INVESTIGATING ADDITIONAL RISK MINIMISATION MEASURES FOR MEDICINES IN THE EUROPEAN UNION

Reynold D.C. Francisca

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INVESTIGATING ADDITIONAL RISK MINIMISATION MEASURES FOR MEDICINES IN THE EUROPEAN UNION

Onderzoek naar additionele risicominimalisatiemaatregelen voor geneesmiddelen in de Europese Unie

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Reynold Daniel Crisanto Francisca
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Erasmus University Rotterdam

PROMOTIECOMMISSIE

Promotor:	Prof.dr. M.C.J.M. Sturkenboom
Overige leden:	Prof.dr. P.G.M. Mol Prof.dr. A.K. Mantel-Teeuwisse Prof.dr. B.H.Ch. Stricker
Copromotoren:	Dr. S.M.J.M. Straus Dr. I.M. Zomerdijk

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R.D.C. Francisca
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INTRODUCTION

Drug safety monitoring has evolved since 1848, when a young girl died after receiving chloroform as an anaesthetic. In response to her death, as well as safety warnings by other surgeons, *The Lancet* Journal established a commission to investigate the safety of chloroform particularly and anaesthesia in general. The commission published its findings in 1893, based on reports of anaesthesia-related deaths, as well as recommendations to promote safe use of chloroform (1). Since then, advancements in the field of drug safety monitoring have been preceded by drug safety issues. One such issue was caused by the Elixer Sulfanilamide, which caused 107 deaths in the United States (US) due to use of the toxic diethylene glycol as a solvent rather than ethanol. This led to the signing into law of rigorous amendments to the US Federal Food, Drug and Cosmetic Act in 1938, which mandated safety testing of medicines (2). The best-known drug safety issue in history was thalidomide, in 1961. It was used as a sedative, hypnotic and anti-emetic for pregnant women and caused congenital anomalies in over 10,000 children worldwide. Following the thalidomide disaster, drug safety monitoring initiatives were setup in multiple countries, including the European Commission directive 65/65, as well as internationally through the World Health Organisation's (WHO) Programme for International Drug Monitoring which was established in 1968 (3-5).

The term "pharmacovigilance" was coined in the 1970s and to this day is described by the WHO as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems". An adverse effect, or more specifically, adverse drug reaction (ADR), was defined as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function". Therefore, the scope of pharmacovigilance was initially limited to the use of medicines in specific conditions (e.g., in the approved doses and for the approved indications). However, that scope has been extended to include other situations that are also relevant to the safe and effective use of medicines. Examples of these situations are medication errors, off-label use, misuse and abuse of medicines, issues with the quality of the medicines and lack of efficacy (5). This is best illustrated by the definition of ADR in the pharmaceutical legislation for medicinal products for human use currently in effect in the European Union (EU), which is "a response to a medicinal product which is noxious and unintended" (6, 7). These changes have been driven by observations that ADRs are a source of considerable morbidity and mortality in the EU: around 3.5-5% of hospitalisations are due to ADRs, and between 5-10% of hospitalised patients experience an ADR during their hospitalisation (8, 9). In addition, medical errors in general and medication errors in particular are a common cause of preventable harm (10, 11)

Broader scope aside, the EU pharmaceutical legislation currently in effect has incorporated many important changes to operational pharmacovigilance in the EU, leading it to be dubbed "the pharmacovigilance legislation" by the European Medicines Agency (EMA). EMA describes that the pharmacovigilance legislation aims to reduce the number of ADRs in the EU through better data collection, rapid and robust assessment of safety-related issues, effective regulatory action, patient empowerment and transparency (12). Moreover, there has been a shift from the reactive nature of pharmacovigilance in the previous decades, to a more proactive approach to optimising the balance of benefits and risks throughout the lifecycle of a medicinal product. At the root of this shift is the guideline on pharmacovigilance planning by the International Council for Harmonisation (ICH), formerly the International Conference for Harmonisation, published in 2004 (13). In the EU, the ICH recommendations were incorporated into the pharmaceutical legislation in 2005, making the Risk Management Plan (RMP) mandatory part of the authorisation dossier of new innovative medicines. The pharmacovigilance legislation of 2012 has made the RMP mandatory for each new drug application (e.g. including generic, hybrid or biosimilar applications and fixed-dose combinations) (6, 7, 14). The RMP is intended to facilitate early identification, monitoring and minimisation of risks related to the use of a medicinal product and to fill gaps in knowledge. To this end, the RMP consists of three key components.

First is the safety specification, in which the available safety data for the medicinal product is described, with a focus on those safety concerns that require further characterisation. These safety concerns are listed as important identified risks, important potential risks and missing information; the definition of these concepts can be found in table 1 (14).

Table 1: Definitions of safety concern categories in the Risk Management Plan

Safety concern category	Definition
Important identified risk	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest and that could have an impact on the risk-benefit balance of the product or have implications for public health
Important potential risk	An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed, and that that could have an impact on the risk-benefit balance of the product or have implications for public health
Missing information	Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant.

Note from the definitions that ,in this context, the term “risks” is not limited to ADRs (e.g., events for which there is sufficient evidence of an association with the medicinal product) but also includes clinically relevant events or situations that may impact the benefit-risk balance of the medicine.

Second is the pharmacovigilance plan, in which the activities are described that are intended to further characterise the important identified and potential risks and missing information. Spontaneous reporting of suspected adverse event remains the cornerstone of pharmacovigilance since it allows for the rapid recognition of safety signals, particularly those related to events that either rare or have an unusual presentation (15-17). However, studies may be required to further characterise certain safety concerns. These studies may range from non-clinical studies to observational clinical studies to randomised controlled trials (18).

Third is the risk minimisation plan, which describes the measures to minimise the risks. Certain risk minimisation measures are applied to all medicinal products. These measures include:

- the prescription status, i.e., whether a prescription is needed or the medicine can be purchased over the counter
- the package design including pack size and colouring
- the name of the medicinal product, particularly important in light of mix-ups due to similar medicine names
- the Summary of Product Characteristics (SPC), which is the basis of information for healthcare professionals to use the medicinal product safety and effectively (19)
- the Package Leaflet, which is drafted in accordance with the SPC and contains information for the user of the medicinal product (i.e., the patient or caregiver)

For the majority of medicinal products, these “routine” measures will adequately minimise the risks. However, some medicinal products may be associated with serious risks that may not be sufficiently minimised by routine measures. Additional risk minimisation measures (aRMM) aim to ensure that the benefits of these products outweigh their risks (14).

ARMMs aim to improve patient selection, timely recognition and adequate management of ADRs and prevention of medication errors through delivery of additional information on the safe and effective use of the medicine, that is supplementary to the safety information already provided in the product information. Moreover, aRMMs may constitute more stringent measures that may (indirectly) restrict patient access to the medicine by lest certain conditions are met. The definitions of the different types of aRMMs can be found in table 2 (20). A medicinal

product may require more than one type of aRMM to effectively minimise one or multiple risks, or reach different target groups.

Table 2: Definitions of the different types of additional risk minimisation measures

Type of aRMM	Definition
Educational programmes	Educational programmes are based on targeted communication with the aim to supplement the information in the Summary of Product Characteristics and Package Leaflet. They can be aimed towards both healthcare professionals and patients or caregivers.
Controlled access programme	A controlled access programme consists of interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimisation measures, i.e., the legal status.
Controlled distribution system	A controlled distribution system refers to the set of measures implemented to ensure that the stages of the distribution chain of a medicinal product are tracked up to the prescription and/or pharmacy dispensing the product.
Pregnancy prevention programme	A pregnancy prevention programme (PPP) is a set of interventions aimed at minimising pregnancy exposure during treatment with a medicinal product with known or potential teratogenic effects.
Direct Healthcare Professional Communication (DHPC)	A communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorisation holder or by a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product.

The need for aRMMs is assessed at the time of authorisation, but may change during the product life cycle as new safety information becomes available after authorisation: aRMMs may become required for medicines after authorisation if new risks are identified, or they may be reduced or discontinued if they are no longer required or their recommendations may become part of clinical practice (20).

Example box 1: sodium valproate as a case study of the role of aRMMs and need for careful evaluation of effectiveness in the life cycle management of medicines

Sodium valproate
- **Year of approval: 1968**
- **Approved indications: treatment of epilepsy, treatment of bipolar disorder and prevention of migraine attacks**
- **Risks requiring aRMMs: congenital malformations (10%) and neurodevelopmental disorders such as autism spectrum disorders and attention deficit/hyperactivity disorder (30-40%) in babies with in utero exposure**

European Medicines Agency safety review 2014 conclusion
- **Valproate should not be used in women of childbearing potential (WCBP) unless other medicines are ineffective or aren't tolerated**
- **WCBP should use effective contraception during valproate treatment and regular treatment review should take place**
- **Use of valproate for preventing migraine in pregnant women became a contraindication**

ARMMs were introduced in the form of educational materials to improve awareness about these risks among both prescribers and patients and to aid in informed decision-making whether to start valproate or not, and avoid use of valproate during pregnancy. These materials included the following:
- **guide for prescribers with the latest data on valproate-associated malformations and developmental issues as well as key actions to mitigate the risks including contraceptive measures**
- **a patient booklet to inform women of childbearing potential of the risk of malformation or developmental delay of children exposed to valproate in utero and to stress the importance of birth control measures**
- **an acknowledgement of risk form, with a checklist for both prescriber and patient to document that starting valproate was an informed decision**
- **a drug utilisation study and a prescriber survey to monitor the effectiveness of these measures**

Evaluation studies' results
- **the materials reached only a small proportion of the targeted healthcare professionals.**
- **healthcare professionals whom received them appeared better informed regarding the risks associated with in utero exposure to valproate**
- **the materials had limited impact on valproate prescribing**
- **pregnancies exposed to valproate still occur (21-23).**

A new comprehensive review of the safety of valproate-containing medicines by EMA was triggered by these results.

European Medicines Agency safety review 2018 updated measures
- **use of valproate during pregnancy for the treatment of bipolar disorder became a contraindication and epilepsy treatment during pregnancy became contraindicated unless there is no suitable alternative treatment available**
- **a pregnancy prevention programme (PPP) was introduced and WCBP should only use valproate when the conditions of the PPP are met, which include effective contraception; pregnancy test before start and periodically; treatment initiation and annual review by specialist; counselling patients about valproate risks and contraceptive measures. educational materials for healthcare providers and patients have been revised, a visual warning on the outer packaging of valproate-containing medicines has been added and the patient card has been attached to the outer packaging.**
- **A drug utilisation study, a patient survey and a healthcare professional survey were imposed to monitor effectiveness of these measures**

Despite aiming to improve patient safety, aRMMs may pose a burden on the health care system and may have other consequences (e.g., financial consequences or restricted patient access to medicines) (24, 25). ARMMs should therefore be risk proportionate, they should be designed with a clear objective and actionable goals

and their distribution should be aimed at reaching relevant prescribers. Importantly, the effectiveness of aRMMs should be evaluated to determine whether the aRMMs are effective and to identify potential areas of improvement (20).

Studies have shown that around 30% of medicines approved in the EU before the pharmacovigilance legislation came into force had aRMMs at the time of authorisation (26, 27). Since the EU's pharmacovigilance legislation introduced a broader scope of pharmacovigilance and made the RMP mandatory for all medicines, we theorised that it might have an impact on the proportion of medicines with aRMMs at the time of authorisation. No descriptive data regarding changes to aRMMs in the EU during the life cycle of medicines was available.

Two studies have described the risks of products with aRMMs, though their findings were not congruent (26, 28). Moreover, we couldn't identify more in-depth analyses of the safety the risks associated with medicines approved in the EU with or without aRMMs or of factors that predict the need for aRMMs.

Many effectiveness evaluation studies of aRMMs have been published in recent years, as well as some reviews of aRMMs effectiveness evaluation studies (29-32). However, evaluation of effectiveness is particularly challenging for medicines with aRMMs at the time of authorisation (33). While the reviews provide an insight in how effectiveness of aRMMs is evaluated in general, we were couldn't discern whether effectiveness is evaluated differently for medicines with aRMMs at the time of authorisation.

Objective of this thesis

The objective of this thesis is to gain a deeper understanding of additional risk minimisation measures, including the role they play in the life cycle management of medicines.

Outline of this thesis

For the first part of this thesis, we focus on medicines at the time of authorisation. In **Chapter 2**, we provide an overview of the medicines approved with aRMMs from 2010 to 2015. We also investigate the effect of the EU's pharmacovigilance legislation 2012 on the proportion of medicines approved with aRMMs. In **Chapter 3**, we dive further into the safety concerns of the medicines approved between 2010 and 2015. We provide an overview of the safety concerns with and without aRMMs, and attempt to identify factors that predict the need for aRMMs. In **Chapter 4**, we focus on medication errors and describe in greater detail the medication error

related safety concerns at the time of authorisation, routine measures as well as aRMMs to minimise medication error risks and the evaluation of effectiveness of these measures.

In the second part of this thesis, we shift our focus to the post-authorisation phase. In **Chapter 5**, we investigate the probability of introduction of aRMMs for medicines authorised without aRMMs as well as discontinuation of aRMMs for medicines authorised with aRMMs. We also provide an overview of the reasons for introduction or discontinuation. In **Chapter 6**, we describe the methods utilised for evaluation of effectiveness of aRMMs specifically of medicines authorised with aRMMs, as well as the available conclusions of regulatory assessment and subsequent actions regarding the aRMMs.

In the third part of this thesis, we explore the implications of the EU Regulation (EU) 2017/745 on medical devices intended to strengthen the post-authorisation surveillance of medical devices in **Chapter 7**. We touch upon similarities to and lessons learned from pharmacovigilance.

Finally, this thesis ends with a general discussion on our main findings and implications for the future in the area of aRMMs in **Chapters 8 and 9.**

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ADDITIONAL RISK MINIMISATION MEASURES AT THE TIME OF AUTHORISATION

Chapter 2

Measuring the impact of the 2012 European pharmacovigilance legislation on additional risk minimization measures

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ABSTRACT

Aims: Additional risk minimization measures (aRMMs) may be needed to ensure that the benefits continue to outweigh the risks for medicines associated with serious risks. Prior research showed an increasing trend in medicines with aRMMs. We assessed whether the European pharmacovigilance legislation may have impacted the number and type of aRMMs.

Methods: We included new active substances approved between January 1st 2010 and December 31st 2015. Information extracted from the summary of the Risk Management Plan at the time of licensing included date and type of marketing authorization, presence and type of aRMMs. We tested for differences using Pearson's χ^2 test and segmented Poisson regression.

Results: We identified 231 medicines approved during the study period, of which 30% had aRMMs at the time of licensing. ARMMs were in place for 38% of medicines before July 2012 and for 28% after ($p = 0.16$). Segmented Poisson regression did not show changes in trend or level of medicines with aRMMs.

Discussion: During the study period, no significant differences in the proportion or trend of products with aRMMs at the time of licensing before and after the pharmacovigilance legislation were identified.

INTRODUCTION

At the time of licensing of a medicinal product, there is relatively limited information with regards to its safety. This is because studies in the development program often have a relatively small number of subjects, relatively short follow-up and are very restrictive with regards to co-morbidity, co-medication, age, sex and ethnicity [1]. Risk management planning has become an integral tool to optimize the benefit-risk balance of medicinal products throughout their life cycle. Risk management systems have been implemented by regulators to facilitate identification, monitoring and minimization of risks [2, 3].

The European Union Risk Management Plan (EU-RMP) is a mandatory part of the authorization of medicinal products in the European Union (EU). The concept was first introduced in the EU in 2005. The EU-RMP describes the important risks and missing information (safety specification), the activities intended to further characterize the safety profile (pharmacovigilance plan) and the measures to minimize the risks (risk minimization plan) [1, 4].

Certain risk minimization measures are routine measures, applicable to all products, such as the Summary of Product Characteristics, the Package Leaflet, package design, pack size, and prescription status. Some products however may be associated with serious risks that may not be sufficiently minimized by routine measures. To ensure that the benefits of these products continue to outweigh the risks, additional risk minimization measures (aRMMs) may be needed [1, 5]. ARMMs aim for example to facilitate adequate patient selection, timely recognition of adverse drug reactions, to provide additional advice on appropriate management of adverse drug reactions or to prevent medication errors. ARMMs range from communication regarding risks beyond the product information to restriction of drug prescribing or dispensing [5].

Several studies have investigated the proportion of products for which additional measures have been required [4, 6, 7]. These studies have shown an increase in the number and proportion of products approved with aRMMs in Europe since the introduction of the EU-RMP. Similarly, a study into the United States' version of aRMMs, Risk Evaluation and Mitigation Strategies (REMS), has also shown an initial increase in the proportion of products of products approved with REMS since the introduction in 2007. This increase was followed by a decrease in 2011, which the authors attributed to amendments in the guidance documents of the Food and Drug Administration [8].

ARMMs may pose additional burden on all stakeholders, such as a financial burden for pharmaceutical companies, although we have found only one study that has

investigated this burden in the US setting [9]. However, the perceived administrative burden for the health care system is of particular importance: the time, effort and paper work involved in complying with aRMMs should therefore remain risk proportionate.

In July 2012, substantial amendments of the EU pharmaceutical legislation and guidance documents came into force that aimed to strengthen the proactive approach to pharmacovigilance [2, 3, 10, 11]. These amendments introduced justification of the need for aRMMs, in contrast to the previous guidance where justification to not have aRMMs was required; suggesting the need for aRMM as default. Furthermore, the new legislation introduced the legal obligation to evaluate the effectiveness of the measures to minimize risks. To our knowledge, no studies have objectively assessed the impact of the new legislation and guidance on the proportion of products approved with aRMMs to date. In this study, we aim to assess the impact of the pharmacovigilance legislation on the frequency and type of aRMMs.

METHODS

Data sources and setting

The European Medicines Agency publishes European Public Assessment Reports (EPARs) for all medicinal products authorized through the centralized procedure on www.ema.europa.eu, which are updated throughout the product life cycle. The EPAR includes the product information, annexes of the marketing authorization (MA) and a summary of the initial assessment at the time of licensing, including a summary of the EU-RMP. If aRMMs are a part of the MA, this also reflected in annex IID of the MA, "Conditions and restrictions with regards to the safe and effective use of the medicinal product".

Drugs of interest

We included medicinal products authorized in the EU through the centralized procedure between January 1st 2010 and December 31st 2015, which were still authorized on January 1st 2016. Products licensed through generic applications were not considered new active substances and were excluded. Hybrid applications involve generic medicines that differ from the reference product in strength, route of administration or indication. These products were also excluded. Products that were subject of multiple or duplicate applications during the study period were only counted once. Biosimilar applications were included since these are required to be similar rather than identical to the reference product.

Outcome and covariates

For all products included in this study, the following information was extracted from the EPARs: active substance, Anatomical Therapeutic Chemical (ATC) classification, date and type of MA, aRMMs (yes/no) and the type of aRMMs. Products could have more than one type of aRMM.

The summary of the EU-RMP and annex II of the MA were reviewed to identify if aRMMs were applicable at time of licensing and to obtain the details on the type the aRMMs. We categorized aRMMs in accordance with GVP module XVI: Risk minimization measures: selection of tools and effectiveness indicators [5]. A description of the types of aRMM categories is presented in table 1.

Table 1: Description of the types of additional risk minimisation measures

Additional risk minimization measures	**Definitions**
Provision of educational materials	The provision of material in addition to the Summary of Product Characteristics and the Package Leaflet that describe specific safety concerns (risks) associated with use of a drug and measures in place to reduce those risks. Educational materials can be aimed towards health care professionals or patients/caregivers.
Controlled access program	Programs in which prescribing or dispensing of a drug is conditional to fulfilment of specific requirements (i.e. screening or monitoring, prescriber training, patient informed consent).
Controlled distribution program	Programs in which the stages of distribution are tracked.
Pregnancy prevention programs	Interventions aimed at minimizing drug exposure during pregnancy, usually comprising a combination of other tools such as educational tools and a controlled access program with negative pregnancy tests as requirement.

The type of marketing authorization was categorized as regular MA, conditional MA and or MA under exceptional circumstances. The conditional MA is granted to medicinal products for which the benefit of immediate availability outweighs the risk of less comprehensive data than normally required. The conditional MA is granted under the provision that comprehensive data will be provided within a defined time-frame, which is determined on a case by case basis. Approval under exceptional circumstances is granted to those products for which the benefit of availability outweighs the risk of less comprehensive data when these data cannot be obtained [2, 12].

Analysis

Descriptive statistics were used to present frequency data.

For our main analysis, we used Pearson's χ^2 test and Fisher's exact test to test for differences in the proportion of products approved with aRMMs in the periods before and after the new legislation came into effect. July 1st 2012 counted as the first day of the period in which the new legislation was in effect. We also conducted stratified analyses per ATC category, type of marketing authorization and type of aRMMs.

We explored the sensitivity of our main analysis by conducting a Poisson regression to analyze the effect of the change in products approved with aRMMs before and after the new legislation came into force. We aggregated the number of products with aRMM and the total number of products approved per quarter. We coded each quarter to a discrete variable to represent the time since start of study. In addition, we also coded a separate binary variable in which each quarter was assigned to the correct time period, i.e. quarters 1-10 (inclusive) to the "old" legislation and quarters 11-24 to the "new" legislation. We performed the Poisson regression analysis with the number of products approved with aRMMs as the response variable, the legislative period and the time since start of study as the explanatory variables and the log of the total number of products approved per quarter as offset variable.

To analyze a potential change in trend, we conducted an interrupted time series analysis. For this analysis, we used the quarterly aggregated data. Aggregating by quarter increased the stability of our data by reducing the number of 0-observations compared to monthly values, while still having more power than 6-monthly values by having more total observations. After analyzing the data for seasonality and autocorrelation, we excluded autoregressive (integrated) moving average processes [13]. We then applied a segmented Poisson regression model [14]. In addition, we augmented our data with the data previously collected by Zomerdijk et al for 2006 to 2009 for an additional analysis to investigate a potential effect of our choice of study period on the segmented regression analysis.[4]

All analyses were performed using Microsoft Excel, R version 3-3-3 and IBM SPSS Statistics, version 23.0.

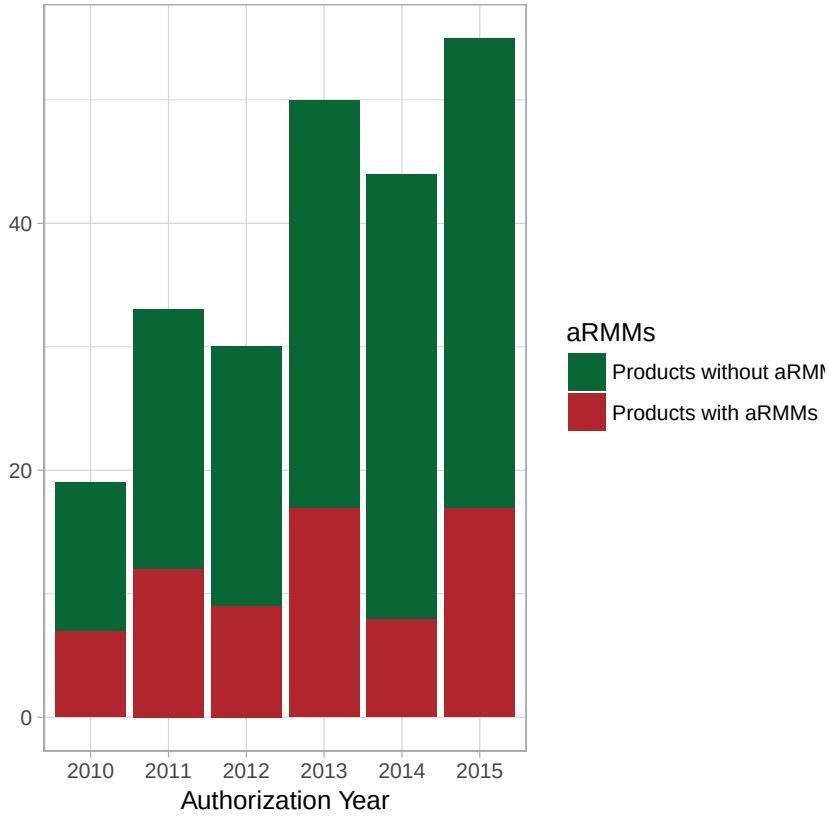
RESULTS

We identified 231 new active substances approved during the study period (January 1st 2010 and December 31st 2015). The number of centrally authorized products increased from 19 in 2010 to 55 in 2015. Products approved during the study period

most frequently concerned ATC groups “Antineoplastic and immunomodulating agents” (L, n= 64), “Anti-infectives for systemic use” (J, n=38) and “Alimentary tract and metabolism” (A, n=29). There were no significant differences in ATC groups for products approved before or after the new legislation. Between 2010 and 2015, 17 products were granted conditional MA and 8 products were approved under exceptional circumstances.

