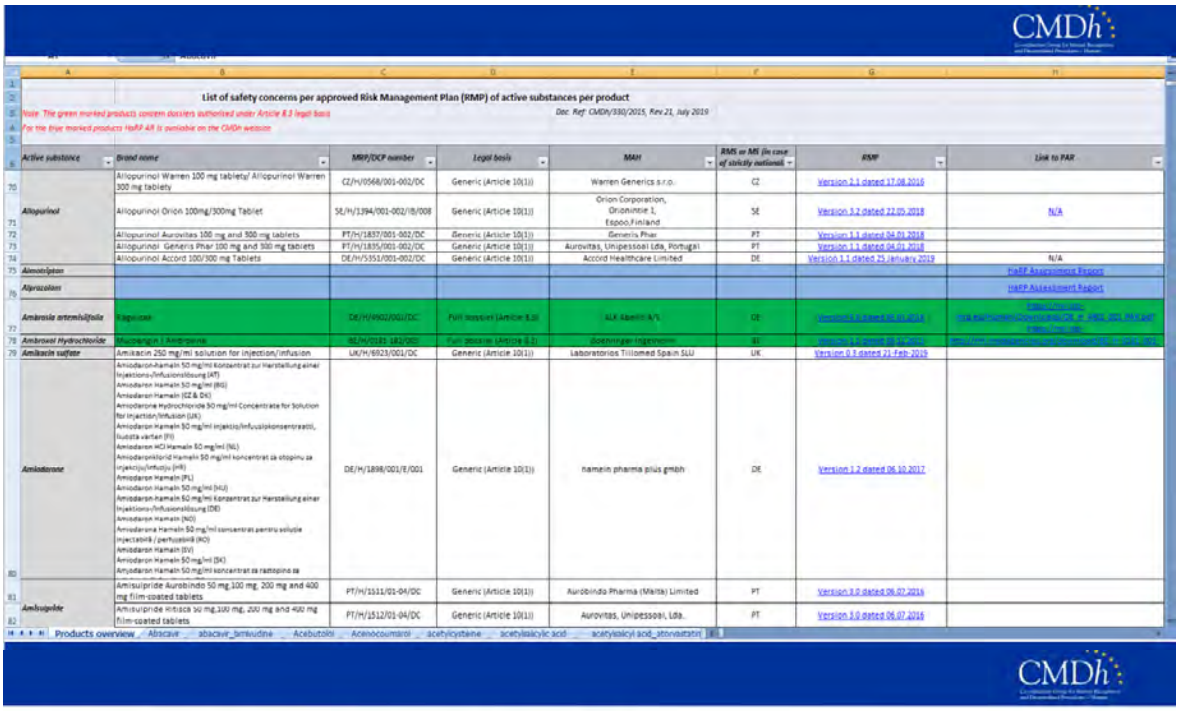

* Harmonised during PSUSA methylphenidate

## Assessment reports finalised and published IN MAY 2020

aciclovir
cineolum
diazepam
dienogest/ethinylestradiol*
diosminum
doxazosin
ethosuximide
fexofenadine
gemcitabine
meropenem
thiamazol
trospium chloride
zolpidem

*(also applicable to the combined oral contraceptive: combinations of the progestogens chlormadinone (CMA), desogestrel (DSG), dienogest (DNG), drospirenone (DRSP), etonogestrel (ENG), gestodene (GSD), norelgestromin (NGMN), norgestimate (NGM) or nomegestrol (NOMAC)) with ethinylestradiol (EE) or with estradiol (E2))


11



List of safety concerns per approved Risk Management Plan (RMP) of active substances per product