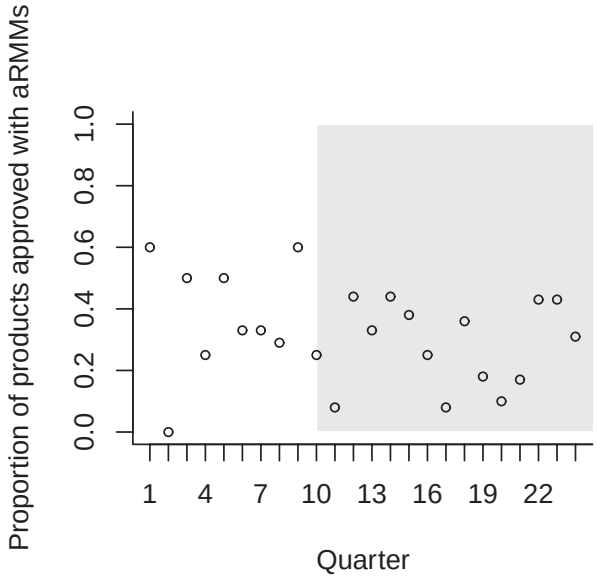
ARMMs were required at the time of approval for 70 (30%) of the products during the study period. The number of products approved with aRMMs, stratified by year of authorization, is presented in figure 1.

Figure 1: Products approved with and without additional risk minimisation measures per year



The proportion of products approved with aRMMs stratified by quarters is presented in figure 2.

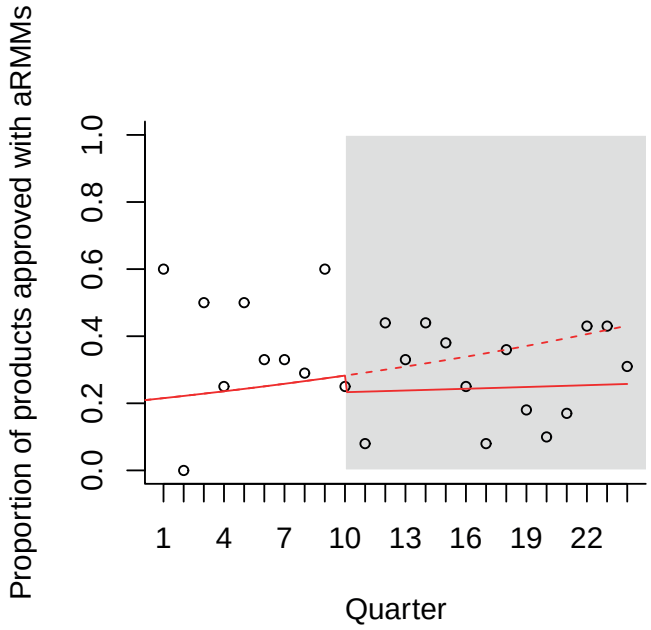
Figure 2: Proportion of products with additional risk minimisation measures per quarter



aRMMs = additional risk minimisation measures

The proportion of products with aRMMs per year ranged between 18% in 2014 and 44% during the first 6 months of 2012. ARMMs were required for 23 of 61 (38%) products approved before the new legislation came into force (July 2012), compared to 47 of 170 (28%) products approved in the period after. This difference was not statistically significant using Pearson's C^2 test (χ^2 1.988, p=0.159) or Poisson regression (b -0.3103, p=0.138). Segmented regression of the data aggregated by quarter did not show a statistically significant change in proportion (b -0.5185, p=0.458) or trend (b 0.0214, p=0.772) of products approved with aRMMs after the new legislation came into force. These results are visualized in figure 3.

Figure 3: Segmented Poisson regression

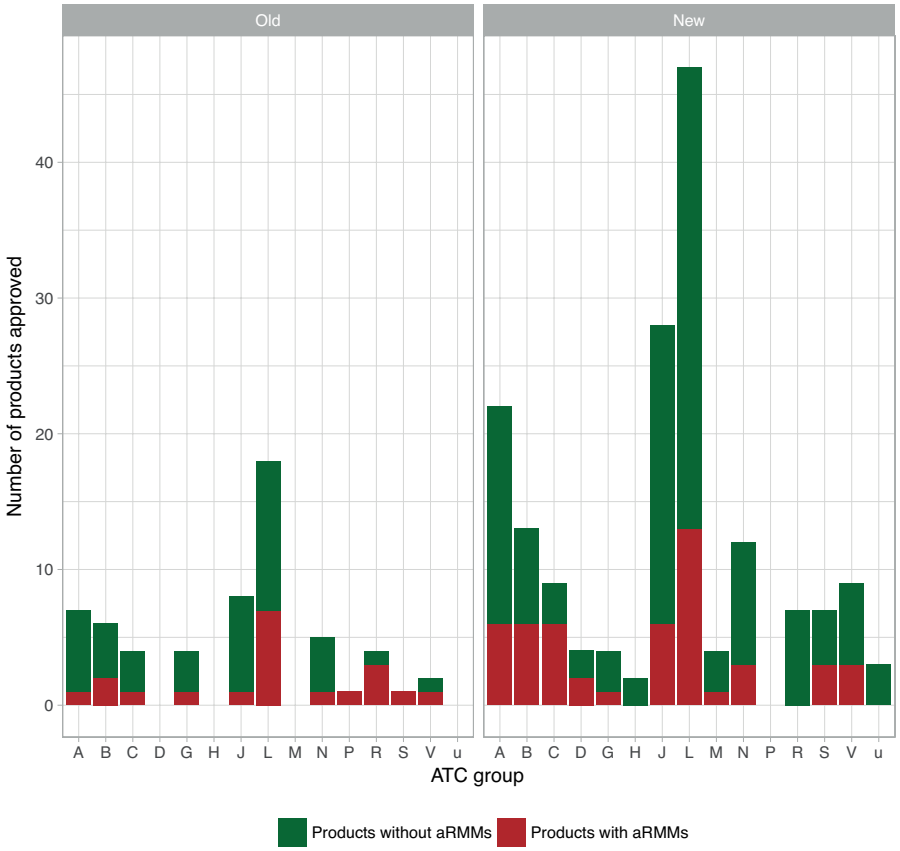


aRMMs = additional risk minimisation measures

Augmentation of our data with the data for 2006-2009 previously collected by Zomerdijk et al showed an overall increasing trend in proportion of products approved with aRMMs (β 0.03020, p=0.045), but no statistically significant effect of the legislation on the proportion (β 0.038, p=0.972) or trend (β -0.023, p=0.501).

The 70 products with aRMMs most frequently concerned ATC groups "Antineoplastic and immunomodulating agents" (L, n=20), followed by products targeted at "Blood and blood forming organs" (B, n=9), "Alimentary tract and metabolism" (A, n=7) and "Cardiovascular system" (C, n=7). Using Fisher's exact test to evaluate a potential difference in the proportions of products with aRMMs before the new legislation compared to after was not possible for the following ATC groups: "Dermatologicals" (D), "Systemic hormonal preparations, excluding sex hormones and insulins" (H) and "Antiparasitic products, insecticides and repellants" (P). For these ATC groups, no 2x2 tables could be created. In the remaining groups, a significant difference was found only for products targeting the "Respiratory system" (R). Before the legislation, three products were approved in this group and all had aRMMs; after the legislation, 8 products were approved in this group but none had aRMMs (p=0.006). The number of products approved with and without aRMMs per ATC class before and after the new legislation are presented in figure 4.

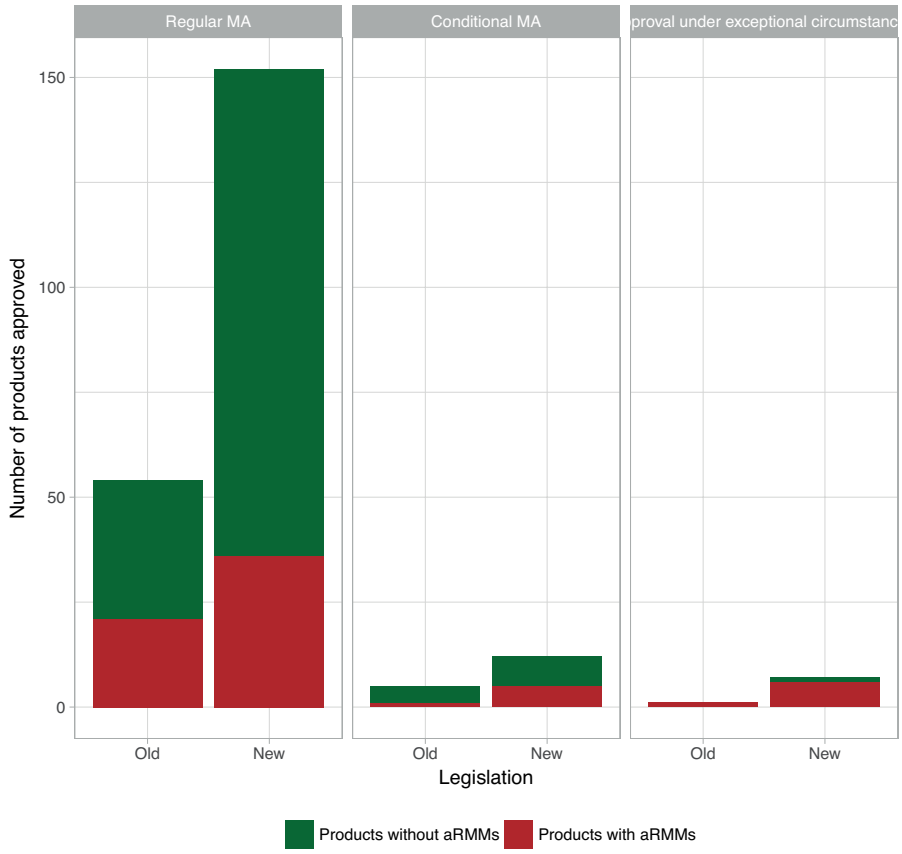
Figure 4: Products approved with and without additional risk minimisation measures per Anatomical Therapeutic Classification group



aRMMs = additional risk minimisation measures, ATC = Anatomical Chemical Classification

ARMMs were in place for 57 of the 206 (28%) products authorized via regular MA, for 6 of the 17 (35%) products authorized with conditional MA and for 7 of the 8 (88%) products approved under exceptional circumstances. For products authorized via regular MA, there was a borderline non-significant decrease in the proportion of products with aRMMs after the legislation (39% before the new legislation vs 24% after, p = 0.05). During the study period, products with non-regular MA were approved with aRMMs significantly more often than products with regular MA (52% of products with non-regular MA vs 28% of products with regular MA, p = 0.02). Figure 5 presents the number of products per type of marketing authorization before and after the pharmacovigilance legislation.

Figure 5: Products approved with and without additional risk minimisation measures per type of marketing authorisation



aRMMs = additional risk minimisation, MA = marketing authorisation

ARMMs always included the provision of educational materials. These materials were directed towards HCP for 93% of all products with aRMMs. There was no significant difference between periods for educational materials for HCPs.

Educational materials were targeted at patients or caregivers in 56% of all CAPs with aRMMs. Notably, educational materials directed towards patients were required more frequently after the pharmacovigilance legislation came into force (44% before vs 62% after, $p < 0{,}001$). There were five products with educational materials targeting patients, but not HCP. There were no similarities in therapeutic area, target population or type of MA between these products. The number of products per type of aRMM is presented in table 2.

Table 2: Frequency of the different additional risk minimisation measures stratified by period before and after the pharmacovigilance legislation came into force, in July 2012.

Additional risk minimization measures	Products authorized before new legislation, 2010-2012 (N=23) (%)	Products authorized after new legislation, 2012-2015 (N=47) (%)	C^2-test
Educational materials	23 (38%)	47 (28%)	Not significant
Educational materials for HCP	22 (96)	43 (92)	Not significant
Educational materials for patients	10 (44)	29 (62)	$p < 0.001$
Controlled access	0	3	Not tested
Controlled distribution	0	2	Not tested
Pregnancy prevention program	0	4	Not tested

More than one type of aRMM can be required for one product
HCP = healthcare professionals

Educational materials directed at patient most often involved products targeting "Sensory organs" (ATC S, 100%), "Antineoplastic and immunomodulating agents" (ATC L, 85%) and "Cardiovascular system" (ATC C, 71%). Interestingly, for "Sensory organs" (ATC S), there were more products with educational materials targeting patients than health care professionals (4 out of 4 vs 3 out of 4 respectively). For all other ATC groups, there were fewer products with educational materials targeting patients than healthcare professionals.

There were 8 products (all licensed after 2012) that required other types of aRMMs in addition to educational materials. One product required both a pregnancy prevention program and a controlled distribution scheme. The products which required other types of aRMMs to supplement educational materials was heterogeneous.

DISCUSSION

During the study period (2010-2015), overall 30% (70 out of 231) of medicinal products approved in the EU had aRMM at the time of approval. The proportion of products with aRMM was higher in the period before the pharmacovigilance legislation came into force than in the period after, 38% before vs 28% after. However, this difference did not reach statistical significance in any of the analyses we performed, nor did we find a significant change in trend. The study by Zomerdijk et al showed an increase in the proportion of products approved between 2005 and 2010, from 15% in 2006 to 42% in 2009, though the authors did not use any statistical methods to confirm the trend [4]. Rubino et al concluded that no time trend could be observed between

2006 and 2015 based on an R^2 of 19% for their adjusted regression line. In contrast, we did observe a statistically significant increasing trend in the proportion of products approved with aRMM during the same period, after augmentation of our data with the data previously collected by Zomerdijk et al. This difference could be attributed to different choices for statistical modelling but could also be the result of slightly different inclusion criteria between the studies. Although products authorized through the central procedure were investigated in all studies, Rubino et al only excluded generic applications while Zomerdijk et al excluded all products for which the active substance was part of multiple applications in addition to generics [4, 6]. In our study, we also excluded hybrid and informed consent applications as well as fixed-dose combinations; these products can be expected to have a similar safety profile to the reference product or mono-components, which was not an exclusion criterion by Zomerdijk et al.

The overall increasing trend observed from 2006 to 2015 (15% to 31%) after combining our data with the data from Zomerdijk et al, although statistically significant, should be interpreted with caution. The introduction of the EU-RMP in 2006 presented regulators and pharmaceutical companies with the opportunity to propose aRMMs, a new tool that did not exist earlier. Consequently, an increase in the application of this tool might be expected, particularly in light of the previously cited requirement to justify the absence of aRMMs [4]. Moreover, data have shown that regulators in the EU became more precautionary over the period 1995-2005, perhaps borne from the belief that society is becoming increasingly risk-averse [15, 16]. Nevertheless, we must also consider that newer therapeutic options, such as advanced therapy medicinal products, might be associated with more serious risks.

Although a change to the overall increasing trend following the introduction of the 2012 legislation did not reach statistical significance, the results suggest that the proportion of products approved with aRMMs following after the new legislation may have become more constant.

We investigated ATC group as factor that might potentially influence which products are approved with aRMMs. Because ATC classification is based on therapeutic targets, we theorized that a change in the distribution of products approved per ATC group could serve as a proxy for a potential shift in targeted therapeutic areas over time [17]. We found that the distribution of products approved per ATC group did not differ significantly before and after the new legislation, despite the addition of drugs targeting viral diseases, autoimmune diseases and other immune dysfunctions to the mandatory scope of the centralized procedure by the new legislation. This mandatory scope previously already included products derived from biotechnology,

orphan medicines and new active substances for the treatment of acquired immunodeficiency syndrome, cancer, neurodegenerative diseases, diabetes mellitus. However, other innovative products that did not meet the aforementioned criteria could also apply for MA through the centralized procedure [2, 4]. The centralized procedure offers the advantage of an MA valid throughout the European Economic Area following a single application and evaluation process; it is therefore plausible that innovative medications targeting autoimmune and viral diseases were already approved centrally before the new legislation came into force.

Comparisons within ATC groups showed a significant decrease in the proportion of drugs targeting the "Respiratory system" approved with aRMMs, but not for other ATC groups. We found no notable differences in route of administration, indication or target population for these products. This finding should be interpreted with caution given the low number of products per ATC group.

Since there is no difference in the distribution of products approved per ATC group and no difference in proportion or trend of products approved with aRMMs, we can offer no conclusion on a potential influence of ATC group on which products are approved with aRMMs.

Products granted conditional MA or approved under exceptional circumstances contained significantly more often aRMMs than products approved with a regular MA, 52% vs 28%. Conditional MA and approval under exceptional circumstances are granted to products that fulfil an unmet medical need, are related to life-threatening or debilitating illnesses or are intended for use in emergency situations [2, 12]. The expected benefits of these products might be such that more serious risks may be accepted. Alternately, the limited clinical data available in the authorization dossier of these products might lead to more uncertainties on risks. Minimization of these risks through aRMMs could help to improve the benefit-risk balance of these products.

The provision of educational materials was required for all products with aRMMs and for more than 90% of these products, the educational materials were targeted at health care professionals. Educational materials targeting patients or caregivers were required significantly more frequently after the pharmacovigilance legislation came into force than before, 62% after vs 44% before. However, it should be noted that the overall proportion of educational materials targeting patients during the study period (56%) was similar to proportions reported by Zomerdijk et al (53%, 2005-2009) and Rubino et al (50%, 2006-2015) [4]. Moreover, no time trend was observed by Rubino et al in linear regression, though the conclusion is based visual inspection and an R^2 of 16% [6].

This study is observational in nature and has several limitations. Since a previous study captured the period till 2010, we only looked at 2010-2015. This means that the study period before the pharmacovigilance legislation came into force was shorter than the study period after the legislation came into effect, 30 months before vs 42 months after, respectively, this might have reduced the power, to find statistical significance especially in subgroups.

Our choice of study period may also have had an impact on the validity of the segmented Poisson regression analysis: while our intervention had a clear date of coming into effect (i.e. the date the legislation came into force), both the Directive 2001/84/EC and Regulation 1235/210 were adopted in December 2010 [2, 3]. In theory, anticipatory effects might have impacted the results for 2010 and 2011, given the lengthy process of drafting and public consultation. A time lag in observing a potential effect of the pharmacovigilance legislation could also be plausible as the assessment duration for marketing authorization applications can last for almost a year. Consequently, the products approved in the first few months after the legislation came into force could have still been subject to the requirements of the old legislation and the first products approved according to new requirements could have occurred in 2013. In addition, there might be a grace period, during which both regulators and pharmaceuticals companies adjust to the requirements and become confident with them. The interrupted time series method takes potential lag times into account; we tested for lag times for a potential effect of the legislation up to a year after it came into force and found no evidence for such a lag time. We did not adjust for a longer grace period, since a longer grace period would lead to a shorter post-intervention period and reduce statistical power

Our study was conducted with publicly available data. Although the structure of the EPARs varied during the study period, the information needed was available and could be identified for all products.

Our study focused on products approved through the central procedure. Evaluating products authorized centrally provides an overview of aRMMs required for the majority of new active substances. In addition, focusing on centrally authorized products minimizes potential influence of local legislation in member states on the results.

ARMMs are intended to protect patients from serious risks, but they can be expected to have other impacts on the health care system. One study found that aRMMs/REMS increase costs for pharmaceutical companies due to lower sales and regulatory fees; although we theorize that aRMMs can lead to an increased administrative burden for all stakeholders, we are not aware of any studies that have investigated

this [9]. The trade-off between health benefit for patients and burden on the health care system is particularly important in light of studies that have shown mixed results in the effectiveness of aRMMs [18, 19, 20, 21]. Research has focused on satisfactory implementation of aRMMs, including consideration for the design of tools using lessons learned from other fields and suggested frameworks for evaluation of effectiveness which incorporate primarily distribution and uptake metrics and drug utilization patterns [1, 5, 21, 22, 23, 24]. In contrast, few studies have described the risks that are addressed by aRMMs and we know of no studies that have performed more in-depth analyses of these risks, i.e. their severity, public health impact, preventability and accessibility [25]. Considering the increase in products approved with aRMMs we observed in the studies by Zomerdijk and Rubino, this appears to be an interesting potential target for future research [4, 6].

Conclusion

During the study period (2010-2015), there was no significant difference in the proportion or trend of medicinal products with aRMMs at the time of licensing before and after the 2012 pharmacovigilance legislation came into force. Further research is needed to determine which factors contribute to the need for aRMM.

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Chapter 3

The safety concerns of medicinal products licensed in the European Union from 2010 to 2015: a descriptive study

R.D.C Francisca
R.D. Williams
I.M. Zomerdijk
M.C.J.M. Sturkenboom
S.M.J.M. Straus

ABSTRACT

Background: Additional risk minimisation measures (aRMMs) may be required to strengthen the benefit-risk balance of medicines associated with serious risks not sufficiently minimised through routine measures. The objective of this study is to identify factors that predict the need for aRMMs at the time of licensing.

Methods: We performed a cross-sectional study with safety concerns of centrally authorised innovator medicines between January 1st 2010 and December 31st 2015. We extracted the risk category and the Anatomical Therapeutic Chemical (ATC) classification. Safety concerns were coded to System, Organ, Class level (SOC) in the Medical Dictionary of the Regulatory Authorities version 19.0. We calculated the proportional reporting ratio to identify factors that could serve as potential predictors of aRMM for each safety concern. In addition, we conducted a classification tree analysis to determine whether risk category, SOC and ATC classification perform as predictors of the decision to address a safety concern by aRMMs.

Results: The probability of aRMMs was significantly increased for safety concerns in ATC groups "Cardiovascular system" (PRR 3.7, 95% CI 2.9 - 4.9), "Sensory organs" (PRR 3.6, 95% CI 2.6 - 5.0), "Dermatologicals" (PRR 3.1, 95% CI 1.8 - 5.1), "Respiratory agents" (PRR 2.0, 95% CI 1.4 - 3.0) and "Blood and blood forming organs" (PRR 1.6, 95% CI 1.1 - 2.3); SOCs "Congenital, familial and genetic disorders" (PRR 3.8, 95% CI 2.1 - 7.2), "Immune system disorders" (PRR 3.6, 95% CI 2.7 - 4.9), "Eye disorders" (PRR 3.5, 95% CI 2.3 - 5.3), "Injury, poisoning and procedural complications" (PRR 2.1, 95% CI 1.6 - 2.9) and "Infections and infestations" (PRR 1.9, 95% CI 1.3 - 2.8); important identified risks (PRR 3.0, 95% CI 2.4 - 3.7) and safety concerns for which the RMP category was unknown (PRR 2.3, 95% CI 1.6 - 3.2). The probability of aRMMs was significantly decreased in ATC groups "Antineoplastic and immunomodulatory agents" (PRR 0.7, 95% CI 0.5 - 0.9), "Antiinfectives for systemic use" (PRR 0.4, 95% CI 0.2 - 0.6) and "Alimentary tract and metabolism" (PRR 0.4, 95% CI 0.2 - 0.6); SOC "Special populations" (PRR 0.2, 95% CI 0.1 - 0.3); and RMP category missing information (PRR 0.2, 95% CI 0.2 - 0.3).No potential predictors could be identified in our classification tree analysis.

Discussion: Our study shows that the probability of safety concerns being addressed by aRMMs differs across ATC groups, SOCs, RMP categories and ATC-SOC combinations. These differences reflect different risk acceptance across indication areas, potentially due to differences in treatment benefits.

INTRODUCTION

Risk management planning has become an integral part of the proactive, life cycle approach to pharmacovigilance. The European Union Risk Management Plan (EU-RMP) is a mandatory part of the authorisation dossier for medicinal products licensed in the European Union (EU) that is intended to aid identification, characterisation, monitoring and minimisation of risks (1, 2).

The EU-RMP consists of the safety specification, which describes safety concerns related to use of the medicinal product that might impact its benefit-risk balance. These safety concerns are categorised as important identified risks when there is adequate evidence of an association with the medicinal product, important potential risks when an association is suspected but not confirmed, and missing information which could be clinically significant. The EU-RMP also consists of the pharmacovigilance plan, which describes the activities intended to further characterise the safety profile of the medicinal product, and the risk minimisation plan, which describes the measures to minimise the risks associated with use of the medicinal product (3).

Routine risk minimisation measures are applicable to all products, such as the product information, prescription status and pack design. For products associated with serious risks, which may not be sufficiently minimised through routine measures, additional risk minimisation measures (aRMMs) may be needed (3). ARMMs may include educational materials or programmes that provide additional information regarding risks; studies have shown that all aRMMs consist of educational materials and occasionally also include more stringent measures to restrict access to patient groups with the largest benefit or lowest risk, to facilitate traceability or to minimise the risk of pregnancy exposure (4-7).

Currently, the need for aRMMs is determined on a case-by-case basis by regulatory authorities. The EU's guidelines on Good pharmacovigilance practices (GVP) describes that selection of the most suitable risk minimisation measures should be considered individually for each important risk or area of missing information, considering factors such as seriousness, severity and preventability of the safety concern (4). To our knowledge, no studies have investigated which factors influence the need for aRMMs, beyond overviews of types of safety concerns addressed by aRMMs published previously (5, 8). As 30% of medicinal products have aRMMs at the time of authorisation, there is need for more insight into why and for which safety concerns aRMMs are required.

The objective of this study is to describe the safety concerns included in the EU-RMP of medicinal products at the time of licensing, in particular those safety concerns addressed by aRMMs. We aim to empirically identify factors that predict the need for aRMMs at the time of licensing.

METHODS

Study design

We performed a cross-sectional study that included the safety concerns of medicinal products authorised in the EU through the centralised procedure between January 1st 2010 and December 31st 2015 that were still authorised on January 1st 2016. We excluded the safety concerns of medicinal products licensed through generic applications, hybrid applications, fixed dose combinations and biosimilar applications. These products are expected to have identical safety concerns and aRMMs as the reference product. Similarly, the safety concerns of medicinal products that were subject of multiple or duplicate applications during the study period were only counted once.

The centralised procedure has been described previously; briefly, the procedure encompasses a single application and evaluation process that results in a marketing application valid throughout the European Economic Area in case of a positive opinion (1, 6).

Data sources and setting

The European Medicines Agency publishes European Public Assessment Reports (EPARs) for all medicinal products authorised through the centralised procedure on www.ema.europa.eu, which are updated throughout the product life cycle. The EPAR that comprises the assessment of the initial application includes a summary of the EU-RMP at the time of authorisation.

The safety concerns at the time of authorisation for each medicinal product in our study were extracted from the EPAR: safety concerns are the unit of analysis of our study.

Outcome and covariates

Our main outcome was whether safety concerns in the RMP were addressed by aRMMs. The types of aRMMs in our study were defined in accordance with GVP module XVI rev 2 and included educational materials for patients or caregivers, educational materials for healthcare professionals, controlled access, controlled distribution and pregnancy prevention programmes (3). One safety concern can be addressed by more than one aRMM.

We used the Medical Dictionary of the Regulatory Authorities (MedDRA) version 19.0 to manually code safety concerns to Lowest Level Terms, which were then matched to the corresponding Preferred Terms (PTs). For each PT, the corresponding System Organ Class (SOCs) was identified. We used the SOCs in analysis; in addition to the 27 SOCs in MedDRA, we used two additional groups: "Not MedDRA" for safety concerns for which there was no match in MedDRA and "Special Populations" for safety concerns describing populations not studied in clinical trials (9).

For each safety concern, we also collected the Anatomical Therapeutic Chemical (ATC) classification of the medicinal product and the category of the safety concern in the RMP.

The category of the safety concern in the RMP was extracted from the EPAR, namely important identified risk, important potential risk or missing information, in line with the GVP module V (4). Safety concerns in the RMP for which the category could not be identified in the EPAR were categorised as 'unknown'.

Analysis

Descriptive statistics were used to present frequency data. The proportion of safety concerns addressed by aRMMs were calculated as the number of safety concerns addressed with aRMMs divided by the total number of safety concerns in each ATC group, SOC or RMP category.

To identify predictors of aRMMs, we calculated the proportional reporting ratio (PRR) defined as the proportion of safety concerns addressed by aRMMs in each specific ATC group, SOC or RMP category of interest, with the comparator being the proportion of safety concerns addressed by aRMMs in all other ATC groups, SOCs or RMP categories (table 1a). This method has been widely used in signal detection (10).

Table 1a: Example of the PRR calculation using SOCs

	Safety concerns addressed by aRMMs	**Safety concerns not addressed by aRMMs**	**Total**
SOC "Blood"	A	B	A+B
All other SOCs	C	D	C+D
Total	A+C	B+D	A+B+C+D

PRR = (A/(A+B))/(C/C+D)) *if A > 5*
PRR = proportional reporting ratio, ATC = Anatomical Therapeutic Chemical, SOC = System Organ Class, aRMMs = additional risk minimisation measures

We investigated potential interaction between ATC group and SOC by calculating the proportion of safety concerns addressed by aRMMs and the PRR for each SOC stratified by ATC group (table 1b). The PRR was only calculated if there were at least five safety concerns with aRMMs in each specific ATC group, SOC, RMP category or ATC-SOC of interest.

Table 1b: Example of the PRR calculation for ATC-SOC combinations

ATC group A	Safety concerns addressed by aRMMs	Safety concerns not addressed by aRMMs	Total
SOC "Blood"	A	B	A+B
All other SOCs	C	D	C+D
Total	A+C	B+D	A+B+C+D

PRR = (A/(A+B))/(C/C+D)) *if A > 5*

PRR = proportional reporting ratio, ATC = Anatomical Therapeutic Chemical, SOC = System Organ Class, aRMMs = additional risk minimisation measures

In addition, we trained a supervised machine learning algorithm called classification and regression tree analysis to determine whether category of safety concern, SOC and ATC classification perform as predictors of the decision to assign aRMMs to a safety concern. Classification and regression trees (CART) is a non-parametric method for determining class membership based upon a set of covariates. The algorithm attempts to classify a target outcome by splitting the data recursively according to categories of the predictor variables until no further gain in group 'purity' can be achieved or until a user-specified stopping rule is reached. For this analysis we used a 65:35 train:test split and trained the model using 5-fold cross validation. We assessed model performance via the area under the receiver operating characteristic curve (AUROC), which is a measure of the discriminatory performance of a classification model. The range is between 0.5 (no discrimination) and 1.0 (perfect discrimination). We also graphically assessed the model calibration.

To perform the analysis we used the rpart implementation of CART from the caret R package (version 6.0-80) (11).

All analyses were performed using Microsoft Excel and R version 3-3-3.

Table 2: Characteristics of safety concerns and safety concerns with aRMMs

	Safety concerns with aRMMs [n=289] (8%*)	Total safety concerns [n=3,588]
ATC code		
Alimentary	13 (3%)	410
Blood	26 (12%)	212
Cardiovascular	53 (26%)	203
Dermatologicals	12 (24%)	50
Genitourinary	5 (6%)	86
Hormonal	0 (0%)	46
Antiinfectives	19 (3%)	565
Antineoplastic	78 (6%)	1256
Musculokeletal	8 (13%)	64
Nervous	14 (5%)	279
Antiparasitic	0	15
Respiratory	4 (27%)	153
Sensory	24 (16%)	104
Various	28 (27%)	102
No ATC code	5 (5%)	43
SOC		
Blood	9 (8%)	110
Cardiac	7 (7%)	95
Congenital	7 (30%)	23
Ear	1 (14%)	7
Endocrine	1 (6%)	18
Eye	18 (27%)	67
Gastrointestinal	27 (8%)	107
General	2 (2%)	345
Hepatobiliary	7 (9%)	74
Immune	36 (27%)	135
Infections	22 (15%)	149
Injury	47 (16%)	299
Investigations	20 (12%)	171
Metabolism	2 (2%)	81
Musculoskeletal	1 (3%)	37
Neoplasms	4 (5%)	88
Nervous	6 (5%)	131
Pregnancy	1 (5%)	22
Product	2 (67%)	3
Psychiatric	3 (8%)	37
Renal	3 (5%)	66
Reproductive	6 (12%)	51
Respiratory	8 (14%)	59
Skin	5 (7%)	73
Social	0	0
Surgical	3 (21%)	14
Vascular	15 (11%)	131
Populations	23 (2%)	1074
Not MedDRA	3 (2%)	121
RMP category		
Identified	143 (16%)	889
Potential	81 (7%)	1,189
Missing	33 (2%)	1,325
Unknown	32 (17%)	185

* number of safety concerns with aRMM / number of total safety concerns

ATC = Anatomical Therapeutic Chemical, SOC = System Organ Class, RMP = Risk Management Plan, aRMMs = additional risk minimisation measures, MedDRA = Medical Dictionary for Regulatory Activities

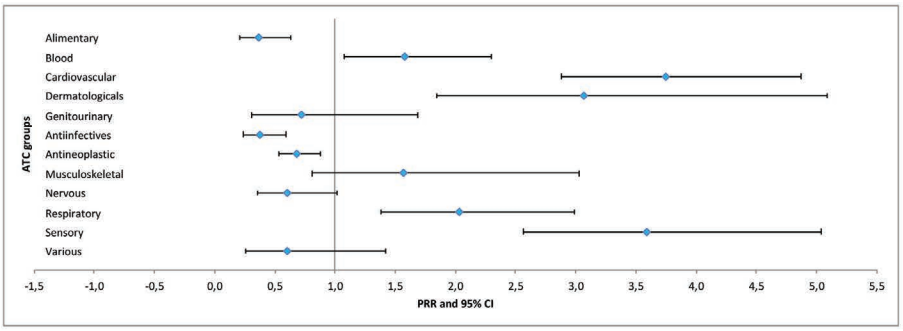
RESULTS

During the study period, we identified 3,588 safety concerns for 222 medicinal products. The median number of safety concerns per product was 16 (range 3-33) and was constant throughout the study period. Median number of safety concerns per product ranged from nine safety concerns for ATC group "Various" to 23 safety concerns for "Systemic hormonal preparations, excluding sex hormones and insulins".

ARMMs were in place for 289 (8%) of the safety concerns. These 289 safety concerns with aRMMs were related to 70 products; the median number of safety concerns with aRMMs per product that had at least one aRMM was 3 (range 1-16). The characteristics of the safety concerns and safety concerns with and without aRMMs are described in table 2.

Univariate analysis showed that there was a higher probability of aRMMs for safety concerns when the drugs comprised one of the following indication areas: "Cardiovascular system" (PRR 3.7, 95% CI 2.9 - 4.9), "Sensory organs" (PRR 3.6, 95% CI 2.6 - 5.0), "Dermatologicals" (PRR 3.1, 95% CI 1.8 - 5.1), "Respiratory agents" (PRR 2.0, 95% CI 1.4 - 3.0) and "Blood and blood forming organs" (PRR 1.6, 95% CI 1.1 - 2.3). The probability of aRMMs was lower for ATC groups "Antineoplastic and immunomodulatory agents" (PRR 0.7, 95% CI 0.5 - 0.9), "Antiinfectives for systemic use" (PRR 0.4, 95% CI 0.2 - 0.6) and "Alimentary tract and metabolism" (PRR 0.4, 95% CI 0.2 - 0.6) (figure 1).

Figure 1: Proportional reporting ratios of aRMMs per ATC group*

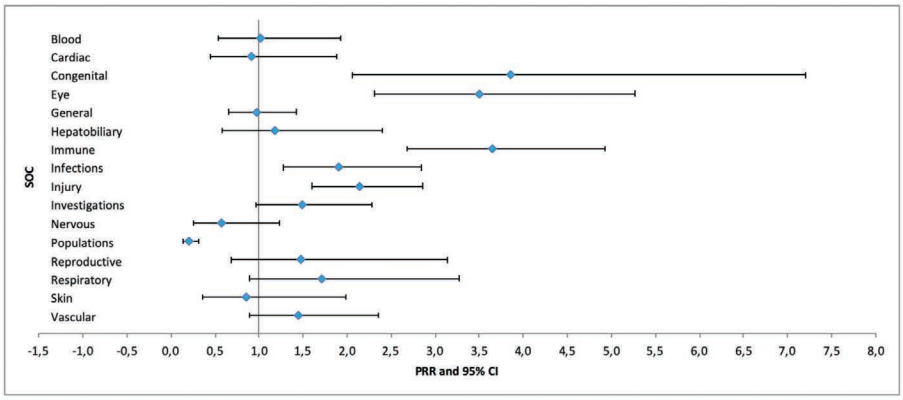


* a PRR was only calculated for ATC groups with at least 5 safety concerns with aRMM, the PRR was not calculated for three ATC groups

ATC = Anatomical Therapeutic Chemical, PRR = proportional reporting ratio, CI = confidence interval, aRMMs = additional risk minimisation measures

The probability of aRMMs was increased for safety concerns in SOCs “Congenital, familial and genetic disorders” (PRR 3.8, 95% CI 2.1 - 7.2), “Immune system disorders” (PRR 3.6, 95% CI 2.7 - 4.9), “Eye disorders” (PRR 3.5, 95% CI 2.3 - 5.3), “Injury, poisoning and procedural complications” (PRR 2.1, 95% CI 1.6 - 2.9) and “Infections and infestations” (PRR 1.9, 95% CI 1.3 - 2.8); the SOC “Special populations” (PRR 0.2, 95% CI 0.1 - 0.3) had a significantly decreased probability of aRMMs (figure 2).

Figure 2: Proportional reporting ratios of aRMMs per SOC



* a PRR was only calculated for SOCs with at least 5 safety concerns with aRMM, the PRR was not calculated for 13 SOCs

SOC = System Organ Class, PRR = proportional reporting ratio, CI = confidence interval, aRMMs = additional risk minimisation measures

The probability of aRMMs was significantly increased for safety concerns categorised as important identified risks (PRR 3.0, 95% CI 2.4 - 3.7) and safety concerns for which the RMP category was unknown (PRR 2.3, 95% CI 1.6 - 3.2); missing information (PRR 0.2, 95% CI 0.2 - 0.3) had a lower probability of aRMMs.

To investigate the interaction between SOC and ATC group, we calculated the proportions of safety concerns with aRMM for each SOC stratified by ATC group (figure 3).

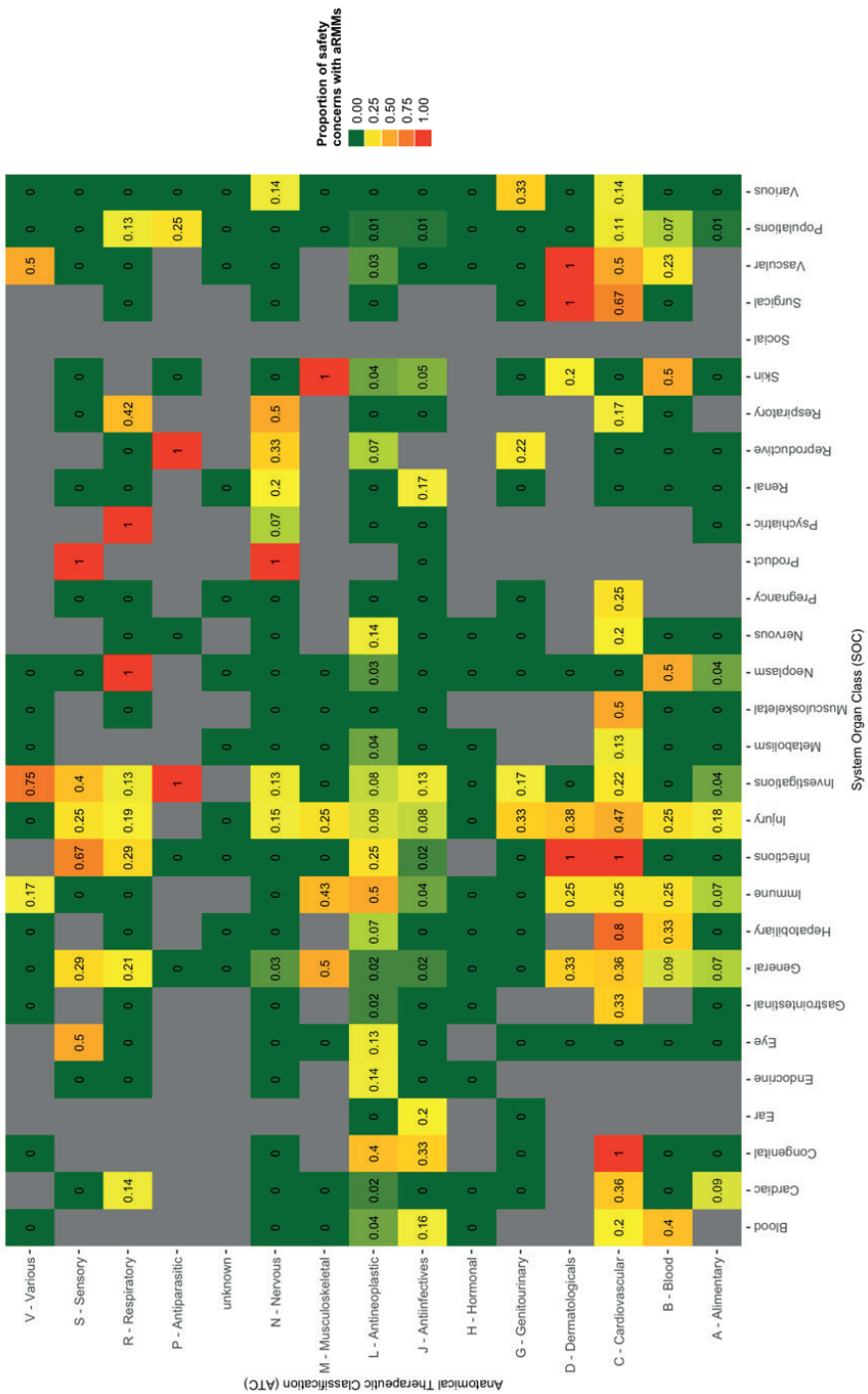


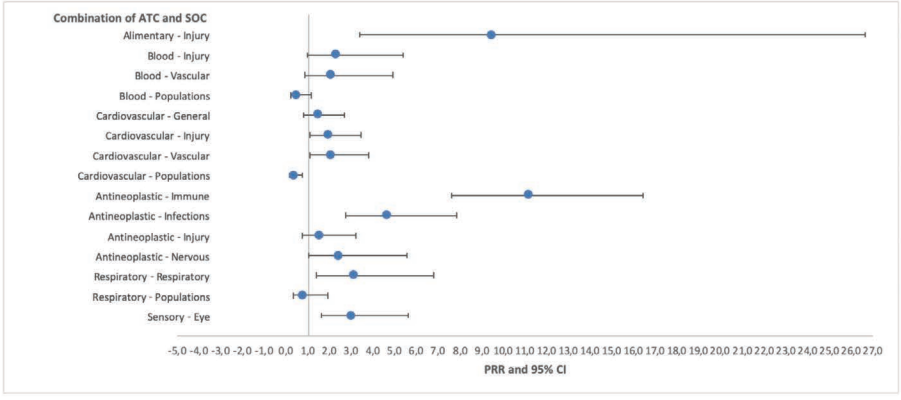
Figure 3: Proportion of safety concerns addressed by aRMM by SOC and ATC group

There were 10 combinations of ATC group and SOC in which all of the safety concerns were addressed by aRMMs:

- "Congenital malformations" (n = 2) and "Infections and infestations" (n = 1) for products targeting the "Cardiovascular system",
- "Infections and infestations" (n = 1), "Surgical and medical procedures" (n = 1) and "Vascular disorders" (n = 1) for "Dermatologicals"
- "Skin and subcutaneous tissue disorders" (n = 1) for products targeting the "Musculoskeletal system"
- "Product issues" (n = 1) for products targeting the "Nervous system"
- "Investigations" (n = 1) and "Reproductive system disorders" (n = 1) for "Antiparasitic products, insecticides and repellents"
- "Product issues" (n = 1) for products targeting the "Sensory organs"
- The probability of aRMMs was not calculated for these combinations of ATC group and SOC, due to low numbers.

The PRR for combinations of ATC groups and SOCs with sufficient number of safety concerns with aRMM are shown in figure 4.

Figure 4: Probability of aRMMs per combination of ATC and SOC



* a PRR was only calculated for ATC-SOC combinations with at least 5 safety concerns with aRMM
ATC = Anatomical Therapeutic Classification, SOC = System Organ Class, PRR = proportional reporting ratio, CI = confidence interval, aRMMs = additional risk minimisation measures

The probability of aRMMs was significantly increased for eight combinations of ATC group and SOC:

- "Injury, poisoning and procedural complications" (PRR 9.5, 95% CI 3.4 – 26.6) for products targeting "Alimentary tract and metabolism"
- "Injury, poisoning and procedural complications" (PRR 1.9, 95% CI 1.1 – 3.4) and "Vascular disorders" (PRR 2.0, 95% CI 1.1 – 3.8) in products targeting the "Cardiovascular system"
- "Immune system disorders" (PRR 11.2, 95% CI 7.6 – 16.4), "Infections and infestations" (PRR 4.6, 95% CI 2.7 – 7.8) and "Nervous system disorders" (PRR 2.4, 95% CI 1.0 – 5.5) in "Antineoplastic and immunomodulatory drugs"
- "Respiratory, thoracic and mediastinal disorders" (PRR 3.1, 95% CI 1.4 – 6.8) for products targeting the "Respiratory system"
- "Eye disorders" (PRR 3.0, 95% CI 1.6 – 5.6) in products targeting the "Sensory organs" and.

The probability of aRMMs was significantly decreased for "Special populations" (PRR 0.3, 95% CI 0.2 – 0.7) in products targeting the "Cardiovascular system".

When performing the classification and regression tree analysis, we obtained an AUROC of 0.53. This indicates that there is almost no discriminative ability that can be learned from our predictors. In addition, calibration plots of our model show that our model always, though erratically, overestimates the probability of having aRMMs. Thus, it seems that through machine learning no potential predictors could be identified with the classification and regression tree analysis of our data.

DISCUSSION

In this study, we investigated whether specific ATC groups, SOCs or RMP categories, as well as combinations of ATC groups and SOCs, were predictive of the decision to address safety concerns with aRMMs. We found that safety concerns related to drugs with indication areas "Blood and blood forming organs", "Cardiovascular system", "Dermatologicals", "Respiratory system" and "Sensory organs" were more likely to be addressed by aRMMs than safety concerns in drugs with other indication areas. Safety concerns for drugs with indications "Alimentary tract and metabolism", "Antiinfectives for systemic use" and "Antineoplastics and immunomodulatory agents" were less likely to be addressed by aRMMs.

We expected that the probability of a safety concern being addressed by aRMMs per ATC group would not be the same for all ATC groups, as differences in treatment benefits in each indication area would lead to differences in acceptance of serious

risks (eg. the benefits of effective anti-cancer treatment might lead to a greater acceptance of liver or kidney injury than the benefits of treatment for acne). However, we note that the three ATC groups with a decreased risk of aRMMs were also the ATC groups with the highest number of safety concerns in our dataset and the highest number of products approved through the central procedure during the study period (6, 7). The probability of a safety concern being addressed by aRMMs per ATC group might also be correlated with the number of products approved centrally for each ATC group, potentially due to greater experience among all stakeholders with pharmacotherapeutic options in these indication areas (i.e. more medicines with similar risks, leading to more experience with prevention and management of these risks). Moreover, almost half of the products approved through the central procedure can be considered pharmacological or technological developments rather than therapeutic innovations, meaning that these products can be expected to have risk profiles that are comparable to already approved medicines (12). Pharmacological or technological developments may be more prevalent amongst the ATC groups with a decreased probability of safety concerns being addressed by aRMMs.

We found that safety concerns related to medical conditions in SOCs “Congenital, familial and genetic disorders”, “Immune system disorders”, “Eye disorders”, “Injury, poisoning and procedural complications” and “Infections and infestations” were more likely to be addressed by aRMMs than safety concerns in other SOCs, while safety concerns in the SOC “Special populations” (meaning lack of data in populations not studied in clinical trials) were less likely to be addressed by aRMMs. “Special populations” is highly correlated with the RMP category missing information, which we also found to be less likely to be addressed by aRMMs than the other RMP categories. This was not entirely unexpected, since missing information entails the absence of data rather than an established risk to be minimised.

Our findings are comparable to the findings of studies investigating aRMMs in the EU between 1995-2009 and Risk Evaluation and Mitigation Strategy (REMS) in the United States between 2008-2016: safety concerns related to “Immune system disorders”, “Injury, poisoning and procedural complications” and “Infections and infestations” were commonly addressed by aRMMs or REMS (5, 13).

Although we found specific indication areas and medical conditions to have a higher probability of having aRMMs, we anticipated that there would be an interaction, namely that conditional on the indication area certain medical conditions would be more or less likely to have an aRMM.

Our results showed that patterns were only found in dedicated univariate and interaction analysis, and could not be found by machine learning algorithms, likely because the number of events was quite low. Machine learning works best with large sample sizes.

Our results thus indicate that drugs in certain indication areas and certain safety concerns may determine whether there will be an aRMM. GVP module XVI indicates that the need for aRMMs must be evaluated for each safety concern individually and that the selection of risk minimisation activity should take into account several factors, such as seriousness, severity and preventability of the risk as well as indication, route of administration, target population and health care setting for use of the product (3). These factors are largely comparable with the United States Food and Drug Administration (FDA) "Statutory Factors in Determining When a Risk Evaluation and Mitigation Strategy (REMS) Is Necessary", the application of which was investigated in a recent publication by Seligman et al. The authors found that the most frequently cited reasons for not requiring a REMS were related to the context of administration of the product and included whether the risk profile was similar to drugs for which there were no REMS, whether health care professionals were considered familiar with or capable of managing the risks of the product and whether it was used in a particular health care setting (14).

In our study, the context of administration could be approximated through safety concerns such as drug interactions (SOC "General condition and administration site disorders"), medication errors and off-label use (SOC "Injury, poisoning and procedural complications"). These safety concerns reflect human behaviour and are therefore related to preventable harm, particularly safety concerns in SOC "Injury, poisoning and procedural complications" which were more likely to be addressed by aRMMs. This indicates a significant contribution of preventability to the requirement of aRMMs.