Doc. Ref. CMDh/330/2015, Rev.21, July 2019

| Active substance | Brand name | MRP/DCP number | Legal basis | MAH | RMS or MS (in case of strictly national) | RMP | Link to PAR |
|---|---|---|---|---|---|---|---|
| Allopurinol | Allopurinol Warren 100 mg tablets/ Allopurinol Warren 300 mg tablets | CZ/H/0568/001-002/DC | Generic (Article 10(1)) | Warren Generics s.r.o. | CZ | Version 2.1 dated 17.08.2016 | |
| | Allopurinol Orion 100mg/300mg Tablet | SE/H/1394/001-002/IB/008 | Generic (Article 10(1)) | Orion Corporation, Orionintie 1, Espoo,Finland | SE | Version 3.2 dated 22.05.2018 | N/A |
| | Allopurinol Aurovitas 100 mg and 300 mg tablets | PT/H/1837/001-002/DC | Generic (Article 10(1)) | Generis Phar | PT | Version 1.1 dated 04.01.2018 | |
| | Allopurinol Generis Phar 100 mg and 300 mg tablets | PT/H/1835/001-002/DC | Generic (Article 10(1)) | Aurovitas, Unipessoal Lda, Portugal | PT | Version 1.1 dated 04.01.2018 | |
| | Allopurinol Accord 100/300 mg Tablets | DE/H/5351/001-002/DC | Generic (Article 10(1)) | Accord Healthcare Limited | DE | Version 1.1 dated 25 January 2019 | N/A |
| Almotriptan | | | | | | | HaRP Assessment Report |
| Alprazolam | | | | | | | HaRP Assessment Report |
| Amarosia artemisiifolia | | DE/H/0902/001/DC | Full dossier (Article 8.3) | ALK-Abelló A/S | DE | | |
| Ambroxol Hydrochloride | | DE/H/0181-182/DC | Full dossier (Article 8.3) | Boehringer Ingelheim | DE | | |
| Amikacin sulfate | Amikacin 250 mg/ml solution for injection/infusion | UK/H/6923/001/DC | Generic (Article 10(1)) | Laboratorios Tiltomed Spain SLU | UK | Version 0.3 dated 21 Feb 2016 | |
| Amiodarone | Amiodaron-hameln 50 mg/ml Konzentrat zur Herstellung einer Injektions-/Infusionslösung (AT)<br>Amiodaron Hameln 50 mg/ml (BG)<br>Amiodaron Hameln (CZ & DK)<br>Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion (UK)<br>Amiodaron Hameln 50 mg/ml injekcio/infuzalpkoncentratol, tiszta vartan (FI)<br>Amiodaron HCl Hameln 50 mg/ml (NL)<br>Amiodaronklorid Hameln 50 mg/ml koncentrat za otopinu za injekciju/infuziju (HR)<br>Amiodaron Hameln (PL)<br>Amiodaron Hameln 50 mg/ml (HU)<br>Amiodaron-hameln 50 mg/ml Konzentrat zur Herstellung einer Injektions-/Infusionslösung (DE)<br>Amiodaron Hameln (NO)<br>Amiodarona Hameln 50 mg/ml sonsentrat pentru solutie injectabilă / perfuzabilă (RO)<br>Amiodaron Hameln (SV)<br>Amiodaron Hameln 50 mg/ml (SK)<br>Amjodaron Hameln 50 mg/ml koncentrat za raztopino za | DE/H/1898/001/E/001 | Generic (Article 10(1)) | hameln pharma plus gmbh | DE | Version 1.2 dated 06.10.2017 | |
| Amisulpride | Amisulpride Aurobindo 50 mg,100 mg, 200 mg and 400 mg film-coated tablets | PT/H/1511/01-04/DC | Generic (Article 10(1)) | Aurobindo Pharma (Malta) Limited | PT | Version 3.0 dated 06.07.2016 | |
| | Amisulpride Hitisca 50 mg,100 mg, 200 mg and 400 mg film-coated tablets | PT/H/1512/01-04/DC | Generic (Article 10(1)) | Aurovitas, Unipessoal, Lda. | PT | Version 3.0 dated 06.07.2016 | |

Products overview | Abacavir | abacavir_lamivudine | Acebutolol | Acenocoumarol | acetylcysteine | acetylsalicylic acid | acetylsalicyl acid_atorvastatin

## Evaluation 2 pilots: wave I and II

- document reviewing the status of the art of the HaRP project and
- containing the proposals to speed up the HaRP assessment process

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## Evaluation 2 pilots: wave I and II: positive aspects

- The need for removing inconsistencies between LoSCs approved for products with the same substances acknowledged by stakeholders
- Generally agreed that harmonization will reduce the burden of preparing RMPs (by MAHs) as well as assessing RMPs (by NCAs)
- Main achievement: the proposed methodology of harmonising and cleaning-up RMPs based on GVP V (Rev 2) is proven to be feasible and is increasingly accepted across stakeholders and NCAs
- The increasing acceptance of having an "empty" RMP is the result of intensive collaboration between HaRP members (and assessors in NCAs)and can be considered a success

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## Evaluation 2 pilots: wave I and II: draw backs


- time consuming process!
- cleaning up RMPs one by one for each substance, requires several rounds to reach consensus across the various stakeholders and, ultimately, adoption by CMDh.
- almost 2 years after the initiation of the project, 33 substances harmonised so far
- considering that several hundred substances are eligible for harmonisation, it will take years before at least a significant proportion of substances will be harmonized

**need to change the current work-up for harmonisation**

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## c) Future plans/new ideas (still under discussion)


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## Ideas to speed up the procedure under discussion

'Regular' process: harmonisation assessment as performed during the pilot waves

- some modifications of the process suggested to reduce the need of several round of assessment in the HaRP group
- A newly approved (empty) LoSCs can be used for further harmonisation purposes (some HaRP ARs have already prepared by the HaRP group