Strengths and limitations

To our knowledge, this is the largest study to investigate important safety concerns of medicinal products authorised in the EU, and the first to analyse safety concerns with and without aRMMs. We used publicly available data, collected from the EPARs of the initial MA, which include a summary of the EU-RMP. With the exception of the category of safety concerns for some products at the beginning of our study period, the required information was readily available for all medicinal products in our dataset. Our study only included products authorised through the central procedure. The mandatory scope of the central procedure includes products derived from bio- technology, orphan medicines, and new active substances for the treatment

of acquired immunodeficiency syndrome, cancer, neurodegenerative diseases, viral diseases, autoimmune diseases, other immune dysfunctions and diabetes mellitus (1). Although it is conceivable that the safety profile of products that do not fall under the mandatory scope of the central procedure is significantly different from products that do, the vast majority of products not authorised through the central procedure concern non-innovator medicines such as generic applications, hybrid applications, informed consent applications, fixed dose combinations and biosimilar applications. The number of new active substances not authorised through the central procedure during the study period is expected to be low, if any.

Conclusion

Our study shows that the probability of safety concerns being addressed by aRMMs differs across ATC groups, SOCs, RMP categories and ATC-SOC combinations. This heterogeneity reflects different risk acceptance across indication areas, potentially due to differences in treatment benefits. Preventability or human error also appears to play a large part. Further research is needed to quantify these differences.

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Chapter 4

A description of the risk management of medication errors for centrally authorised products in the EU

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ABSTRACT

Introduction: Medication errors can have serious consequences for patients. To prevent the occurrence of medication errors in clinical practice, safety concerns may be included in the risk management plan and subsequently be addressed with routine and/or additional risk minimisation measures.

Objectives: This study aims to describe safety concerns around ME and the risk minimisation measures for centrally authorised products in the EU.

Methods: All safety concerns included in the risk management plans of originator centrally authorised products, authorised between 1 January 2010 and 31 December 2017, were collected from the European Public Assessment Report registry. Medication error safety concerns were categorized by Anatomical Therapeutic Classification code, year of authorisation, type of medication error and type of risk minimisation measure.

Results: During the study period 311 centrally authorised products were approved, of which 84 had at least one medication error safety concern. The proportion of centrally authorised products with medication error safety concerns showed variation between 2010-2017 ranging from 15.2% to 36.4%. In total, 95 medication error safety concerns were identified. The type of medication error was highly variable, *drug administration error* was listed most frequently (n=17). For 27 out of 95 medication error safety concerns, corresponding to 23 centrally authorised products, additional risk minimisation measures were required. All additional risk minimisation measures consisted of educational material targeted at healthcare professionals (85.2%) and/or patients (51.9%). For 78.3% of centrally authorised products with additional risk minimisation measures for medication errors, studies to evaluate the effectiveness of additional risk minimisation measures were agreed upon.

Conclusion: Medication error safety concerns were listed for almost a quarter of centrally authorised products approved during the study period. Further research is needed to evaluate the effectiveness and continued need for additional risk minimisation measures for medication errors.

Key points:

- Over a quarter of medicines authorised in the European Union have medication errors as an important risk included in the Risk Management Plan.
- Medication errors frequently require additional risk minimisation measures.
- Studies are needed to confirm the effectiveness of measures implemented to minimise the risk of medication errors.

INTRODUCTION

In November 1999, the US Institutes of Medicine released a report titled "To err is human", which concluded that between 44,000 and 98,000 patients in the US died each year as a result of preventable medical errors [1]. Varying numbers of patients suffering from medication errors have been described. In a recent report, WHO has marked medication errors as a leading cause of avoidable harm to patients [2]. Medication errors (MEs) are "an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient" [3]. Numerous heterogeneous factors have been described as a cause for the occurrence of MEs, ranging from e.g. phonetic (sound-a-like) and orthographic (look-a-like) medication names to confusion relating to appropriate dosage and route of administration to time pressure on medical personnel [4]. In view of the many different factors associated with MEs, reducing the risk of MEs by one single intervention is often not achievable. In addition, many stakeholders such as pharmaceutical companies, regulators, health care professionals, patients and their caretakers have a role in the prevention of MEs. Therefore, strategies to minimise MEs should include all stakeholders and need to address the different causes and phases of product development and the post-licensure treatment process. Pharmaceutical companies, responsible for product development and design, should consider possibilities to minimise MEs as early as possible in the development process.

If MEs are identified during the clinical development phase these should preferably be resolved before the medicine enters the market. For example, if reconstitution and preparation of the final product is complicated and pose challenges already in the strictly controlled environment of the clinical trial, the pharmaceutical company should improve product preparation, whenever feasible, since the risk in daily practice might be even larger. In 2015 the European Medicines Agency (EMA) released guidance describing common areas of risks to be considered by industry and regulators before authorisation [5, 6]. It is highlighted here that the focus regarding medication errors should not only be on within-product risks but also between-product risks, such as name similarity with already licensed products. In the EU the

Committee for Medicinal Products for Human Use (CHMP)'s Name Review Group evaluates the similarity of new product names with already approved products in order to limit confusion between products [7]. Despite pre-marketing efforts not all ME risks can be completely eliminated, e.g. if multiple strengths of the same product are on the market there will be the potential of confusion between strengths. Routine risk minimisation through warnings and instructions in the Summary of Product Characteristics (SmPC) and patient leaflet, or colour-coding of the product name or dosages on packaging may be sufficient to minimise the risk of MEs. If routine measures are not expected to be sufficient to minimise the risk of MEs, additional risk minimisation measures (aRMM) should be implemented.

Since 2012 an EU Risk Management Plan (EU-RMP) is mandatory for all medicinal products newly licensed in the EU. The EU-RMP describes the knowledge of the safety profile of a product at the moment of approval and provides a plan for areas that need further identification, characterization and/or risk minimisation [8, 9]. The EU-RMP stimulates a pro-active approach towards risk management and minimisation. The EU-RMP is a dynamic document that is updated continuously during the lifetime of the medicinal product to reflect newly available information. A discussion on the risk of MEs is a mandatory part of the EU RMP [10] and if appropriate MEs can be included as an important risk in the RMP. In addition, pharmacovigilance activities and (additional) risk minimisation measures to prevent MEs can be proposed [11, 12].

Limited summary information is available concerning risk minimisation measures (RMM) regarding medication errors. Rubino et al reported in an overview of additional RMM (aRMM) that MEs are among the risks most frequently addressed with aRMMs [13]: in their study over the period 2005 and 2015 a total of 32 centrally authorized products (CAPs) required aRMM for MEs. A study by the UK Medicines and Healthcare products Regulatory Agency (MHRA) showed that MEs represented almost a quarter of the risks described in RMPs in the UK [14]. However, both studies lacked information regarding the medications it concerned and how these medication errors were identified. Therefore, a more detailed review of risk minimization measures for medication errors is warranted.

In this study, we review the important risks for centrally authorised products (CAP) in the EEA licensed between 2010 and 2017 regarding MEs, including the routine and aRMMs as laid down in the EU-RMP of these products at the time of licensing.

METHODS

Study design

We performed a cross-sectional study including all originator CAPs authorised in the EEA between 1 January 2010 and 31 December 2017. Applications for generic, biosimilar and hybrid products were excluded, as these are expected to follow the originator product in the design of their EU-RMP and the aRMM. In the EU, medicines can be authorised through centralised or decentralised procedures. Application through the centralised procedure leads to a marketing authorisation for the entire European Economic Area (EEA), whereas for decentralised procedures the applicant can choose to have the product approved in selected EEA countries. The majority of originator medicines are authorised through the centralised procedure [15].

Data collection

Data was collected from the European Public Assessment Reports (EPARs) published on the website of the European Medicines Agency (EMA) on (www.ema.europa.eu). The EPAR of the initial application procedure includes a summary of the EU-RMP from which all safety concerns (i.e. both relating to ME and other) were extracted as described before by Francisca et al [11]. The Summary of Safety Concerns describes the important identified and potential risks and the missing information of the medicinal product based on knowledge at the moment of the authorisation.

Outcome and covariates

For each medicinal product included in the study, the following data was collected from the EPAR: date of authorisation, Anatomical Therapeutic Classification (ATC) code, pharmaceutical form, safety concerns (SC), the categories for the summary of the safety concerns (important identified risk, important potential risk, or missing information), and the way ME are addressed (routine and aRMMs, and studies investigating the effectiveness of (a)RMM for MEs).

All risks included in the Summary of Safety Concerns regarding ME were translated manually into the most appropriate Preferred Terms (PTs) based on the Medical Dictionary for Regulatory Activities (MedDRA®)[1] terminology. After that, all ME safety concerns that are in the narrow Standard MedDRA query (SMQN) from MedDRA 19.0 where included in the study. The SMQN is a collection of PTs which are assembled to support the identification of MEs in MedDRA coded databases. The full PTs list for the ME SMQN is provided in the supplementary table A.

1 MedDRA® is the international medicinal terminology developed under the auspices of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

The EU-RMPs were reviewed in detail to identify the exact type of error that was being referred to for safety concerns defined as the general term 'medication error'. If a 'medication error' PT was translated to two or more PTs then each of these were counted separately in the analysis. Where the type of error could not be established based on the information in the EPAR, the first approved full EU-RMP document was retrieved for more information. Finally, ME safety concern PTs were categorised into nine groups based on the nature of the MEs, according to MedDRA Higher level terms (HLT) (as per table 1).

Table 1: PTs are classified into groups as per MedDRA HLT classification.

HLT	PT
Accidental exposures	Accidental exposure to product
Administration	Accidental overdose, contraindicated drug administered, drug administration error, inappropriate schedule of drug administration, incorrect dose administered, incorrect drug administration rate, incorrect product formulation administered, incorrect route of drug administration, wrong drug administered, wrong patient received medication
Confusion	Product dosage from confusion, product name confusion
Dispensing	Drug dispensing error
General	Device use error, drug titration error, medication error, multiple use of single-use product, wrong dose, wrong technique in product usage process
Monitoring	Medication monitoring error, therapeutic drug monitoring analysis incorrectly performed
Preparation	Product preparation error
Prescribing	Drug prescribing error
Selection	Product selection error

In the summary of safety concerns in the EU-RMP, safety concerns are classified into three categories: Important identified risks, important potential risks and missing information according to the guideline on good pharmacovigilance practices (GVP) Module V rev2 [10]. As specified in GVP Module V rev1, important identified risks are defined as "untoward occurrences for which there is adequate evidence of an association with the medicinal product of interest", important potential risks are "untoward occurrences for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed", and missing information is defined as "gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant"[16]. All risk minimisation measures (RMMs) are either routine or additional. Routine RMMs are categorized by section of the Summary of Product Characteristics (SmPC) in which specific information is included to address ME risks. An overview of all SmPC sections is provided in table 2.

Table 2. Structure of the EU Summary of Product Characteristics.

SmPC section	Section topic
1	Name of the medicinal product
2	Qualitative and quantitative composition
3	Pharmaceutical form
4	Clinical particulars
4.1	Therapeutic indications
4.2	Posology and method of administration
4.3	Contraindications
4.4	Special warnings and precautions for use
4.5	Interactions with other medicinal products and other forms of interaction
4.6	Fertility, pregnancy and lactation
4.7	Effects on ability to drive and use machines
4.8	Undesirable effects
4.9	Overdose
5	Pharmacological properties
5.1	Pharmacodynamics properties
5.2	Pharmacokinetic properties
5.3	Preclinical safety data
6	Pharmaceutical particulars
6.1	List of excipients
6.2	Incompatibilities
6.3	Shelf life
6.4	Special precautions for storage
6.5	Nature and contents of container
6.6	Special precautions for disposal and other handling of the product

Data regarding other routine RMMs (e.g. design of product packaging, prescription status) was not collected from the EPAR, as this data is not structurally available. ARMMs were categorised as educational materials for health care professionals, educational materials for patients, controlled access, controlled distribution or pregnancy prevention programs [17]. The need for risk minimization effectiveness studies is described in the EU-RMP. Information on the need for effectiveness studies was obtained from the EPAR, or if not provided, from the EU-PAS registry.

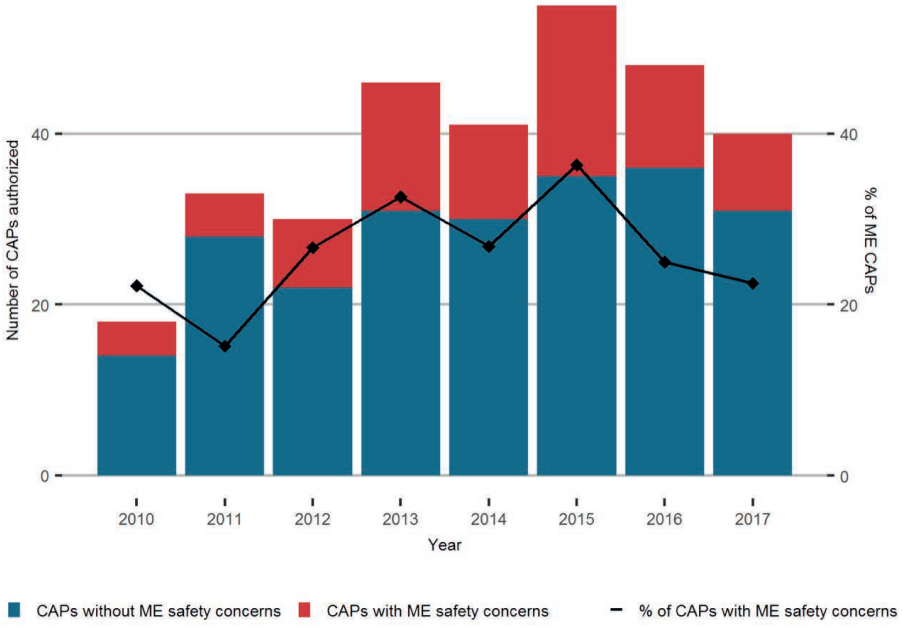
Data analysis

Descriptive statistics were used to present frequency data. All analyses were performed in Microsoft Excel 2010.

RESULTS

Between 1 January 2010 and 31 December 2017, a total of 311 CAPs were authorised in the EEA through the centralised procedure. In total, 4668 safety concerns were included in the EPARs of these products at time of marketing authorisation (both ME and non-ME safety concerns). Of the 311 CAPs, 84 products (27.0%) had at least one safety concern related to MEs. The proportion of CAPs approved with a ME safety concern showed variation between 2010 and 2017, ranging from 15.2% in 2011 to 36.4% in 2015 (see fig 1). For the 84 products with ME safety concerns a total of 95 separate ME safety concerns were identified.

Figure 1: Number of medication error (ME) centrally authorised products (CAPs) approved yearly with and without ME safety concerns



Type of ME Safety concerns

After translation of all 95 ME safety concerns to MedDRA PTs, it was observed that 'medication error' was the PT used most often to describe ME safety concerns (50; 52.6% of all ME safety concerns). Based on the information provided in the EPAR, 43 of the 50 ME safety concerns could be further classified into a PT more specific than 'medication error'. This resulted in a total of 103 PTs. Finally, as shown in table 3, 'drug administration error' was the most frequently reported safety concern (n=17),

followed by 'product dosage form confusion' (n=10) and 'product preparation error' (n=9). For 7 of the 50 safety concerns translated to the PT 'medication error' no additional information on the ME safety concerns could be identified in the EPAR nor in the fully approved EU-RMP. Therefore, it remains unclear what exactly the risk of ME entails for these products. Eight of the 103 ME safety concerns described in addition the clinical consequence of the ME.

Table 3. Description of the medication error safety concerns

Updated PTs	**Frequency***
Accidental exposure to product	8
Accidental overdose	4
Contraindicated drug administered	2
Device use error	6
Drug administration error	17
Drug dispensing error	1
Drug prescribing error	1
Drug titration error	1
Inappropriate schedule of drug administration	3
Incorrect dose administered	7
Incorrect drug administration rate	1
Incorrect product formulation administered	1
Incorrect route of drug administration	3
Labelled drug-drug interaction medication error	5
Medication error	7
Medication monitoring error	1
Multiple use of single-use product	3
Product dosage form confusion	10
Product name confusion	1
Product preparation error	9
Product selection error	1
Wrong dose	3
Wrong drug administered	3
Wrong patient received medication	1
Wrong technique in product usage process	4
Total	**103**

* These numbers are obtained after re-categorization of 'medication error' safety concerns. One safety concern may be translated into multiple PTs as a medication error may relate to multiple treatment stages. Therefore the 95 safety concerns identified for 84 CAPs resulted in 103 PTs.

Level of evidence for ME safety concerns

Of all ME safety concerns, 10.5% were categorised in the RMP as important identified risks, 82.1% were categorised as important potential risks and 2.1% were categorised as missing information (the remaining 5.3% of safety concerns were not categorised in the RMP). ME safety concerns classified as important identified risks required aRMM in 70%, important potential risk in 21.8% and for ME safety concerns classified as missing information, no aRMM was required.

Type of medicinal products

As presented in table 4, blood and blood forming organs products had ME safety concerns most often (18 of 84 products), followed by anti-infectives for systemic use (15 of 84 products) and antineoplastic and immunomodulating agents (13 of 84 products). Furthermore, when compared to the overall number of CAPs authorised in each ATC group, medicines for blood and blood forming organs most frequently had ME safety concerns, as 62.1% of products authorised in this ATC group had at least one ME safety concern (table 4).

Table 4. CAPs with and without ME safety concern per ATC group.

ATC group	CAPs with ME safety concerns (n=84)	CAPs without ME safety concerns (n=227)	% of CAPs with ME safety concerns	CAPs with ME*
A - Alimentary tract and metabolism	8	29	21.6	Fiasp®, **Kolbam®**, Revestive®, Ryzodeg®, **Strensiq®**, **Tresiba®**, Trulicity®, **Vimizim®**
B - Blood and blood forming organs	18	11	62.1	Afstyla®, Alprolix®, **Cinryze®**, Elocta®, Evarrest®, Iblias®, Idelvion®, Kovaltry®, **Lixiana®**, NovoEight®, **NovoThirteen®**, Nuwiq®, **Obizur®**, Raplixa®, Respreeza®, **Uptravi®**, VeraSeal®, Voncento®
C - Cardiovascular system	4	9	30.8	Adempas®, Brinavess®, **Glybera®**, **Hemangiol®**
D - Dermatologicals	2	4	33.3	Mirvaso®, **Scenesse®**
G - Genito urinary system and sex hormones	1	7	12.5	Silodyx®
H - Systemic hormonal preparations, excl. sex hormones and insulines	2	2	50.0	Natpar®, Somatropin Biopartners®

ATC group	CAPs with ME safety concerns (n=84)	CAPs without ME safety concerns (n=227)	% of CAPs with ME safety concerns	CAPs with ME*
J - Antiinfectives for systemic use	15	33	31.3	Eviplera®, Exviera®, Fluenz Tetra®, Gardasil 9®, Genvoya®, HyQvia®, Imvanex®, Nimenrix®, Pandemic influenza vaccine H5N1 AstraZeneca®, Sirturo®, Stribild®, Victrelis®, Vitekta®, Zavicefta®, Zerbaxa®
L - Antineoplastic and immunomodulating agents	13	82	13.7	**Blincyto®**, Cabometyx®, Cometriq®, **Farydak®**, **Imlygic®**, **Kadcyla®**, Lynparza®, Onivyde®, Qarziba®, Teysuno®, Tookad®, Unituxin®, Venclyxto®
M - Musculo-skeletal system	3	4	42.9	Krystexxa®, **Spherox®**, **Xiapex®**
N - Nervous system	2	19	9.5	**Ionsys®**, Sycrest®
P – Antiparasitic products, insecticides and repellents	0	1	0.0	-
R - Respiratory system	3	9	25.0	**Colobreathe®**, Eklira Genuair®, Seebri Breezhaler®
S - Sensory organs	6	4	60.0	Cystadrops®, Eylea®, **Holoclar®**, Ikervis®, Jetrea®, Omidria®
V - Various	6	10	37.5	EndolucinBeta®, **Lutathera®**, Lymphoseek®, Scintimun®, SomaKit TOC®, Tybost®
Not assigned yet	1	3	25.0	Viekirax®
Total	84	227	27.0	

CAPs=Centrally authorised products; ATC=Anatomical Therapeutic Chemical Classification System; ME=medication error; aRMM=additional risk minimisation measures.
* Products presented in bold had aRMM in place for ME.

Other ATC groups with a high rate of products with ME safety concerns were medicines for sensory organs (60.0%) and systemic hormonal preparations (excl. sex hormones and insulins, 50.0%). When considering pharmaceutical formulations, it was observed that more than half (53.6%) of the products with ME safety concerns concerned injections or infusions.

Routine risk minimisation measures

The SmPC sections most frequently used to address risks of MEs were sections 4.2 (posology and method of administration), 4.4 (special warnings and precautions for use), 4.9 (overdose) and 6.6 (special precautions for disposal) (table 5).

Table 5. SmPC sections listed as routine risk minimisation measures for MEs.

MedDRA HLT	2	3	4.1	4.2	4.3	4.4	4.5	4.8	4.9	5.1	5.2	6.2	6.3	6.4	6.6	Number of SCs*	Number of references per SC
Accidental exposures	0	0	1	4	0	4	0	0	1	0	0	0	0	1	5	8	2.0
Administration errors	1	0	2	29	1	22	4	1	9	1	1	0	0	0	7	45	1.7
General errors	0	1	1	16	1	6	1	3	3	0	0	1	1	2	7	24	1.8
Dispensing errors	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1.0
Prescribing errors	0	0	0	2	0	1	0	0	1	0	0	0	0	0	0	2	2.0
Monitoring errors	0	0	0	2	8	1	8	0	0	0	0	0	0	0	0	10	1.9
Confusion errors	2	0	0	6	0	2	0	0	0	0	0	0	0	0	1	11	1.0
Preparation errors	0	0	3	5	0	5	0	0	3	0	0	0	0	0	4	9	2.2
Selection errors	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1.0
Total	**3**	**1**	**7**	**65**	**10**	**42**	**13**	**4**	**17**	**1**	**1**	**1**	**1**	**3**	**24**	**111**	**1.7**

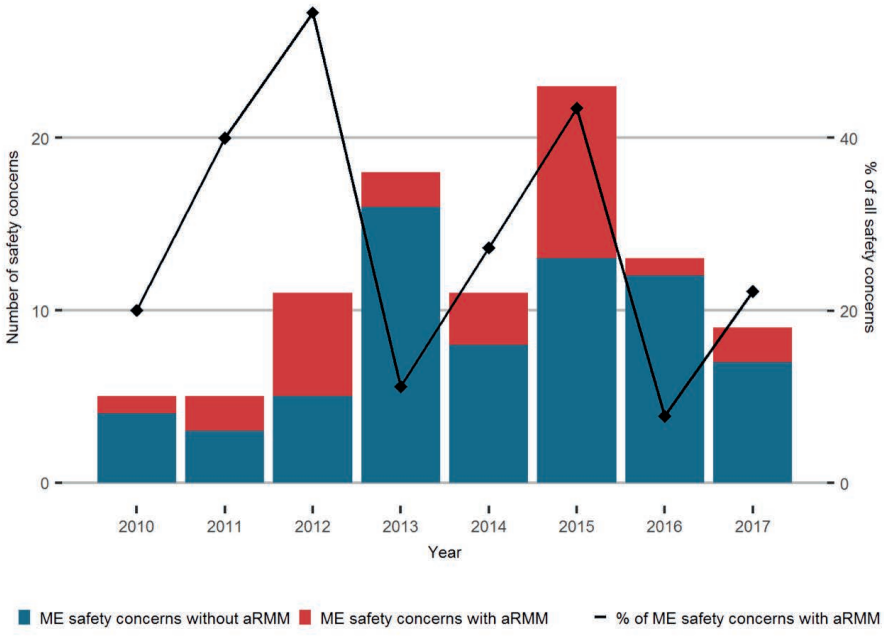
*As a safety concern may be included in more than one SmPC section and be classified into more than one HLT, the total number adds up to more than 95 safety concerns. SmPC Sections never used are not included in the table.

Per High Level Term group, different SmPC sections were chosen to minimise the risk of MEs. Safety concerns relating to preparation errors had the highest number of SmPC references per safety concern (2.2), and were often warned for in section 4.1 (33% of preparation errors), 4.2 (56% of preparation error safety concerns), 4.4 (56% of preparation errors), and 6.6 (44% of preparation errors). Safety concerns relating to accidental exposures were most frequently covered in section 6.6 (63% of accidental exposure safety concerns), followed by 4.2 and 4.4 (both 50% of accidental exposure safety concerns). Safety concerns relating to prescribing errors were most frequently covered in sections 4.3 and 4.5 (both 67% of prescribing error safety concerns). The single safety concern relating to product selection errors was covered in section 4.4 of the SmPC only. All other ME groups were most frequently covered in section 4.2.

Additional risk minimisation measures

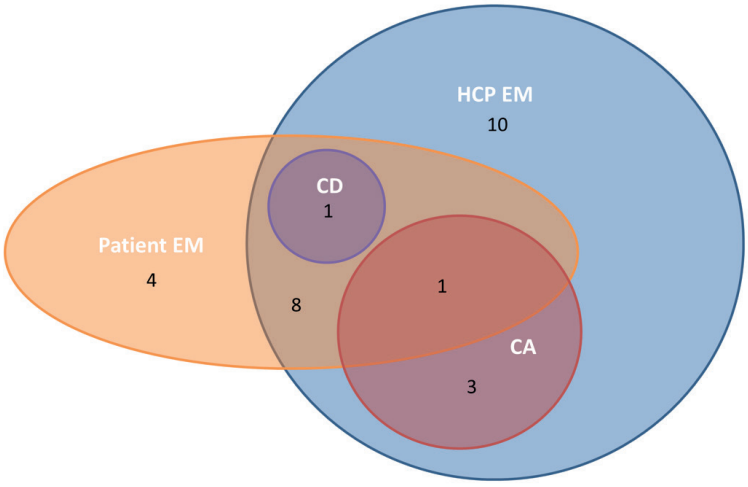
During the study period, 23 of the 84 products received aRMMs for 27 ME safety concerns. The rate of aRMMs for ME safety concerns was higher than for the remaining non-ME safety concerns (28.4% vs 7.5%). The proportion of ME safety concerns for which aRMM was implemented was variable over calendar time, ranging from 7.7% in 2016 to 54.5% in 2012 (fig 2).

Figure 2: Medication error (ME) safety concerns with and without additional risk minimisation measures (aRMM) per marketing authorisation year



For all 23 products aRMM included educational material that targeted HCPs in 85.2% and patients in 51.9% (fig 3). For eight of the 23 products (referring to 10 safety concerns), educational material targeted both HCP and patients. In addition to educational material, other aRMM were requested for 4 products (referring to five safety concerns). Controlled access was requested for three products to address the following four ME safety concerns: risks of exposure of HCPs and close associates/transmission to third parties (n=1), risks associated with (unintended) re-administration (n=1), risk of administering the drug to the wrong patient (n=1), and risk of dosing errors in the titration phase (n=1). Controlled distribution was requested for one product to prevent accidental exposure of healthcare professionals: an oncolytic immunotherapy, indicated for treatment of melanoma. It should be noted that the controlled distribution program for this product is not related solely to the ME safety concern, but also to other safety concerns. The controlled distribution program aims to minimise inappropriate handling and administration of the product and also aims to minimise the risk of damage to the product through inappropriate storing (56).

Figure 3: Number and types of additional risk minimisation measures (aRMM). Who is targeted by educational material? All products with aRMM utilised either educational material (EM) for patients, healthcare professionals (HCPs) or for both. *CA* controlled access, *CD* controlled distribution



Effectiveness of risk minimisation measures

A total of 29 studies to analyse the effectiveness of aRMMs for ME safety concerns were listed in the EPARs for 18 products (78.3% of products with aRMMs for ME safety concerns). For the remaining five products, no effectiveness studies were described. Multiple studies may have been requested for one safety concern or CAP.

Different designs were chosen for analysis of effectiveness. Registry studies were listed most frequently to analyse the effectiveness of aRMM for MEs (n=9). Other studies were described in the EPAR as follows: non-interventional observational studies not otherwise specified (n=6), analysis of spontaneous reports (n=5), surveys (n=5), clinical trials (n=4), and a drug utilization study (n=1). In two cases, the studies were primarily designed to investigate the effectiveness of the aRMM for MEs and, in the remaining 27 cases, the studies aimed to review the effectiveness of RMM for multiple safety concerns simultaneously. Of the 68 ME safety concerns that did not require aRMMs, 13 were studied further in post-marketing studies. This was achieved through multiple study designs: drug utilisation studies (n=5), disease registries (n=3), a survey (n=1), and observational studies not otherwise specified (n=6). Five studies focused only on characterizing the risk of a ME, whereas the remaining eight studies were general investigations into the post-marketing safety profile of the drug.

DISCUSSION

We observed that more than a quarter of the newly authorised medicines in the EU between 2010 and 2017 had ME safety concerns at the time of licensing. The high rate of products with ME safety concerns in this period may have several reasons. First, this high rate of products may reflect a high awareness of the seriousness and importance of MEs and the need to minimize these risks [6, 5]. Over the last years several actions have been taken by the EMA to increase awareness of MEs and to provide tools to reduce the risk of MEs, e.g. a stakeholder workshop on MEs, a CHMP opinion paper, and release of two good practice guides (one on *recording, coding, reporting and assessment of medication errors* and one on *risk minimisation and prevention of medication errors*) [19, 3, 6]. Second, it is also possible that this high proportion is due to the authorisation of products with high complexity in reconstitution and/or administration. It has been reported that products for intravenous use are associated with the highest complexity and highest risk of harm [20]. In addition, it has been reported that IV administration leads to the most serious outcomes from MEs [21]. This is in line with our data where we observed that more than half the CAPs with ME safety concerns were injections and infusions, or other specialised pharmaceutical products such as implants or sealants. An example of injectables are insulin products, for which specific risk minimisation measures and guidance to minimise the risk of ME have been developed [22].

Another important finding is the fact that a large proportion of ME safety concerns was just described in the EPAR as *medication error*, without indicating the exact type of medication error. Moreover, less than 10% of ME safety concerns specified the clinical consequence of the medication error. However, it is preferable to include the

undesirable clinical outcomes as a consequence of the ME in the EPAR in addition to the ME itself. Further, clearer descriptions of the type of medication error and its consequences could aid in the development of more tailored RMMs and better identification of the target population for these RMMs. For example, a safety concern as included in the Lixiana (Edoxaban) RMP (bleeding due to inappropriate administration) specifies what the cause is for the ME and the clinical consequences of the error. Since the current GVP Module V revision 2 states that the RMP "should address only the risks that are undesirable clinical outcomes … [which] … may be linked to situations such as … medication errors", the consequences of MEs may be better described in the future [10].

A third important finding is that the most common ME safety concerns are related to incorrect administration of medication. Different ME safety concerns were found in medicines of all ATC classes (supplementary table B), and it did not appear that specific errors were identified more often in certain ATC classes. Although some errors were very specific, e.g. multiple use of medicines intended for single-use only, others were more general e.g. administration errors. No clear pattern could be identified, which shows that there is not one single approach to address and minimise MEs, but that a case by case review is performed for each new medicine.

Fourth, we found that 10.5% of ME safety concerns were classified as important identified risk in the EU-RMP. ARMM were required for almost three-quarters of the ME safety concerns classified as important identified risks. While it is preferable that appropriate steps are taken to minimise or eliminate the risk of medication errors prior to drug approval, there may be situations where the risk is difficult to be resolved before the licensing, e.g. the complex administration methods associated with some products. In cases where the intended benefits of the product outweigh the risks or there is an unmet medical need, appropriate measures should be taken to further minimise the risk of MEs in the post-marketing setting.

Fifth, when ME safety concerns were classified as important potential risks, mainly routine RMMs were used to address these potential risks. ME safety concerns classified as important identified risks received aRMMs more often compared to ME safety concerns classified as important potential risks. This suggests that the certainty of the ME risks is a determinant for the necessity of aRMM. In addition, we observed that ME safety concerns were more often addressed with aRMM than all other safety concerns of the products. This is in line with recently published data which showed that MEs are among the safety concerns with the highest proportion of aRMMs [13, 14]. An explanation for the higher proportion of aRMM for ME safety concerns compared to all other safety concerns could lie in the difference in preventability. Non-ME safety

concerns are often adverse drug reactions that are intrinsic properties of the medicine and are therefore not always preventable in all patients. ME on the other hand, are in theory preventable for all patients and may benefit more directly from aRMMs. This is reflected by the fact that aRMM were often implemented for risks associated with administration or handling of the product. Educational material for this kind of errors often consists of a leaflet for HCPs, patients or carers with further instructions on how to handle, prepare and administer the product. The fact that all aRMM always consist of educational material is in line with previous findings [13, 14]. This is understandable as it is a useful tool to create awareness of risks among healthcare professionals and/or patients, before taking more restrictive measures.

Finally, we found that for 78% of products with aRMM for ME safety concerns studies were in place to measure the effectiveness of these measures. The effectiveness of educational materials is debated and the materials may not always have the intended effect [23]. Effectiveness studies are important to decide whether RMMs are adequate or should be amended, although the execution often remains a challenge [24-26]. Since the aRMMs discussed in this study are implemented at the time of the product approval, a comparison between before and after implementation of the aRMM is not feasible in these cases. Studies focus mainly on the observed rate of medication errors after marketing. When using spontaneous reports for this purpose, underreporting is a known problem [27]. Identifying the occurrence of medication errors may also be a challenge when existing electronic healthcare databases are used since particular errors (e.g. administration errors) can be difficult to identify in such data. Surveys to investigate whether HCPs understand the material may be biased as HCPs who are more aware of the educational material may be more inclined to participate in such a survey [28]. In addition, it is possible that those who read the material, but also experienced the ME, are less likely to participate due to social desirability bias. We observed that non-interventional observational studies, analysis of spontaneous reporting data and surveys were most frequently used for evaluation of effectiveness of RMMs for MEs. Despite the challenges, these may be the most feasible tools currently available for measuring ME in real-life. The advantage of spontaneous reporting data is that they can describe a wide variety of errors. However, better methods are needed to study medication errors in real life. Improvement may be sought in the application of already available digital tools (e.g. bar-code scanning). Our study did not investigate the effectiveness of the RMMs. We observed that for most CAPs in our dataset studies to assess the effectiveness of aRMMs for ME were agreed upon. However, only few effectiveness studies concerning ME have been published in public available domains [28, 29]. Public availability of these studies could aid the field in developing new techniques to measure the effectiveness of aRMMs and improve outcomes.

Strengths and limitations

To our knowledge, this is the first study providing a review of ME safety concerns and their planned risk minimisation measures. This study shows how often ME safety concern are included as important risks in the summary of safety concern of the EU-RMP and which measures are taken to prevent these risks. A review of ME and their risk minimisation measures may support regulators and biopharmaceutical medicine developers in future decision making and product development. Our study also has some limitations. The data collected in our study is based on EPAR documents which are publicly available on the EMA website. As these documents contain summarised information, data may be missing e.g. the complete overview of routine RMM. For example, it is not always described whether packaging and labelling is used to minimise the risk of ME. Therefore, this variable is not included in the study. This may have resulted in an underestimation of the efforts to prevent MEs. In addition, details of the studies that are planned to evaluate the effectiveness of risk minimisation are not always clearly presented in the EPAR. Availability of the complete EU-RMP in the public domain could improve data analysis. The lack of information in the EPAR was dealt with by investigating the original EU-RMPs for products with ME safety concerns identified form the EPAR where there was missing data. Another limitation of our study is that we only included products that had ME safety concerns at the moment of authorisation, therefore we could not address MEs that were identified later in the product cycle. Our study only focused on risk minimisation of medication errors in the EU. Other approaches to minimise the risk of medication errors may exist in other areas and comparison between approaches between different agencies is worth investigating.

CONCLUSION

Our study shows that over a quarter of medicines authorised in the EU have MEs as a safety concern in the EU-RMP. The high number of products with ME safety concerns and the high proportion of ME safety concerns with aRMM suggest awareness regarding medication errors at the level of the pharmaceutical industry and regulators. There is limited knowledge regarding the effectiveness of the measures available to prevent MEs. Therefore, studies are necessary to evaluate the suitability of the current risk minimisation framework for MEs.

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ADDITIONAL RISK MINIMISATION MEASURES POST-AUTHORISATION

Chapter 5

Introduction or discontinuation of additional risk minimisation measures during the life cycle of medicines in Europe

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ABSTRACT

Introduction: Additional risk minimisation measures (aRMMs) may be required to minimise important risks of medicines. ARMMs may be required at the time of authorisation, but may also be introduced or discontinued during the product life cycle as new safety information arises. The aim of this study is to describe post-authorisation introductions of new aRMMs and discontinuations of existing aRMMs for medicines authorised in the European Union (EU).

Methods: We performed a retrospective cohort study that included all new active substances authorised through the EU centralised procedure between January 1st 2006 and December 31st 2017. Data was extracted from European Public Assessment Reports available on the website of the European Medicines Agency (ema.europa.eu). Medicines were followed up from the date of marketing authorisation (MA) until first introduction or discontinuation of aRMMs excluding Direct Healthcare Professional Communications (DHPCs), withdrawal/suspension/revocation of the MA or July 1st 2018, when data extraction took place. Descriptive statistics were used to analyse frequency data and survival analysis was used to calculate 5- and 10-year probability of introduction or discontinuation of aRMMs.

Results: 476 medicines were authorised during the study period. The probability of getting aRMMs post-authorisation for products authorised without aRMMs was 3.5% (95%CI 1.2%-5.7%) within 5 years after authorisation and 6.9% (95%CI 2.6%-11%) within 10 years after authorisation. For products authorised with aRMMs the probability of discontinuation of aRMMs was 0.9% (95%CI 0%-2.6%) within 5 years and 8.3% (95%CI 0%-16.1%) within 10 years after authorisation.

Conclusions: We found low probabilities of introduction and discontinuation of aRMMs (excluding DHPCs) during the product life cycle for medicines authorised between 2006-2017. The low rate of discontinuation may potentially be due to lack of robust data on effectiveness of aRMMs. Further research is needed to get more insight in the dynamics of aRMMs during the medicine life cycle.

KEY POINTS

1. Medicines authorised between 2006 and 2017 without aRMMs have a low probability that aRMMs will be introduced within 5- and 10 years after authorisation and medicines authorised with aRMMs during that period have a low probability that aRMMs will be discontinued.
2. Post-authorisation introduction of aRMMs is most often triggered by new safety information arising from spontaneous reports or clinical trials.
3. The role of effectiveness evaluation of aRMMs in the life cycle management of medicines is currently unclear.

INTRODUCTION

The European Union Risk Management Plan (EU-RMP) has become an integral tool in the proactive life cycle management of medicinal products and facilitates identification, characterisation, monitoring and minimisation of risks. The EU-RMP first became a mandatory part of the authorisation dossier of innovative medicinal products authorised in the European Union (EU) in November 2005, and became mandatory for all medicinal products in 2012.[1, 2] The EU-RMP consists of three key components: the safety specification, the pharmacovigilance plan and the risk minimisation plan.[3] The safety specification describes the safety data available for the medicinal product, with focus on those safety concerns that require further activities post-authorisation. These safety concerns are listed as important identified risks, important potential risks and missing information. The pharmacovigilance plan describes the methods used to monitor and/or further characterise the important risks described in the safety specification. The risk minimisation plan describes the measures to minimise the important risks.[3]

Routine risk minimisation measures are in place for all medicinal products, for example the Summary of Product Characteristics (SPC), Patient Information Leaflet, pack design and prescription status. However, some medicinal products may be associated with important risks that may not be sufficiently minimised by these routine measures alone. Additional risk minimisation measures (aRMMs) may be needed to ensure that the benefits of these products outweigh their risks. Types of aRMMs include educational materials, that provide information to healthcare professionals and/or patients regarding risks on top of the information in the SPC; controlled access, in which prescription or dispensing of a medicinal product is conditional on fulfilling certain criteria (i.e. following a training program or performing certain diagnostic testing); controlled distribution, in which all stages of the product distribution are tracked; and pregnancy prevention programmes, which may include one of more

of the measures described above.[3, 4] ARMMs are conditions to the marketing authorisation (MA) and are therefore listed in annex IID of the MA, "Conditions and restrictions with regard to the safe and effective use of the product".

A need for aRMMs is assessed at the time of the authorisation. Studies have shown that, between 2006 and 2015, the proportion of products with aRMMs at the time of authorisation ranged from 26% to 42%.[5-8] However, risk management is an iterative process that is continuously applied throughout the product life cycle. New information regarding risks may become available post-authorisation, requiring introduction of new aRMMs or strengthening of already existing aRMMs. Conversely, new information regarding risks post-authorisation may also allow for the reduction or discontinuation of existing aRMMs. Currently, there is no published data on post-authorisation changes to aRMMs for products authorised in Europe, which translates to an important deficit in our knowledge regarding the life cycle management of medicinal products.

The aim of this study is to describe post-authorisation introductions and discontinuations of aRMMs for medicinal products authorised in the EU.

METHODS

Study design

We performed a retrospective cohort study that included all new active substances authorised through the centralised procedure between January 1st 2006 and December 31st 2017. Medicinal products included in our study were followed up from the date of marketing authorisation (MA) until first occurrence of an introduction or discontinuation of aRMMs, withdrawal or suspension or revocation of the MA, or date of data extraction (July 1st 2018), whichever came first. One or more types of aRMM can be introduced or discontinued simultaneously.

Data sources and setting

We extracted all centrally authorised medicines from the website of the European Medicines Agency (EMA) on www.ema.europa.eu. We excluded non-innovator applications, such as generic applications, as they have an EU-RMP aligned with the reference product. EMA publishes European Public Assessment Reports (EPARs) for all products authorised through the centralised procedure. We extracted data from the following EPARs: "EPAR – Public assessment report", the "EPAR – Product information" and the "EPAR - Procedural steps taken and scientific information after authorisation". The "EPAR – Public assessment report" is the summary of the initial assessment of the marketing authorisation application and includes a summary of

the RMP at the time of authorisation. The "EPAR – Product information" includes the most up-to-date product information with the annexes of the MA. The "EPAR - Procedural steps taken and scientific information after authorisation" is a log of all variations to the MA, i.e. any changes in the administrative information (such as transfers of the MA), changes in the manufacturing process, and changes in the benefit-risk profile of the product.

Study outcomes

Our main outcome was either a first introduction of aRMM(s) for medicines without aRMMs at the time of authorisation, or first discontinuation of at least one of the aRMMs for medicines with aRMMs at the time of authorisation.

We identified products with post-authorisation introduction or discontinuation of aRMMs in two ways to ensure completeness. First, for all products included in the study the "EPAR – Public assessment report" was reviewed to identify whether aRMMs were in place at the time of MA and the "EPAR – Product information" was reviewed to identify whether aRMMs were in place at the time of data extraction. Discrepancy between these two EPARs was regarded as a change (introduction if the aRMM was not in the initial RMP, but present in annex IID and discontinuation if vice versa).

Secondly, for all products included in the study, we reviewed the "EPAR - Procedural steps taken and scientific information after authorisation". All regulatory procedures that included amendments to annex II of the MA were screened to identify whether aRMMs were introduced or discontinued.

We also used the "EPAR - Procedural steps taken and scientific information after authorisation" to identify the regulatory procedure in which the introduction or discontinuation occurred and find the corresponding EPAR.

Covariates

The following information was extracted from the EPARs for all products included in our study: active substance, Anatomical Therapeutic Chemical (ATC) classification first level, date and type of MA, authorisation status (authorised, suspended, withdrawn), orphan designation (yes/no), aRMMs at the time of MA (yes/no), aRMMs at the time of data extraction (yes/no) and type of aRMMs.

Categorisation of type of aRMMs was based on the current definitions as laid down in the Good pharmacovigilance practices (GVP XVI rev 2) guidelines of the EMA, as described in table 1.[4, 5] Dear Healthcare Professional Communications (DHPCs)

were not included in our study, as these are generally not included in annex IID of the marketing authorisation and could not be systematically collected from the website of the EMA. One product can have one or more types of aRMM. Educational materials targeting HCP and educational materials targeting patients and/or caregivers were counted as different categories of aRMMs.

Table 1: Definition of additional risk minimisation measures as laid down in GVP Module XVI rev 2.(20)

Additional risk minimisation measures	
Educational programmes	Educational programmes are based on targeted communication with the aim to supplement the information in the Summary of Product Characteristics and Patient information Leaflet. Any educational material should focus on actionable goals and should provide clear and concise messages describing actions to be taken in order to prevent and minimise selected risks. Educational materials can be aimed toward health care professionals and/or patients/caregivers.
Controlled access programme	A controlled access programme consists of interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimisation measures, i.e. the legal status.
Controlled distribution system	A controlled distribution system refers to the set of measures implemented to ensure that the stages of the distribution chain of a medicinal product are tracked up to the prescription and/or pharmacy dispensing the product.
Pregnancy prevention programme	A pregnancy prevention programme (PPP) is a set of interventions aimed at minimising pregnancy exposure during treatment with a medicinal product with known or potential teratogenic effects.

The type of MA was categorised as regular MA, conditional MA or MA under exceptional circumstances.[1, 9]

For products with introduction or discontinuation of aRMMs, we extracted the following information from the EPAR of the corresponding regulatory procedure: the date of the amendment, the risk addressed with aRMMs, categorisation of the risk in the EU-RMP and the sources of the evidence that formed the basis for the introduction or discontinuation of the aRMM.

Categorisation of risks in the EU-RMP was based on the current definitions as laid down in GVP Module V rev 2, i.e. important identified risks, important potential risks and areas of missing information.[3] We categorised sources of evidence that formed the bases for the variation to the MA as non-clinical studies, clinical trials, observational studies and spontaneous reports. We also assessed whether aRMMs were imposed on medicines following EU referral procedures, i.e. (urgent) reviews of the benefit-risk balance of a medicine or class of medicines due to quality, safety or efficacy issues.

Data analysis

Descriptive statistics were used to provide frequency data. We used Pearson's χ^2 test or Fisher's exact test to investigate differences in categorical covariates between products with and without introduction or discontinuation of aRMMs.

To account for the time needed to accumulate sufficient data as justification for an introduction or discontinuation, we calculated the probability of introduction or discontinuation of aRMMs within five and 10 years after authorisation using Kaplan-Meier survival analysis. The cut-offs of five and 10 years are of particular interest, since MAs in the EU have initial duration of five years, after which the MA may be renewed with unlimited validity following a re-examination of the benefit-risk balance. Additionally, 10 years is the duration of market protection for innovative medicines.

All analyses were conducted using Microsoft Excel and R version 3-6-1.

RESULTS

We identified 476 medicinal products authorised during the study period (January 2006-December 2017) with a total of 32.514 months of follow-up. The median follow-up time was 60 months (range 8-150). The characteristics of the products included in the study are presented in table 2.

Of the 476 products, 91% were granted regular MA, 4% were granted conditional MA and 5% were granted MA under exceptional circumstances; 18% were intended for treatment of an orphan disease. Of the 476 products, 27% concerned "Antineoplastic and immunomodulatory agents", 19% concerned "Antiinfectives for systemic use" and 12% concerned medicines targeting the "Alimentary tract and metabolism". ARMMs were required at the time of authorisation for 27% (n=130) of the products. For all 130 products with aRMMs at the time of authorisation, the aRMMs included the provision of educational materials, targeted at health care professionals in 94% and at patients in 55%. For 14% (n=18) of the products with aRMMs, other measures were required in addition to the educational materials. This includes two products that had controlled distribution and a pregnancy prevention programme (ambrisentan, pomalidomide) and one product that had controlled access and a pregnancy prevention program (sitaxentan sodium). At the time of data collection (July 2018), 91% of the products were still authorised, 9% of the products had been withdrawn and for one product the MA had been suspended (autologous cultured chondrocytes). Medicines with aRMMs at time of MA had an orphan designation more often than medicines without aRMMs at the time of MA. There were no other significant differences in product characteristics between medicines authorised without and with aRMMs.

During the study period, aRMMs were introduced for 14 of 346 products authorised without aRMMs. All 14 aRMMs introduced post-authorisation included the provision of educational materials, which were aimed at healthcare professionals in 12 (86%) products and at patients or caregivers in seven (50%). For two products (gadoversetamide and split influenza virus inactivated, containing antigen equivalent to A/California/07/2009 (H1N1)-derived strain used NYMC X-179A), controlled distribution systems were introduced in addition to the educational materials. Among the 14 medicines for which aRMMs were introduced post-authorisation, one (antithrombin alfa) was authorised under exceptional circumstances and one (velaglucerase alfa) was intended for the treatment of an orphan disease. For the 14 medicines where aRMMs were introduced post-authorisation, five (36%) targeted "Blood and blood forming organs", three (21%) were "Antiinfectives for systemic use" and two (14%) targeted the "Musculoskeletal system". The remaining four belonged to the ATC groups "Alimentary tract and metabolism", "Antineoplastic and immunomodulatory agents", "Nervous system" and "Various". Of the 14 medicines with introduction of aRMMs post-authorisation, 11 were still authorised and three (gadoversetamide, ferumoxytol and split influenza virus inactivated, containing antigen equivalent to A/California/07/2009 (H1N1)-derived strain used NYMC X-179A) were voluntarily withdrawn from the market at the time of data collection (July 2018) (table 2).

ARMMs were discontinued for four of 130 medicines authorised with aRMMs during the study period. The products for which aRMMs were discontinued post-authorisation all had regular MA and none had an orphan designation. The four medicines for which aRMMs were discontinued post-authorisation belonged to the ATC groups "Blood and blood forming organs", "Antiinfectives for systemic", "Respiratory agents" and "Various". All aRMMs were discontinued for these four products. The discontinued aRMMs involved educational materials targeted at HCP for all four medicines and educational materials targeted at patients/caregivers for two medicines. All four medicines for which aRMMs were discontinued post-authorisation were still authorised at the time of data collection (table 2).

Median follow-up time of medicines for which aRMMs were introduced post-authorisation was 43 months (range 17-137 months) and median follow-up time of medicines for which aRMMs were discontinued was 90 months (range 25-96 months) (table 3). The probability of introduction of aRMMs post-authorisation for medicines without aRMM at authorisation was 3.5% (95%CI 1.2%-5.7%) within 5 years after authorisation and 6.9% (95%CI 2.6%-11%) within 10 years after authorisation. For medicines with aRMMs at authorisation, the probability of discontinuation of aRMMs was 0.9% (95%CI 0%-2.6%) within 5 years and 8.3% (95%CI 0%-16.1%) within 10 years after authorisation (figure 1 and figure 2).