Grouped assessment of substances based on class, pharmacological similarities etc.. with overlapping safety concerns which could be assessed at the same time

- appropriateness to be verified


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## Maintenance of existing HaRP ARs

Maintenance. How to keep harmonised lists up-to-date?

list of regulatory procedures that will impact RMPs considered

still to be defined how and by whom outcomes of relevant procedures could be monitored in a systematic manner

**UNDER DISCUSSION.....**


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## Take home messages

HaRP project can only be successful if all stakeholders will collaborate and commit

- to actively participate in the project
- to utilise the final agreed list of safety concerns/ARs both in the building

and the assessment of RMPs in EU!


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## Appendix III – CMDh presentation (2) Status on the CMDh HaRP project, January 2019

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

Status on the CMDh HaRP project

30 January 2019

### What we will see

1. Update on the status of the HaRP Project

2. Next steps/challenges

## HaRP = **Ha**rmonisation of **RMP**s

Aim of the project:

to harmonise the Risk Management Plans of the same active substances for which marketing authorisations have already been granted with different RMPs in place

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## HaRP - Project proposal: 2 domains

Domain 1

Developing up-to-date RMPs for the innovator product for active substances for which the data exclusivity of the reference product will expire soon (prospective approach)

Domain 2

Clean-up of the Excel List of safety concerns as published on the CMDh website

(first step for substances with no reference product or with reference product without an RMP in place)

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## 1. Update on the status of the HaRP Project (Domain 2 of the project)

## RMP PeerReview Group (RMP PRG) (1/2)

- RMP PRG set up for (initially) especially domain 2
- Chaired by NL
- Twenty-seven volunteers (CMDh members/assessors and PRAC members) appointed!
- Start in April 2018: 7 meetings via TC to date

**HaRP Group**

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## RMP PeerReview Group (RMP PRG) (2/2)

What has been done so far:

- selection of a first set of active substances to start a pilot
- methodology/algorithm agreed for "old" well established substances under domain 2 of the project
- template suitable for the assessment procedure agreed
- AR (assessment reports)/proposals for harmonised safety concerns finalised for 22 substances

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## Update: 22 assessment reports produced by the HaRP group

almotriptan
alprazolam
amlodipine
bemiparin
bisoprolol
calcium carbonate
cetirizine
colchicine
donepezil
etoposide (for infusion)
fluorouracil (systemic use)
gemcitabine
haloperidol (oral solution)
hyoschine butylbromide
macrogol 3350, sodium chloride, sodium hydrogen carbonate, potassium chloride
melphalan
menotrophin
montelukast
pantoprazole
rupatadine
testosterone (transdermal/topical)
vilnorebine (for infusion)

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## 2. Next steps/challenges

## Actions from CMDh/NCAs

- ✓Assessment reports sent to MSs for comments/agreement
- ✓Comments awaited by end of January 2019
- ✓Products assessed: possible incomplete picture of existing RMPs not included in CMDh list of safety concerns?
- ✓Assessment reports sent to members CMDh ad hoc WP on RMP Initiatives (participation of representatives of EFPIA/ Medicines for Europe/AESGP/Eucope) for **joint** comments/input

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## Actions – Pharmaceutical industry


- ✓ To date: the CMDh list contains 453 active substances (1289 products). Not known if also innovator products of substances included in the list have an RMP
- ✓ Request to Industry to provide information on existing RMPs for innovator products for which the active substance is included in the list of safety concerns published by CMDh
- ✓ Provide feedback on first assessment reports circulated by mid February

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## Challenges (1/2)

- ✓ To consider to include also "old" substances in domain 2 where the innovator product has an RMP (which is not harmonised yet): to develop a procedure to enable clean-up of safety concerns of substances for NAPs (where the innovator product has an RMP in place)
- ✓ To work on a procedure together with PRAC on RMPs involving CAPs (centrally authorised products): to develop a procedure to enable clean-up of safety concerns of substances with a CAP [either innovator or generic] (involving PRAC and MAHs)

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## Challenges

- ✓How to involve/reach all MAHs (i.e. MAHs not part of Trade associations)
- ✓To agree on a procedure for Industry (MAHs) ▶ input on assessment reports agreed by the HaRP Group
- ✓To work further on a procedure to finalise and publish the ARs
- ✓Once harmonised: to keep the harmonisation reached!

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CMDh

**HaRP project can only be successful if all stakeholders will commit to the final agreed list of safety concerns/ARs!!**

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## Erklärung

Hiermit erkläre ich, Rumyana Atanasova, an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Frankfurt am Main, 24.12.2021

*(Unterschrift)*

*Rumyana Atanasova*