Table 2: Characteristics of products authorised with and without aRMMs

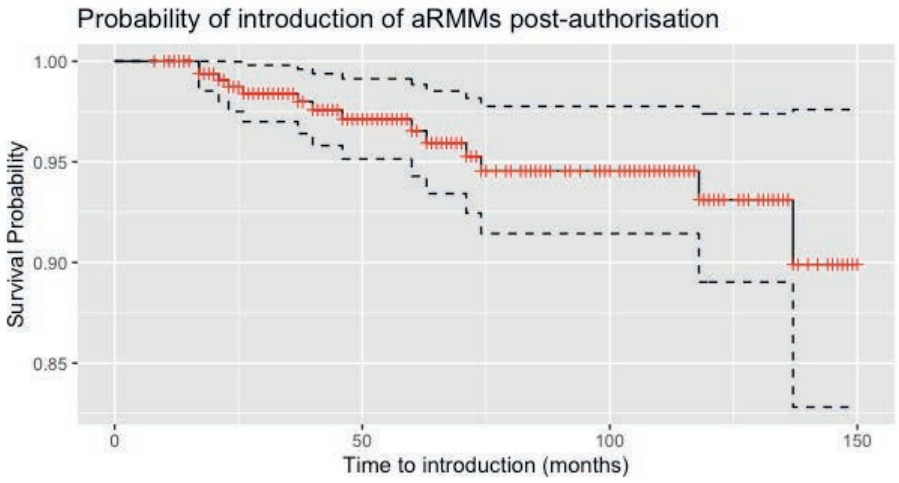
	Total (N, %)	Products without aRMMs at approval (N, %)	Products with introduced aRMMs (N, %)	Products with aRMMs at approval (N, %)	Products with discontinued aRMMs (N, %)
Number of products	476	346	14	130	4
Median follow-up time in months (range)	60 (8-150)	58 (8-150)	43 (17-137)	65 (8-150)	90 (25-96)
Type of marketing authorisation					
• Regular MA	431 (91%)	320 (92%)	13 (93%)	111 (85%)	4 (100%)
• Conditional MA	20 (4%)	12 (3%)	0	8 (6%)	0
• MA under exceptional circumstances	25 (5%)	14 (4%)	1 (7%)	11 (8%)	0
Orphan designation** (yes)	86 (18%)	54 (16%)	1 (7%)	32 (25%)	0
ATC group					
• Alimentary tract and metabolism (A)	57 (12%)	47 (14%)	1 (7%)	10 (8%)	0
• Blood and blood forming organs (B)	38 (8%)	25 (7%)	5 (36%)	13 (10%)	1 (25%)
• Cardiovascular system (C)	25 (5%)	15 (4%)	0	10 (8%)	0
• Dermatologicals (D)	7 (1%)	5 (1%)	0	2 (2%)	0
• Genitourinary tract (G)	15(3%)	12 (3%)	0	3 (2%)	0
• Hormones for systemic use (H)	6 (1%)	5 (1%)	0	1 (1%)	0
• Antiinfectives for systemic use (J)	91 (19%)	77 (22%)	3 (21%)	14 (11%)	1 (25%)
• Antineoplastic and immunomodulatory agents (L)	129 (27%)	82 (27%)	1 (7%)	47 (36%)	0
• Musculoskeletal system (M)	13 (3%)	9 (3%)	2 (14%)	4 (3%)	0
• Nervous system (N)	37 (8%)	29 (8%)	1 (7%)	8 (6%)	0
• Antiparasitic drugs (P)	1 (0.2%)	0	0	1 (1%)	0
• Respiratory system (R)	16 (3%)	13 (4%)	0	3 (2%)	1 (25%)
• Sensory organs (S)	16 (3%)	10 (3%)	0	6 (5%)	0
• Various (V)	25 (5%)	17 (5%)	1 (7%)	8 (6%)	1 (25%)
Type of aRMMs					
• Educational materials for HCP			12 (86%)	122 (94%)	4 (100%)
• Educational materials for patients/caregivers			7 (50%)	72 (55%)	2 (50%)
• Controlled access			0	7 (5%)	0
• Controlled distribution			2 (14%)	6 (5%)	0
• Pregnancy prevention programme			0	8 (6%)	0
Authorisation status*					
• Authorised	433 (91%)	316 (91%)	11 (79%)	117 (90%)	4 (100%)
• Suspended	1 (0.2%)	1 (0.3%)	0	0 (0%)	0
• Withdrawn	42 (9%)	29 (8%)	3 (21%)	13 (10%)	0

aRMMs = additional risk minimisation measures; MA = marketing authorisation

* at time of data collection (1 July 2018)

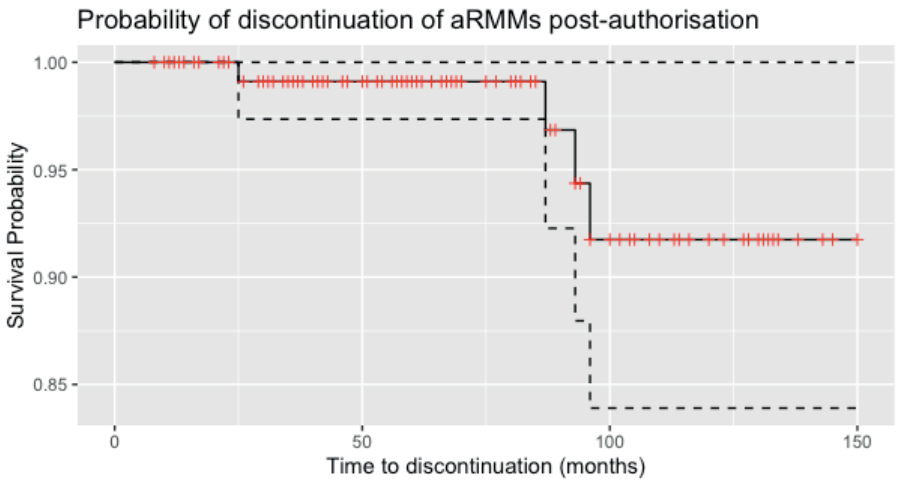
**Statistically significant difference between products without aRMMs at approval and products with aRMMs at approval

Figure 1: Kaplan-Meier estimate for post-authorisation introduction of aRMMs



aRMMs = additional risk minimisation measures

Figure 2: Kaplan-Meier estimate for post-authorisation discontinuation of aRMMs



aRMMs = additional risk minimisation measures

Table 3: Safety concerns involved in post-authorisation amendments to additional risk minimisation measures

Type of amendment	Product concerned	Safety concern description	Source of evidence	Follow-up time (months)
Introduction	ATryn©, Laboratoire Francais du Fractionnement et des Biotechnologies, France (antithrombin alfa)	Off label use	Spontaneous reports	137
	Rotarix©, GlaxoSmithKline Biologicals S.A., Belgium (human rotavirus, live attenuated)	Administration error (accidental parenteral instead of oral)	Spontaneous reports	63
	Cubicin©, Merck Sharp & Dohme B.V., The Netherlands (daptomycin)	Skeletal muscle toxicity	Clinical trials Non-clinical studies	118
		Reduced susceptibility in S. aureus		
	Optimark©, Mallinckrodt Deutschland GmbH, France (gadoversetamide)	Nephrogenic systemic fibrosis	Clinical trials Non-clinical studies Spontaneous reports	37
	Vectibix©, Amgen Europe B.V., The Netherlands (panitumumab)	Lack of response and negative effects in combination with oxaliplatin-based chemotherapy in patients with mutant KRAS tumours	Clinical trials	40
	Evicel©, Omrix Biopharmaceuticals N.V., Belgium (human fibrinogen / human thrombin)	Air or gas embolism	Spontaneous reports	23
	Effentora©, Teva B.V., The Netherlands (fentanyl)	Misuse, abuse and diversion	Spontaneous reports	21
		Use in patients who are not already receiving maintenance opioid therapy		
		Unintended (accidental) exposure		

Type of amendment	Product concerned	Safety concern description	Source of evidence	Follow-up time (months)
Introduction	Pandemrix©, GlaxoSmithKline Biologicals S.A., Belgium (split influenza virus inactivated, containing antigen equivalent to A/California/07/2009 (H1N1)-derived strain used NYMC X-179A)	Medical errors/ misidentification of vaccine	Spontaneous reports	17
		Coring of the rubber stopper on the antigen vial		
		Contamination of multiple-dose vials		
	Pradaxa©, Boehringer Ingelheim International GmbH, Germany (dabigatran etexilate mesilate)	Haemorrhage	Clinical trials	74
	Vpriv©, Shire Pharmaceuticals Ireland Ltd, Ireland (velaglucerase alfa)	Infusion-related reactions	Observational studies	71
	Prolia©, Amgen Europe B.V., The Netherlands (denosumab)	Osteonecrosis of the jaw	Clinical trials Observational studies Spontaneous reports	60
	Eliquis©, Bristol-Myers Squibb / Pfizer EEIG, Ireland (apixaban)	Bleeding	Clinical trials	17
		Severe renal or hepatic impairment		
		Liver injury		
	Xgeva©, Amgen Europe B.V., The Netherlands (denosumab)	Osteonecrosis of the jaw	Clinical trials Observational studies Spontaneous reports	46
	Rienso©, Takeda Pharma A/S, Denmark (ferumoxytol)	Hypersensitivity	Spontaneous reports	26

Type of amendment	Product concerned	Safety concern description	Source of evidence	Follow-up time (months)
Discontinuation	Hirobriz Breezhaler©, Novartis Europharm Limited, Ireland (indacaterol maleate)	Off label use	Observational studies	93
	Renvela©, Genzyme Europe BV, The Netherlands (sevelamer carbonate)	AV fistula site adverse drug reactions	Unknown	96
		Peritonitis		
		Vitamin deficiency		
	Revolade©, Novartis Europharm Limited, Ireland (eltrombopag olamine)	Hepatotoxicity	Unknown, considered part of clinical practice	87
		Thromboembolic events		
		Post therapy reoccurrence of thrombocytopenia		
		Potential for increase in bone marrow reticulin formation		
		Haematological malignancies		
	HyQvia©, Baxalta Innovations GmbH, Austria (human normal immunoglobulin)	Safety in pregnant and lactating women	Non-clinical studies	25

Table 3 describes the safety concerns and sources of evidence of the medicines for which aRMMs were introduced or discontinued. The aRMMs of the 14 products introduced post-authorisation addressed 21 safety concerns (median 1, range 1-3), of which 57% involved important identified risks, 38% important potential risks and 5% missing information. The data sources that triggered the introduction of aRMMs post-authorisation concerned spontaneous reports (64%), post-authorisation clinical trials (50%), observational studies (21%) and non-clinical studies (14%). These percentages do not add up to 100% since multiple sources of evidence could form the basis for the introduction of aRMMs post-authorisation. ARMMs were imposed on gadoversetamide following an EU review of the benefit-risk balance (referral) of gadolinium-containing contrast agents in light of the risk of nephrogenic systemic fibrosis.

The aRMMs of the four products that were discontinued post-authorisation addressed 10 safety concerns (median 2, range 1-5), of which 40% involved important identified risks, 40% important potential risks and 20% missing information. For the discontinuation of aRMMs, the sources of evidence were a non-clinical study (25%)

and an observational study (25%). The observational study was a multi-database drug-utilisation study for indacaterol maleate, which was authorised only for use in chronic obstructive pulmonary disease and had aRMMs to reduce the risks associated with off-label use in asthma; the authors concluded that there was little to no off-label use of indacaterol in the EU.[10] The data sources could not be identified in two products (50%).

DISCUSSION

The aim of our study was to describe discontinuations and introductions of aRMMs post-authorisation for centrally authorised medicinal products in the EU. We assessed the probability of post-authorisation introduction or discontinuation of aRMMs, rather than proportions, to account for the time required to accumulate sufficient data as justification for an introduction or discontinuation. During the study period, the probability of post-authorisation introduction of aRMMs was 3.5% (95%CI 1.2%-5.7%) within 5 years and 6.9% (95%CI 2.6%-11%) within 10 years after authorisation, while the probability of discontinuation of aRMMs was 0.9% (95%CI 0%-2.6%) within 5 years and 8.3% (95%CI 0%-16.1%) within 10 years after authorisation.

The probability of introduction of aRMMs within 5- and 10-years in our study is low. Besides introduction of aRMMs, regulatory action for safety issues emerging post-authorisation may include further investigation/monitoring, changes to routine risk minimisation measures or suspension/revocation of the MA. Studies have shown that the vast majority of important post-authorisation safety issues are either investigated further or monitored, or are sufficiently minimised through routine risk minimisation measures.[11] Moreover, the probability of introduction of aRMMs within five and 10 years post-authorisation found in our study is lower than the probability of a safety-related DHPC post-authorisation in a study that investigated whether probability of DHPCs increased with increasing level of innovation of medicines.[12] DHPCs are listed as a type of aRMM in GVP XVI rev 2, but differ from the aRMMs investigated in our study due to their one-off mode of action and broader scope of use. Between 1 January 1999 and 1 January 2009, 157 DHPCs have been sent out for 112 different active substances available in the Netherlands and 131 DHPCs were issued between 1 January 2010 and 31 December 2014 in the UK.[13, 14].

Spontaneous reports and clinical trials were the most frequent triggers for introduction of post-authorisation aRMMs in our study. These findings are comparable with results of other studies, in which spontaneous reports and post-marketing clinical trials are the most frequent sources of new safety information post-authorisation. ARMMs were imposed on one medicine in our study (gadoversetamide) following

a review of the benefit-risk balance of gadolinium-containing contrast agents, i.e. a referral procedure. Although several referrals were conducted and concluded during the study period, these concerned medicines approved before our study period (such as vitamin A derivatives) or medicines not approved centrally (such as sodium valproate). In addition, some referrals did not lead to imposition of aRMMs, such as both referrals concerning sodium glucose co-transporter 2 inhibitors.

The probability of discontinuation observed in our study is low compared to the discontinuation rates reported in literature for the United States' Food and Drug Administration's (FDA) Risk Evaluation and Mitigation Strategies (REMS). Studies have reported discontinuation rates of REMS between 57% and 75%, with an average time to REMS discontinuation of 1.7 years.[15-17] Median time to discontinuation of aRMMs in our study was 7.5 years. However, when comparing discontinuation rates of aRMMs in the EU and REMS in the US, some key factors should be considered. First and most importantly, medication guides (paper handouts which may help patients avoid serious risks) were always considered a REMS until November 2011, when FDA released new guidance clarifying that medication guides may not always be a REMS.[18] In one study, almost all the discontinued REMS consisted of only a medication guide.[15] The high reported rate of REMS discontinuation may be partly explained by re-evaluation of these medication guide-only REMS. Second, high discontinuation rates reported for REMS included multiple product-specific REMS programs for both innovator and non-innovator medicines with the same active substances and REMS programs for non-innovator medicinal products containing active substances with a long history of use. To avoid multiple counting of aRMMs, we excluded non-innovator medicines from our study as they are expected to follow the RMP of the reference innovator medicine. The discontinuation rate of REMS as reported in literature is therefore not directly comparable to the discontinuation rate of aRMMs in our study. Different conclusions regarding safety between different regulators have been shown to lead to differences in frequency, timing and content of safety communications both within the EU and between the US, Canada and the UK.[14, 19] This may also impact the decision to require or discontinue either aRMMs or REMS. Lastly, REMS requirements include mandatory assessment of the effectiveness of the measures after 18 months, three years and seven years. In contrast, time lines for evaluation of effectiveness of aRMMs are determined on a case-by-case basis, although GVP Module XVI rev 2 provides guidance on time points of particular interest, namely one year after implementation and five years after MA.[4]

Evaluation of the effectiveness of risk minimisation programs became mandatory with amendments to the EU's pharmaceutical legislation in 2012, with updated guidelines highlighting the importance of evaluation of effectiveness of aRMMs.

[1] Studies have found that effectiveness of aRMMs is evaluated through routine pharmacovigilance for more than half of the products with aRMMs.[7, 20] Recent reviews of studies evaluating the effectiveness of product-specific risk minimisation measures have shown heterogeneous methodology and mixed study outcomes.[21-23] In one review of effectiveness evaluation studies, the outcome of effectiveness evaluations led to discontinuation of the aRMMs under investigation in 9% of effectiveness evaluation studies. Further action such as updates to the content or improved distribution or follow-up assessment was required following half of the evaluations, and the evaluation did not lead to any changes in the remaining 40%.[24] However, these reviews concerned effectiveness evaluations in a subset of medicines (those intended for chronic treatment) or have been conducted using data available in the EU PAS register.[21-24] They may not provide an exhaustive overview of all effectiveness studies performed in the EU, since registration in the EU PAS register is only mandatory for studies imposed on the MA or studies that are a specific obligation to the MA – effectiveness evaluation studies rarely fall in these categories.[25] In our study, effectiveness evaluation was the trigger for only one discontinuation (Hirobriz breezhaler). This effectiveness evaluation study was not registered in the EU PAS register.

Notably, GVP module V was updated in 2017 to emphasize that aRMMs may be discontinued when no longer considered necessary, thus we expect the probability of discontinuation of aRMMs to rise in the coming years.[3]

Our study has limitations. First, we did not include DHPCs in our study as they differ substantially from the other aRMM modalities due their non-recurring nature and broader scope of use. Importantly, DHPCs are the only type of aRMM that are not recorded in annex IID of the MA and information on issued DHPCs is not systematically reflected on the EMA website. Although several national competent authorities publish DHPCs on their websites, studies have shown inconsistencies between national competent authorities with regards to dissemination and content of DHPCs.[19]

Second, our study included only centrally authorised products in the EU. However, due to the mandatory scope of the central procedure, the majority of new active substances approved during the study period is expected to be included in our study.[1] In addition, the vast majority (80-98%) of medicines approved through national, mutual recognition and decentralised procedures concern non-innovator applications such as generics: in 2018, 80-98% of the applications submitted to the Coordination Group for Mutual Recognition and Decentralised Procedures over the year 2018 concerned non-innovator applications. We excluded non-innovator products as their EU-RMP should be in line with the EU-RMP of the reference product.

Third, our study was conducted with publicly available data. The structure and quality of the EPARs, in particular the "EPAR – Public Assessment Report", evolved over time to include more information in a standardised manner. Particularly for the first part of the study period, identifying aRMMs at the time of MA could be challenging, leading us to develop the two-step approach we used in this study. Although there is residual potential for misclassification, for instance if the content of the EPARs is not updated correctly, this probability is considered to be small.

CONCLUSION

We found low probabilities of introduction and discontinuation of aRMMs (excluding DHPCs) during the product life cycle for medicines authorised between 2006-2017. The low probability of discontinuation may be due to lack of robust data on effectiveness of aRMMs. Further research is needed to get more insight in the dynamics of aRMM during the medicine life cycle.

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Chapter 6

Effectiveness of additional risk minimisation measures in the EU: a review of studies between 2012-2017

R.D.C. Francisca
I.M. Zomerdijk
M.C.J.M. Sturkenboom
S.M.J.M. Straus

ABSTRACT

Introduction: Effectiveness of additional risk minimisation measures (aRMMs) should be evaluated to assess success or failure and identify the need for amendments. Effectiveness evaluation is an integral part of the life cycle management of medicines in the EU, but is challenging for medicines with aRMMs at the time of authorisation. We aimed to provide a comprehensive review of effectiveness evaluation for medicines with aRMMs at the time of authorisation.

Methods: Medicines authorised with aRMMs between August 1st 2012 and December 31st 2017 were identified on the website of the European Medicines Agency (EMA). Data regarding planned, ongoing and finalised effectiveness evaluation studies were then extracted from the European Union Risk Management Plans, study protocols and final study reports submitted to EMA.

Results: We identified 44 studies for 35 of the 62 medicines with aRMMs at authorisation. Data was available for 38 of the 44 studies: 16 were surveys, 11 involved review of medical records. Median planned study duration was 3 years; interim reports were planned for 28 studies. Data was collected from healthcare professionals in nine (24%) studies, patients in 25 (66%) studies and both health care professionals and patients in four (10%) studies. 22 (58%) studies evaluated process indicators, six (16%) studies evaluated outcome indicators and nine (24%) studies evaluated both process and outcome indicators. Regulatory conclusions were available for seven studies, one of which was deemed effective and six which were inconclusive due to mixed reasons. ARMMs were updated for one product and a follow-up study was requested for another study.

Conclusion: Methodology of effectiveness evaluation studies was heterogeneous. This study shows that more in-depth regulatory guidance on methodology of effectiveness evaluation could be useful.

INTRODUCTION

Additional risk minimisation measures (aRMMs) may be required for medicines associated with serious risks that are not sufficiently minimised through routine measures, such as the Summary of Product Characteristics and labelling (1). ARMMs may consist of different tools, for example: educational materials for health care professionals and/or patients to convey additional communication regarding risks; controlled access, where prescribing or dispensing of the medicine is conditional on fulfilling set criteria or controlled distribution, in which all the stages of distribution of the medicine are tracked. In a pregnancy prevention programme, different risk minimisation tools are combined to minimise the risk of exposure during pregnancy (2).

ARMMs are intended to improve the safe and effective use of medicines, but may also pose a burden on the healthcare system, healthcare professionals and patients. ARMMs should therefore be risk-proportionate and the effort involved in complying with the measures should be carefully considered when designing the measures (3). Further, the effectiveness of the aRMMs overall as well the effectiveness of the individual components should be monitored after implementation to decide on success or failure and to identify opportunities for optimisation.

Frameworks have been developed for evaluation of the effectiveness of aRMMs, incorporating both data on the safety outcome of the intervention program and data on the process of implementation (4-6). Process indicators describe whether patients or healthcare professionals have received aRMMs, what knowledge they have retained from the aRMMs and whether they adhere to the aRMM recommendations. Outcome indicators describe the safety outcome, e.g., risk reduction achieved through the aRMMs. The European Medicines Agency (EMA) has adopted this approach in the guidance, but there are challenges to its application (2). For example, assessment of process indicators is susceptible selection and information bias (7). EMA's guidance also emphasises the need to carefully consider which aspects of process and outcome indicators may be realistically and accurately measured to avoid the collection of non-valid data and undue burden to clinical practice and other stakeholders (2). Moreover, a recent commentary by the EMA emphasizes the need to focus on public health impact and relevant patient outcomes (8).

Recent reviews of risk minimisation measure effectiveness studies have been conducted in only a subset of medicines, have addressed more than only effectiveness of aRMMs or are limited to the studies registered in the EU PAS register (9-13). The EU PAS register may not include all effectiveness studies since EU PAS registration is only mandatory for post-authorisation safety studies imposed by an EU competent

national authority (i.e. considered key to the benefit risk profile), and is voluntary for other studies (14). ARMM effectiveness studies are rarely considered key to the benefit-risk profile and may therefore not be registered in the EU PAS register. In addition, these reviews do not distinguish between studies conducted for medicines with aRMMs since the time of authorisation or studies conducted for medicines for which aRMMs became required during the life cycle (10-12). Around 30% of newly authorised medicines in the EU have aRMMs at the time of authorisation however an overview of the evaluation studies for these medicines is not yet available(15). This is particularly of interest since for medicines with aRMMs since marketing authorisation there is lack of reference data to interpret outcome indicators.

The aim of our study is to provide a review of effectiveness evaluation of aRMMs for medicines with aRMMs at the time of authorisation in the EU.

METHODS

Study design

We conducted a cross-sectional study that included medicines approved through the European Union centralised procedure between August 1st 2012 and December 31st 2017 which had aRMMs at the time of marketing authorisation (MA). The centralised procedure involves a single application and evaluation process for a marketing authorisation of a medicinal product valid throughout the European Economic Area(16).

Data sources and setting

First, we extracted all centrally authorised medicines from the website of the European Medicines Agency (EMA) on www.ema.europa.eu. We excluded non-innovator applications (i.e. generic applications, hybrid applications, informed consent applications, multiple or duplicate applications, fixed dose combinations and biosimilar applications). The European Union Risk Management Plan (EU-RMP) of these medicines is expected to be in line to the EU-RMP of the reference medicine. EMA publishes European Public Assessment Reports (EPARs) for all medicines authorised through the centralised procedure. We identified medicines with aRMMs at the time of the MA by screening the “EPAR – Public assessment report”, which is the summary of the initial assessment of the marketing authorisation application and includes a summary of the EU-RMP at the time of authorisation. If required, aRMMs are part of the risk minimisation plan of the EU-RMP.

Then, for medicines with aRMMs at the time of authorisation, we used the approved EU-RMP at time of marketing authorisation to identify planned effectiveness studies. Consequently, we searched for study protocols submitted to and approved by the EMA. Data regarding studies was extracted from study protocols (either approved or under assessment), or from final study reports if no study protocol was available, or from study synopses in the EU-RMP. Study results were extracted from the final study reports submitted to the EMA; regulatory conclusions and actions following assessment of the final study report were extracted from the final assessment report of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC).

Study outcomes

For all medicines included in our study, we extracted the following information from the EPAR: date of MA, Anatomical Therapeutic Chemical (ATC) classification, type of aRMM and whether a study or studies were planned to evaluate the effectiveness of aRMMs.

Type of aRMM was based on current definitions of the Good pharmacovigilance practices (GVP) XVI rev 2 of the EMA (2). We stratified educational materials by target group, i.e. materials targeting healthcare professionals and materials targeting patients/caregivers. One product can have more than one type of aRMM.

We screened both the pharmacovigilance plan and risk minimisation plan in the EU-RMP and counted any study included that evaluated the effectiveness of aRMMs as an effectiveness study.

For the medicines for which an effectiveness study was identified, we extracted the variables listed in table 1.

Table 1: Definition and sources for collection of the study variables

Variable name	Variable definitions	Data source
Study protocol approved	Yes/no	Post-authorisation variations to the MA or post-authorisation measures (PAM)
Study design	Cohort/cross-sectional/case-control/other	"Research methods" in approved study protocol, else final study report, else synopsis
Study duration	In years, from study start to submission of final study report	"Time lines" in approved study protocol, else final study report, else synopsis
Interim reports	Yes/no	"Time lines" in approved study protocol, else final study report, else synopsis, else EU-RMP
Data collection	Primary data collection/secondary use of data	"Research methods" in approved study protocol, else final case study report, else synopsis
Data collection method	Survey/registry/field study/medical record review/other	
Countries	All countries in the European Economic Area	
Effectiveness indicators	Process indicators: Receipt, Knowledge, Behaviour Outcome indicators	
Study population	Healthcare professionals/patients/both	
Study size	Stratified by healthcare professionals/ patients	
Effectiveness threshold	Yes/no	
Statistical methods	Stratified by measures of occurrence (yes/ no), measures of association (yes/no) and control for confounding (yes/no)	
Results available	Yes/no	Final study report
Study size reached	Stratified by healthcare professionals/patients	
Threshold achieved	Yes/no	
Regulatory conclusion	Effective/Ineffective/Inconclusive	Final Assessment report of PRAC
Regulatory action	No change/materials updated/distribution updated/materials discontinued	

MA = marketing authorisation; EU-RMP = European Union Risk Management Plan; PRAC = Pharmacovigilance Risk Assessment Committee

Data analysis

Descriptive statistics were used to provide frequency data. For categorical variables, data will be presented as counts and percentages. For continuous variables, data will be presented as median and range.

All analyses were conducted using Microsoft Excel 2019 and R version 3.6.1. Plots of the number of studies conducted in each European country were created using the tmap package (17). UpSet plots of the relationships between effectiveness indicators were created using the UpSetR package (18).

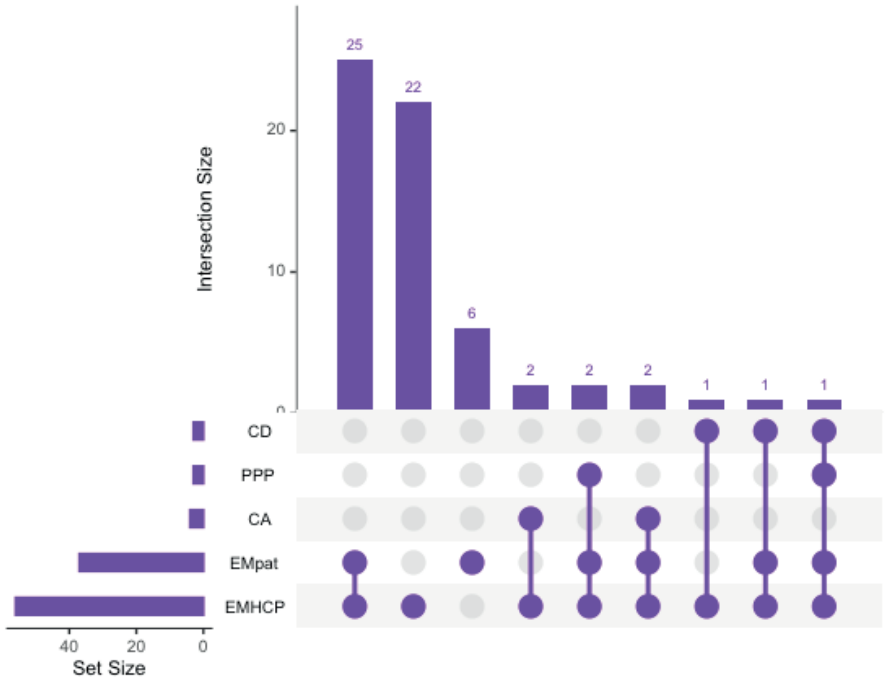
RESULTS

During the study period, 62 of 251 medicines were approved with additional risk minimisation measures at the time of MA. The characteristics of these medicines are presented in table 2. Of the 62 medicines, 56 (90%) had educational materials for healthcare professionals, 37 (60%) educational materials for patients, four (6%) controlled access, three (5%) controlled distribution and three (5%) a pregnancy prevention programme (figure 1).

Table 2: Characteristics of the medicines approved with aRMMs

	Number of medicines without effectiveness studies (n = 27)	Number of medicines with effectiveness studies (n = 35)	Total (n = 62)
Year of authorisation			
2012	1 (25%)	3 (75%)	4
2013	7 (50%)	7 (50%)	14
2014	3 (38%)	5 (62%)	8
2015	6 (35%)	11 (65%)	17
2016	1 (17%)	5 (83%)	6
2017	9 (69%)	4 (31%)	13
ATC group			
A – Alimentary tract and metabolism	6 (67%)	3 (33%)	9
B – Blood and bloodforming organs	3 (50%)	3 (50%)	6
C – Cardiovascular	1 (25%)	3 (75%)	4
D – Dermatologicals	0	2 (100%)	2
J – Antiinfectives for systemic use	1 (25%)	3 (75%)	4
L – Antineoplastics and immunomodulating drugs	12 (46%)	14 (54%)	26
M - Musculoskeletal	1 (100%)	0	1
N – Nervous system	0	2 (100%)	2
S – Sensory organs	0	3 (100%)	3
V – Various	3 (60%)	2 (40%)	2
Type of MA			
• Regular	21 (41%)	30 (59%)	51
• Conditional	2 (40%)	3 (60%)	5
• Exceptional	4 (67%)	2 (33%)	6
Orphan designation			
Yes	8 (42%)	11 (58%)	19
Type of aRMM			
• Educational materials for HCP	25 (45%)	31 (55%)	56
• Educational materials for patients	12 (32%)	25 (68%)	37
• Controlled access	1 (25%)	3 (75%)	4
• Controlled distribution	0	3 (100%)	3
• Pregnancy prevention programme	1 (33%)	2 (67%)	3

Figure 1: Number of medicines with aRMMs per combination of aRMM tools



CD = controlled distribution; PPP = pregnancy prevention programme; CA = controlled access; EMpat = educational materials for patients/caregivers; EMHCP = educational materials for healthcare professionals. The vertical bar chart with "intersection size" as Y-axis depicts the number of medicines per combination of aRMM tools (i.e. how many medicines require which aRMM tool or combination of multiple aRMM tools). For example, 25 medicines require educational materials for both healthcare professionals and patients/ caregivers while 22 medicines only require educational materials for healthcare professionals alone. The horizontal bar chart with "set size" as X-axis depicts the number of medicines in total that that require a certain aRMM tool, for instance there are 56 medicines that require educational materials for healthcare professionals, either alone in combination with other aRMM tools.

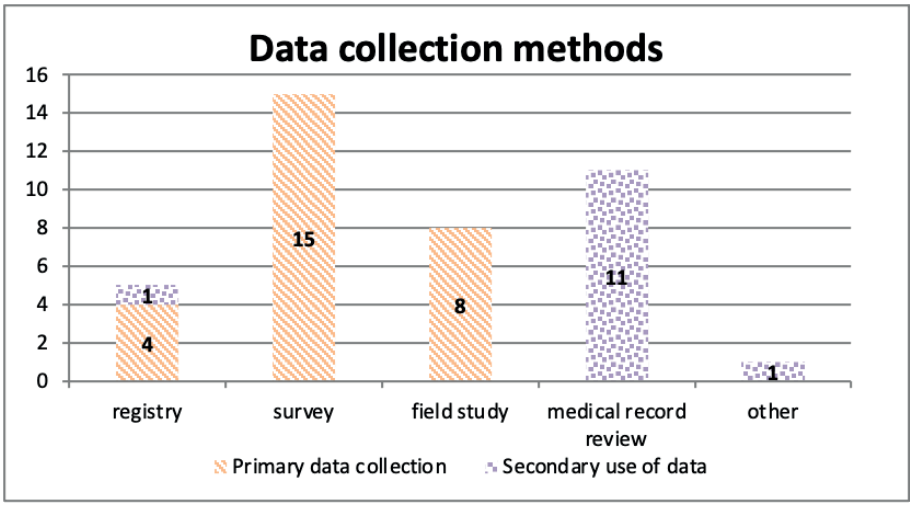
Table 3: Characteristics of aRMM effectiveness studies (studies are coded because of confidential nature)

Study	Study design	Type of data collection	Target population	Planned study size	Effectiveness indicators	Analysis methods
Drug A, study 1	cohort	Primary	Patients	1000	Process	Descriptive statistics
Drug A, study 2	cohort	primary	patients	1500	Both	Incidence
Drug B, study 1	Cohort	Primary	Patients	100	Both	Incidence, stratification
Drug B, study 2	Cohort	Secondary	Patients	Unknown	Process	Descriptive statistics
Drug B, study 3	cohort	Secondary	patients	unknown	process	Descriptive statistics
Drug C, study 1	Cross-sectional	primary	HCP	400	Process	Descriptive statistics
Drug D, study 1	Cohort	Primary	Patients	250	Both	Incidence
Drug E, study 1	Cross-sectional	Primary	Both	500 HCP 500 patients	Process	Descriptive statistics
Drug F, study 1	Cohort	Primary	Patients	425	Both	Incidence
Drug G, study 1	Cohort	Primary	Patients	unknown	Outcome	Incidence
Drug H, study 1	cohort	Primary	patients	700	Both	Incidence rates, hazard ratios
Drug I, study 1	Cross-sectional	Primary	Patients	500	Process	Descriptive statistics
Drug I, study 2	Cohort	Secondary	patients	800	Process	Descriptive statistics
Drug J, study 1	Cross-sectional	Both	Patients	75 primary 300 secondary	Both	incidence
Drug K, study 1	Cross-sectional	Primary	Both	400 HCP 400 patients	process	Descriptive statistics
Drug K, study 2	Cohort	Primary	Patients	5000	Outcome	Incidence rate
Drug K, study 3	cohort	primary	Patients	204	outcome	Incidence rate, rate ratio/ hazard ratio, propensity scores
Drug L, study 1	Cohort	Both	Both	100 HCP 1200 patients	process	Descriptive statistics
Drug M, study 1	Cross-sectional	primary	HCP	100	Both	Descriptive statistics

Study	Study design	Type of data collection	Target population	Planned study size	Effectiveness indicators	Analysis methods
Drug N, study 1	cohort	secondary	patients	160	Both	Incidence rate, logistic regression
Drug O, study 1	Cross-sectional	Primary	HCP	200	Process	Descriptive statistics
Drug O, study 2	cohort	secondary	Patients	8000	process	Descriptive statistics
Drug P, study 1	Cross-sectional	primary	HCP	300	process	Descriptive statistics
Drug Q, study 1	cohort	secondary	patients	660	process	Descriptive statistics
Drug R, study 1	cohort	secondary	patients	400	Both	Incidence
Drug S, study 1	Cross-sectional	primary	HCP	300	process	Descriptive statistics with stratification
Drug T, study 1	Cross-sectional	Primary	patients	200	process	Descriptive statistics
Drug U, study 1	Cross-sectional	primary	patients	400	process	Descriptive statistics
Drug U, study 2	Cross-sectional	Primary	HCP	400	Process	Descriptive statistics
Drug V, study 1	Cohort	Secondary	patients	600	Outcome	Descriptive statistics
Drug W, study 1	Cohort	Secondary	patients	100	outcome	Incidence
Drug X, study 1	Cross-sectional	primary	HCP	200	process	Descriptive statistics
Drug Y, study 1	Cross-sectional	primary	HCP	225	process	Descriptive statistics
Drug Z, study 1	cohort	primary	patients	unknown	unknown	Incidence
Drug AA, study 1	cohort	secondary	patients	1000	outcome	Adjusted incidence rates
Drug AB, Study 1	Cross-sectional	primary	both	60 HCP 400 patients	both	Descriptive statistics
Drug AC, study 1	Cross-sectional	primary	HCP	300	Process	Descriptive statistics
Drug AC, study 2	cohort	secondary	patients	unknown	process	Descriptive statistics

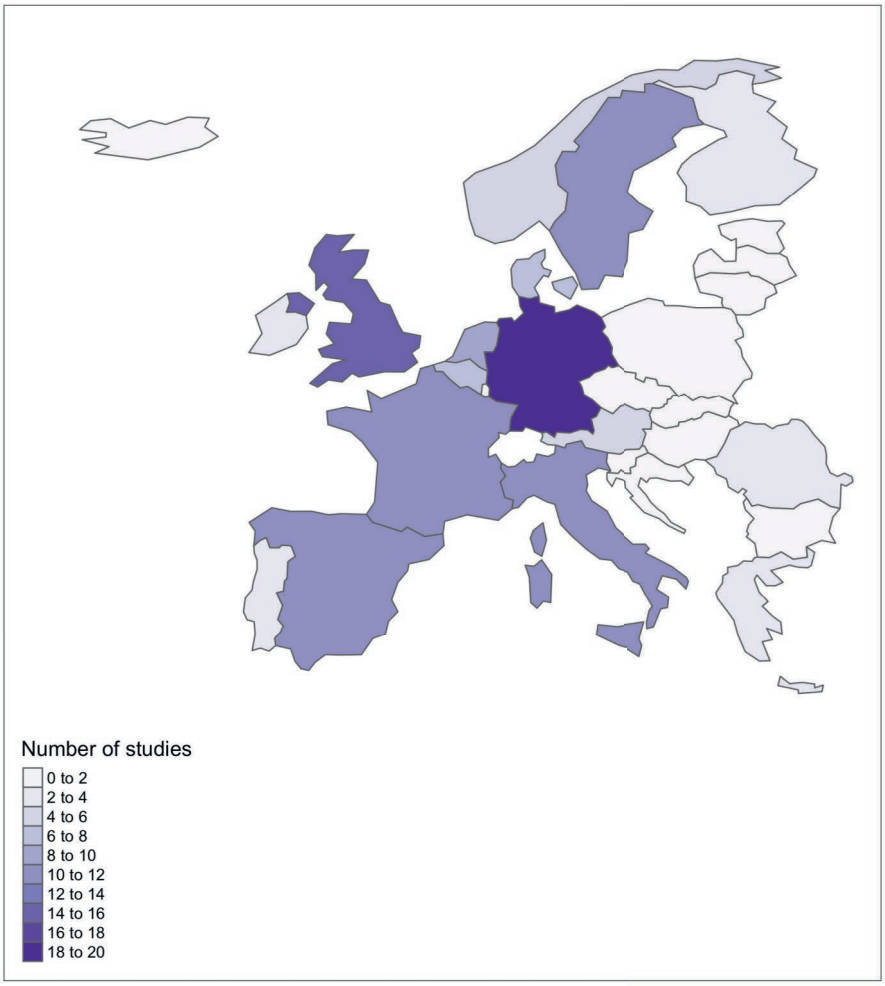
All 38 studies for which data on study characteristics could be retrieved were observational in nature, using a cross-sectional design in 16 (42%) and a cohort design in 22 (58%). Median planned study duration (specified for 35 studies) was 3 years (range 1-20 years). Interim reports or updates in PSURs were planned for 28 (74%) of the studies. Of the 38 studies, 25 (66%) studies used primary data collection (collected specifically for the purpose of the study), while 11 (30%) studies made use of data that was collected for routine healthcare delivery (i.e. secondary use of data). The remaining two (4%) studies combined secondary use of health data with a survey designed for the study. Data collection methods were categorised into 5 groups: surveys, registries, field studies, (electronic) medical record review and other. Surveys were the most frequently used data collection method, followed by medical record review (figure 2).

Figure 2: Data collection methods in effectiveness assessment studies



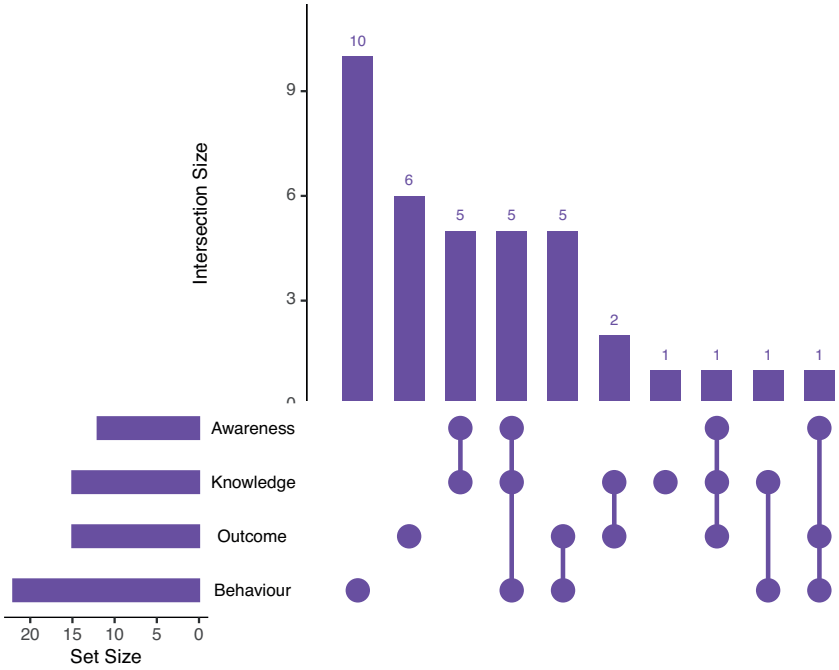
Of the 38 studies, 36 (95%) were conducted in more than one European Member State and one study (3%) was conducted only in the US. The country or countries in which the remaining study was conducted could not be identified. The median number of countries in which studies were carried out was five (range 1-9). For 24 (63%) studies, the countries in which the study would be carried out could be identified. As shown in figure 3, studies were most often carried out in Germany (n = 19) and the United Kingdom (n = 15).

Figure 3: Member states from which participants were included for effectiveness evaluation studies (n = 24)



Effectiveness indicators could be extracted for 37 of the 38 studies: 22 (58%) studies evaluated process indicators, six (16%) studies evaluated outcome indicators and nine (24%) studies evaluated both process and outcome indicators. As shown in figure 4, studies most frequently assessed behaviour of healthcare professionals as a measure of effectiveness of aRMMs (n = 22).

Figure 4: Number of studies per combination of effectiveness indicators evaluated



The vertical bar chart with "intersection size" as Y-axis depicts the number of studies per combination of effectiveness indicators evaluated (i.e. how many studies evaluated more than one effectiveness indicator). The specific effectiveness indicators can be seen below each bar, for example 10 studies assessed only behaviour while 6 studies assessed only outcome.
The horizontal bar chart with "set size" as X-axis depicts the number of studies in total that assess an effectiveness indicator, for instance there are 22 studies that have assessed behaviour, either alone in combination with other indicators.

Data was collected from healthcare professionals in nine (24%) studies, patient level data in 25 (66%) studies and both health care professionals and patients in four (10%) studies. One of the four studies collecting data from both healthcare professionals and patients consisted of a drug utilisation study combined with a survey of participating healthcare professionals, submitted as a single protocol; the remaining three studies were surveys targeting both patients and healthcare professionals. All the studies aimed at healthcare professionals (n=13) were surveys. Of the 29 studies collecting patient level data, five were surveys and the remaining 24 were cohort studies. The planned study size could be identified for all 13 studies collecting data from healthcare professionals; the median number of healthcare professionals to be included was 300 (range 100-500). The planned study size could be identified for 24 of the 29 studies collecting patient level data; the median number of patients to be included 500 (range 100-8000).

A pre-defined threshold for effectiveness of risk minimisation measures was available for 11 (29%) of the 38 studies. These studies were all survey studies; effectiveness was defined as either the proportion of participants answering each individual question correctly, with one study outlining key questions, or as the proportion of correctly answered questions. The pre-defined thresholds for effectiveness in these 11 studies ranged between 70% and 80%.

Analysis methods beyond descriptive statistics were planned for 13 (34%) studies. All of these studies calculated measures of occurrence in the form of either incidence proportions or incidence rates of adverse drug events of interest. In addition, two of these studies also calculated measures of association in the form of hazard ratios (both studies) and rate ratios (one study). Additional methods were employed to achieve control for confounding in five studies: propensity score matched regression, multivariate Cox regression, adjustment, logistic regression and stratification were each applied in one study. One additional study stratified results by subgroups, but only presented descriptive statistics without testing or comparison between subgroups.

Final study results at the time of review were available for 11 (30%) studies. The pre-planned sample size was achieved for two of five studies collecting data from healthcare professionals and for four of five studies collecting patient level data, 2 studies did not provide a pre-planned sample size. There were six studies that had pre-specified a threshold for risk minimisation success; the threshold was achieved in one study. The regulatory conclusion following assessment of the results was available for seven of the 11 studies: aRMMs in one study were considered effective and the results of six studies were considered inconclusive: two studies failed to reach achieve the pre-specified threshold of success, two studies had methodological (bias) issues, one study was conducted outside the EU, one study showed poor but stable adherence to the risk minimisation program among healthcare professionals over a longer period of time. In five of the seven studies, the aRMM program remained unchanged and no follow-up or additional studies were requested. For one study, a follow-up survey was requested and for the remaining study, the contents of the aRMMs as well as the product information was amended. For one study that failed to achieve the pre-specified threshold of success, the aRMMs were left unchanged because healthcare professionals designated the aRMMs as useful in the survey and for the other, pre-defined key questions were answered correctly despite the overall threshold not being achieved. The results of four studies were still under assessment at the time of data collection. For one medicine, aRMMs were no longer required after new scientific evidence form non-clinical studies became available that disproved an association between the medicine and the risk to be minimised by the aRMMs. The aRMM effectiveness evaluation was therefore not continued.

DISCUSSION

In our study, we have reviewed how effectiveness of aRMMs is evaluated specifically for medicines with aRMMs at the time of authorisation. Effectiveness studies were planned for 56% of the medicines with aRMMs at the time of authorisation.

Surveys were the most frequently used to evaluate effectiveness of aRMMs (42% of all studies), in line with recent reviews on this topic (9, 10, 12). EMA's GVP XVI rev 2 states: *In order to assess the awareness of the target audience, their attitude and level of knowledge achieved by educational interventions or other information provision (e.g. via an educational programme with a goal of preventing drug exposure during pregnancy), scientifically rigorous survey methods should be used* (2).

Surveys have important limitations such as potential for social desirability bias and selection bias; a recent systematic review and meta-analysis of survey studies evaluating the effectiveness of risk minimisation measures has shown that less than 10% of invited participants complete the survey (11). Despite the limitations, surveys appear nevertheless an important method to evaluate knowledge on aRMMs and behaviour in the real-world setting due to their possibilities. Other approaches to assess knowledge or behaviour have also been explored, such as the observational study conducted for romiplostim, in which patients were trained and directly observed by their healthcare providers on their compliance with instructions in the home-administration pack (19). Such an approach could provide direct information on the effectiveness of aRMMs, though not necessarily real-world effectiveness e.g., the effectiveness outside of the controlled conditions of a study.

Thresholds for effectiveness were pre-specified in one third of the studies, all surveys. The pre-specified thresholds ranged from the proportion of correct answers per question to the overall proportion of correctly answered questions. These findings may be explained by the lack of available guidance on how to define thresholds for effectiveness; regulators and pharmaceutical companies may be hesitant to suggest approaches beyond descriptive statistics due to a lack of robust scientific evidence on setting effectiveness thresholds in pharmaceutical risk management (7).

Notably, no thresholds were specified for studies assessing outcome indicators, such as incidence rates. One of the key challenges in specifying thresholds for outcome indicators of aRMMs required at the time of authorisation, is selecting an adequate control group (7). For medicines approved with aRMMs, there are no incidence rates prior to introduction of aRMMs (i.e. trends) to use as comparator, outside of the incidence rates in clinical trials. Real world incidence rates are expected to be higher than those in clinical trials due to substantial differences between the populations

studied in clinical trials and real-world users, as well as the controlled trial environment. However, a recent study by Hampp et al showed an interesting approach to utilise clinical trial incidence rates: standardised incidence ratio calculated by using the number of observed events divided by the number of events that would be expected if the study population experiences the event at the rate observed in clinical trials (20). Incidence rates in active comparators (i.e. benchmarking) may not be a suitable control group, for instance if the active comparator doesn't have an increased risk of the event or if the active comparator requires aRMMs for which the effectiveness has not been demonstrated. This approach offers interesting possibilities.

ARMM programs remained unchanged following regulatory assessment for six of seven studies with an available final assessment report. The results of the effectiveness evaluation study were considered inconclusive for six of these seven studies due to mixed concerns. This includes two products for which the pre-defined thresholds for success were not achieved, but aRMMs remained unchanged due to HCPs finding the materials useful in one study and the key questions being answered correctly in the other. The high proportion of studies with inconclusive results highlights that regulatory guidance on methodology and thresholds of effectiveness evaluation would be welcome. Evaluating the effectiveness of aRMMs is essential to identify potential areas of improvement and to minimise unintended effects. First, the time and effort involved in complying with aRMMs may pose a burden on the healthcare system. It is particularly important to design and optimise aRMMs to integrate optimally in existing processes within healthcare delivery systems, made all the more important because administration time in general (ie. not related to aRMMs) is increasingly recognised as an issue in multiple national healthcare systems (3, 21, 22). For example, studies could identify when educational brochures are effective on top of the Summary of Product Characteristics, and when they are not (23, 24). Second, aRMMs may also have financial consequences for the healthcare system, such as the costs involved in diagnostic testing prior to treatment initiation or during treatment, as well as for pharmaceutical companies (25). Third, risk minimisation programs may limit patient access to medicines, for instance due to decreased prescribing or discontinuation in patients for which the benefit-risk balance remains positive (26).

In our study, we have reviewed industry-sponsored studies evaluating the effectiveness of aRMMs agreed/requested by EU regulators. One limitation of our study is that identification of effectiveness studies was based on titles and objectives in the first approved EU-RMP. Therefore, it is possible that studies for which the title or objective did not clearly specify that effectiveness of aRMMs would be evaluated were not counted as effectiveness studies. Moreover, protocols of effectiveness evaluation studies may not have been correctly identified for studies for which title and objective differed significantly from the title and objectives in the EU-RMP.

Effectiveness studies were not planned for all medicines approved with aRMMs, despite the previously established importance of effectiveness evaluation. However, conducting effectiveness studies may not be feasible for all aRMMs. First, the real-life use of the medicine may be so low that adequate power to evaluate effectiveness of aRMMs cannot be achieved. This might be the case for medicines approved with conditional MA, MA under exceptional circumstances and medicines with an orphan designation. Conditional MA and MA under exceptional circumstances are granted to medicines for which their (potential) benefit outweigh the risks associated with less comprehensive data than usual. Medicines with an orphan designation are intended for the treatment of rare diseases. These medicines have been shown to have a higher probability of having aRMMs, but evaluating effectiveness of aRMMs may be more challenging for them due to the low numbers of use (15). Conversely, not all medicines granted conditional MA have low numbers of use, as evidenced by the COVID-19 vaccines. For these medicines, multiple post-authorisation studies have been pre-planned to investigate adverse events of special interest and several ad-hoc studies have been conducted to investigate specific concerns such as venous cerebral thrombosis (27).

Second, the data required to evaluate the effectiveness of aRMMs may not be systematically captured in medical records. A study by Zomerdijk et al found that 22% of key elements of aRMM (ie. key messages to be delivered by aRMMs) could be assessed in electronic medical record databases. These key elements were mainly aimed at behavioural changes, like recommendations regarding the dose, concomitant medications or to perform a laboratory test(28). The results of this study suggested that the design of aRMMs could be improved. More recently, the RIMES statement was developed as a tool to assess the quality of reporting of effectiveness evaluation studies, similar to the STROBE guidelines and the RECORD statement. Improvement of the quality of reporting effectiveness studies through standardisation of reporting requirements could lead to an improvement of evaluation studies and ultimately lead to better design of aRMMs themselves (29).

CONCLUSIONS

Effectiveness of aRMM was evaluated through studies for half of the medicines with aRMMs at the time of authorisation. Applied methodologies were heterogenous and led to mixed concerns from regulatory agencies. This study shows that more in-depth regulatory guidance on methodology of effectiveness evaluation, e.g. pre-defining thresholds, could be useful.

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POST-MARKETING SURVEILLANCE OF MEDICAL DEVICES

Chapter 7

EU Post-Market Surveillance Plans for medical devices

Pane J, Francisca RDC, Verhamme KMC, Orozco M, Viroux H, Rebollo I, et al. EU postmarket surveillance plans for medical devices. Pharmacoepidemiol Drug Saf. 2019;28(9):1155-65.

ABSTRACT

Recent public health safety issues involving medical devices have led to a growing demand to improve the current passive-reactive Post-Marketing Surveillance (PMS) system. Various European Union (EU) National Competent Authorities have started to focus on strengthening the post-market risk evaluation. As a consequence, the new EU Medical Device Regulation was published; it includes the concept of a PMS Plan.

This publication reviewed Annex III Technical Documentation on PMS and Annex XIV Part B: Post-Market Clinical Follow-Up from the new Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices.

The results of the PMS activities will be described in the PMS plan, and will be used to update other related documents. A modular approach to structure the contents of the PMS plan will help to consistently update other PMS information. It is our suggestion that the PMS plan should consist of a PMS plan Core and a PMS plan Supplement. The PMS plan Core document will describe the PMS system and the PMS plan Supplement will outline the specific activities performed by the manufacturer for a particular medical device.

The PMS plan may serve as a thorough tool for the benefit-risk evaluation of medical devices. If properly developed and implemented, it will function as a key player in the establishment of a new framework for proactive safety evaluation of medical devices.

INTRODUCTION

A medical device is defined as ‘‘any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease, replacement or modification of the anatomy or of a physiological process, and control of conception’’(1). Medical devices are a great resource for enhanced diagnosis and disease management.

Recent public health safety issues involving medical devices have highlighted the need to update the European Union (EU) Medical Device Regulation (MDR). The Poly Implant Prothèse (PIP) breast implant scandal in 2012 affected thousands of women and damaged the confidence of the different stakeholders involved in Post-Market Surveillance (PMS) of medical devices (2). More than 400,000 women around the world received PIP implants that were made of industrial-grade silicone gel, prone to rupture, leading to inflammation and irritation. Another incident in 2012 involving hip implants raised a public health concern: metal-on-metal total hip replacements were successfully implanted, but metal abrading against metal caused erosion and leaching of metal particles into soft tissue (3). Such metal debris weakens tissue and bone around the implant, leading to implant failure, requiring additional surgery. The manufacturers did not provide an adequate response to the competent authorities with regard to these adverse events and there was always the belief that they could have been avoided (4).

As a consequence, various National Competent Authorities (NCAs) and other health organizations started focusing on strengthening post-market risk evaluation of medical devices. One of the important novelties in the new Regulation on medical devices (EU) 2017/745, published May 5, 2017 is the concept of a PMS Plan for each medical device family (5). A regulation is a legal act of the EU that becomes immediately enforceable as law in all member states simultaneously. Regulations can be distinguished from directives which, at least in principle, need to be transposed into national law (6). The current Medical Device Directive 93/42/EEC states that *“The manufacturer shall institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase, including the provisions referred in Annex X, and to implement appropriate means to apply any necessary corrective action”.* Annex X says that “The clinical evaluation and its documentation must be actively updated with data obtained from the post-marketing surveillance. Where a post-marketing clinical follow-up as part of the post-marketing surveillance plan for the device is not deemed necessary, this may be duly justified and documented” (7). Contrary to what happens with the new regulation,

there are no instructions or guidance on the contents of the PMS plan and on how to implement this requirement in the current Medical Device Directive 93/42/EEC although the concept of a PMS plan is mentioned.

According to the new regulation, the PMS Plan will have to define the process for collecting, recording and investigating complaints and reports from healthcare professionals, patients and users on events suspected to be related to a medical device. A PMS system that is correctly designed should allow for early detection of possible malfunctions and/or complications of medical devices that may occur only after years or even decades of usage, and implement appropriate risk minimization measures.

Today, many medical device manufacturers have a “reactive” PMS system that is based on collection of post-market data received from spontaneous reporting of complaints and incidents. Unfortunately, there are few proactive PMS processes designed to actively gain knowledge on the safety and performance of the medical device through external sources like registries, electronic healthcare records, safety evaluation sites, claim databases, social networks, and literature (8).

The new EU Regulation aims to reinforce key elements of the existing regulatory approach, including vigilance and market surveillance, at the same time ensuring transparency and traceability, to improve health and safety(5). The objective of this article is to describe the new EU Regulation on PMS of medical devices, to compare it with our experience in the drug area and to provide recommendations for implementation.

Post-Market Surveillance system for medicinal products and medical devices in the EU

Medicinal products: manufacturers may submit a marketing authorization application to either EMA or to the national competent authorities of the member states. Authorization through the European Medicines Agency, also known as the centralized procedure, offers the benefit of a single assessment process and a marketing authorization valid throughout the European Economic Area. Authorization through the centralized procedure is mandatory for innovative medicines derived from biotechnology, orphan medicines and new active substances for the treatment of acquired immunodeficiency syndrome, cancer, neurodegenerative diseases, diabetes mellitus, autoimmune diseases and other immune dysfunctions, and drugs targeting viral diseases (9).

Similarly to medical devices, safety issues involving medicinal products showed a need for a more proactive risk management approach of medicinal products. This led to the development of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2E guidance on risk management planning. This guidance was implemented in EU regulation in 2005 in the form of the EU Risk Management Plan (EU-RMP), which is a mandatory template document for the authorization dossier of innovative drugs licensed in the EU(10-12). The EU-RMP describes the important risks and areas of missing information, the activities intended to further characterize the safety profile and the measures to minimize the risks (13, 14). The EU-RMP is updated throughout the product life cycle as studies are completed or new information becomes available that may change the benefit-risk balance (15). Significant variation exists in the requirements and execution of post-authorization safety studies and additional risk minimization measures (16-19). This is partly because the EU-RMP is product-specific and strategies are tailored to be risk-proportionate (i.e. taking into account variables such as seriousness and severity of the risk, target population and health care setting of use of the product) (20). However, some variation is also due to marketing authorization holders: there is no gold standard for an optimal risk management organizational structure, and it depends on the magnitude and complexity of the company's pipeline, economic and staffing limitations, and organizational commitment to patient centeredness (21). Cross-functional review of the risk minimization programs is recommendable and inclusion of senior management in final approval. The Pharmacovigilance Risk Assessment Committe (PRAC), an EMA scientific committee responsible for the review of all aspects of risk management planning, has been instrumental to overseeing post-approval commitments, and has played a key role in centralizing all the efforts to design and evaluate Post-Authorization Safety Studies (PASS) (22). Table 1 describes some of the lessons learned from the Pharmaceutical world and provides recommendations for implementation of the PMS plan for medical devices.

Medical devices: NCAs, Notified Bodies (NBs) and Manufacturers are all involved in the CE marking process that allows marketing of a medical device in the EU. The NB is an entity that has been accredited by an EU Member State to assess whether a manufacturer's Quality Management System procedures and product technical documentation meets certain standards described in EU Medical Devices Directive. With the NB's certificate, the manufacturer can then issue the Declaration of Conformity, and apply the CE Mark, which is required for sale in the EU. The Conformity assessment can include inspection and examination of a product, its design, and the manufacturing environment and processes associated with it, including the safety evaluation of the medical device.

Table 1. Lessons Learned from the pharmaceutical world and recommendations for implementation of the PMS plan for medical devices

Topic	Lessons Learned from the pharmaceutical world	Recommendations for implementation of the PMS plan for medical devices
Enforcement of post-approval commitments	Pharmacovigilance Risk Assessment Committe (PRAC) has played a key role to centralize all efforts to design and evaluate PASS; PRAC has been instrumental to enforce post-approval commitments related to PASS.	As part of the NB's oversight, there should be a centralized group responsible for monitoring and assessing the safety of medical devices. This group should include CA and notified bodies, and should enforce the completion of CE mark commitments; such as post-market studies or registries included in the Post-Market Clinical Follow-up Plan.
Documentation, monitoring and enforceability of post-approval commitments	Implementation of the EU-RMP template triggered more proactive approaches and the documentation of many additional risk minimization activities. Enforceability of these post-approval commitments came from making these commitments conditions to the marketing authorisation of the medicinal product.	Implementation of an actual PMS plan template is also important to document the post-approval commitments (e.g.; post-market studies, risk minimisation activities). Enforceability of these post-approval commitments will come from making these commitments conditions to the marketing authorisation of the medical device and verification during the annual PMS audits performed by the notified body.
Inclusion of risks in the PMS documents	Only important risks (risks that have an impact on the benefit-risk balance) from the Safety Specification should be included into the Pharmacovigilance (PV) plan.	Regulator-led initiative to develop risk based approach guidances to recommend the inclusion of only important risks (risks that have an impact on the benefit-risk balance) in the PMS documents (based on ISO 14971). Due to the wide range of medical devices and the different levels of complexity, these documents should be product–specific.
Manufacturer's Organizational adaptation	Cross-functional review of the risk minimization programs and inclusion of Senior Management in final approval is recommended.	Cross-functional review of the PMS plan is recommendable. The final approval of the PMS plan should be made by the person responsible for regulatory compliance (PRRC) within the company.

NCA's exist in each European Member State and are nominated by each government to monitor and ensure compliance with its provisions of the Medical Device Directive (MDD) 93/42/EEC. The NCA designates a NB to ensure that conformity assessment procedures are completed according to the relevant criteria. The authorized representative, designated by the manufacturers (There is only an Authorized representative when the manufacturer is not based in the EU. When the manufacturer is based in the EU, the manufacturer is the direct point of contact.), is legally responsible for compliance with the regulations and acts as the first point of contact for the EU authorities. It is the manufacturer's responsibility to ensure that their product complies with the essential requirements of the relevant EU legislation. Medical devices are classified based on the risk associated with them, using the classification rules listed in Directive 93/42/EEC Annex IX. The categories are Class I, Class IIa and IIb and Class III, with Class III ranked as the highest. The higher the classification, the greater the level of assessment required by NBs. The classification is based on the intended purpose of the device and not the particular technical characteristics. There are different aspects that are being taken into consideration for classification; grade of invasiveness, duration of contact with the body, and local versus systemic effect (23) (7).

In order to obtain the CE mark that allows marketing of a medical device in the EU (24), the manufacturer is obliged to identify and describe the risks detected during the pre-market phase (1, 5). The Risk Management File (RMF) of the medical device or its family should contain clear definitions of the hazardous situations associated with use of the medical device. In addition, it should also describe the potential harms associated with these situations as well as the applicable risk minimization measures to avoid or mitigate these harms in both patients and healthcare users.

Table 2. Post-Market Surveillance System: Comparison between the current Medical Device Directive (MDD) (7) vs the new MDR (5):

MDD PMS Key Principles	MDR additional PMS requirements compared to MDD
Systematic procedure to review experience gained from the market. Obligation to report incidents and increase in trends.	PMS Oversight: Notified bodies and Competent Authorities have increased post-market surveillance authority for unannounced audits, samples checks, and annual safety reports. Clinical Evidence: Manufacturers need to conduct clinical investigations and collect post-market clinical data as part of ongoing safety assessment. PMCF plan to be part of the PMS plan. One PMS plan and one PSUR per device/ device group/family.

Table 3. Medical Device Vigilance System: Comparison between Meddev 2.12-1 (27) vs the new MDR (5)

Topic	Meddev 2.12-1	MDR
What to report?	• Near incident (serious) • Serious incident	• Serious incidents
Reporting timelines	• Serious public health threat: 2 days • Death or unanticipated serious deterioration in state of health: 10 days • Other Reportable incidents: 30 days	• Serious public health threat: 2 days • Death or unanticipated serious deterioration • in state of health: 10 days • Other Serious incidents: 15 days
Periodic Summary Reports	When agreed with the coordinating competent authority: • For similar incidents with known root cause or FSCA implemented • For common, well documented incidents	When agreed with the coordinating competent authority: • For similar incidents with known root cause or FSCA implemented • For common, well documented incidents
Report to	• NCA	• Centralized electronic reporting in EUDAMED
Trend reporting	Trend reporting is used by the MANUFACTURER when a significant increase in events not normally considered to be INCIDENTs and for which pre-defined trigger levels are used to determine the threshold for reporting.	Mandatory reporting of: • Statistically significant increase in frequency or severity of non-serious incidents or expected side-effect that could impact risk/benefit ratio • 'statistically significant increase' needs to be defined upfront in the Tech File as part of the PMS plan for the device The EU Commission will perform trending and signal detection based on the data in Eudamed.
Field Safety Corrective Action (FSCA)	• The details of FSCAs are communicated by manufacturers to the National Competent Authorities via FSCA form and to the users in field safety notices (FSNs).	• The details of FSCAs are communicated by manufacturers to the National Competent Authorities via FSCA form and to the users in field safety notices (FSNs). • The NCA may perform their own risk assessment, manufacturer has to provide the supporting documentation. • The national competent authority may intervene in the manufacturer's investigation. • The Field Safety Notice needs to contain the UDI and the manufacturer's SRN and needs to be uploaded in Eudamed. National Competent authorities may ask Manufacturers for corrective actions and will inform the NB, other Manufacturers and the EU Commission.

Topic	Meddev 2.12-1	MDR
Periodic Safety Update Reports	Not included in the current guideline.	• Class I devices: PMS report updated when necessary, but at least every 5 years. • Class IIa: Periodic Safety Update Report to be updated when necessary, but at least every 2 years. • Class IIb (non-implantables): PSUR to be updated annually. • Class IIb (implantables), III: PSUR to be updated annually and sent to the NB for evaluation. • Analysis of post market surveillance data. • Description of preventive and corrective actions. • Conclusion of the benefit/risk evaluation. • Main findings of the PMCF report. • Sales volumes, estimate of the population using the device, usage frequency of the device.

According to the new EU MDR for medical devices, a comprehensive RMF demonstrating a positive benefit/risk profile, is conditional to marketing and required to be monitored post-marketing in a timely manner. The new EU MDR has additional requirements in PMS and Vigilance compared to the current Medical Device Directive (MDD); tables 2 and 3. The new EU MDR states that the PMS plan, *"shall be suited to the actively and systematically gathering, recording and analysing relevant data on the quality, performance and safety of a device throughout its entire lifetime, and to drawing the necessary conclusions and to determining, implementing and monitoring any preventive and corrective actions"* (5). Table 4 specifies the main technical requirements of the PMS plan. The final approval of the PMS plan should be made by the person responsible for regulatory compliance (PRRC) within the company.

Table 4. Essential Requirements from the EU regulation for medical devices that are relevant to the Technical Documentation on Post-Market Surveillance – Extract of the EU regulation (5).

EU MDR (Annex III Technical Documentation on Post-Market Surveillance):
The manufacturer shall prove in a post-market surveillance plan that it complies with the obligation referred to in Article 83 (a) The post-market surveillance plan shall address the collection and utilization of available information, in particular: • Information concerning serious incidents, including information from periodic safety update reports (PSURs), and field safety corrective actions (FSCA); • Records referring to non-serious incidents and data on any undesirable side-effects; • Information from trend reporting; • Relevant specialist or technical literature, database and/or registers; • Information, including feedbacks and complaints, provided by users, distributors and importers; • Publicly available information about similar medical devices; (b) The post-market surveillance plan shall include at least: • A proactive and systematic process to collect any information referred to in point (a). The process shall allow a correct characterization of the performance of the devices and shall also allow a comparison to be made between the device and similar products available on the market; • Effective and appropriate methods and processes to assess the collected data; • Suitable indicators and threshold values that shall be used in the continuous reassessment of the risk benefit analysis and of the risk management as referred to in Section 3 of Annex I; • Effective and appropriate methods and tools to investigate complaints or market experiences collected in the field; • Methods and protocols to manage the events subject to trend report as provided for in Article 88, including the methods and protocols to be used to establish any statistically significant increase in the frequency or severity of incidents as well as the observation period; • Methods and protocols to communicate effectively with competent authorities, notified bodies, economic operators and users; • Reference to procedures to fulfil the manufacturers obligations laid down in Articles 83, 84, and 86; • Systematic procedures to identify and initiate appropriate measures including corrective actions; • Effective tools to trace and identify devices for which corrective actions might be necessary; and • A Post-market clinical follow-up (PMCF) plan according to in Part B of Annex XIV, or a justification why a PMCF is not applicable.

To understand the key differences between the flow of risk management documents for a medical device and a medicinal product, it is important to understand main differences between medical devices and medicines during new product development (figure 1) and the main differences during the development pathway (figure 2) (104).

Figure 1. Overview of the main differences during new product development between medical devices and medicines

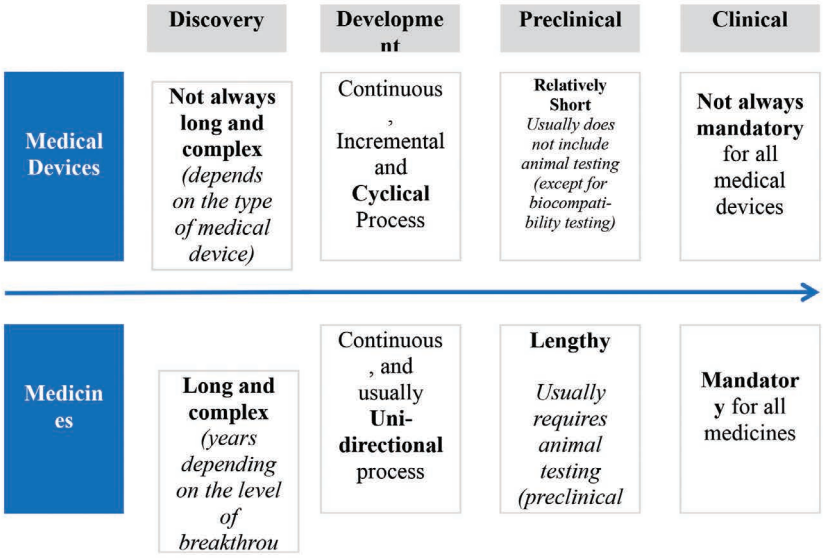
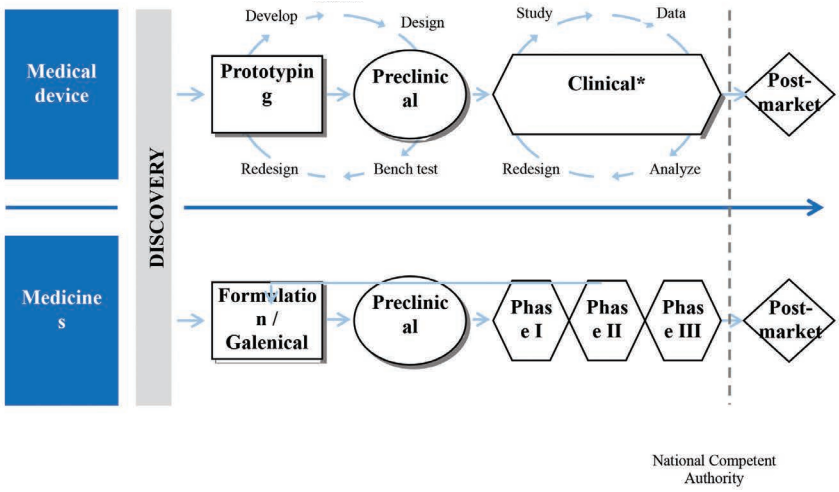


Figure 2. The medicinal product and the medical device development pathway in the EU

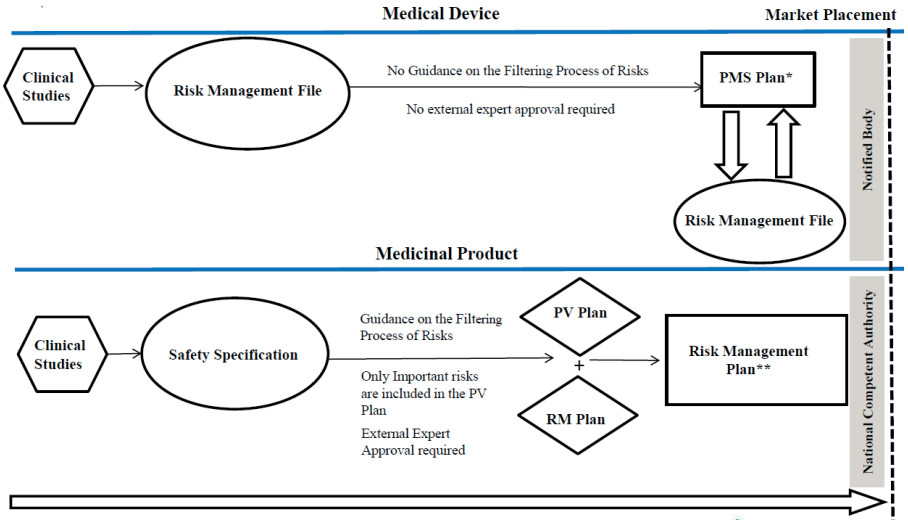


***Not always mandatory**

Note: Some low risk (class I) medical devices may be "self certified" (without requiring a CE certificate from the NB) (117)

Figure 3 describes the flow of risk management documents that are required for a medical device and a medicinal product. One of the key differences between the two products is the filtering performed for medicinal products: only important risks (risks that have an impact on the benefit-risk balance) from the Safety Specification should be included into the Pharmacovigilance (PV) plan. For medical devices there are no regulatory documents that provide guidance on filtering the risks from the RMF into the PMS plan. The RMF of a medical device includes the risk analysis, the risk evaluation, the implementation and verification of the risk control measures and the assessment of the acceptability of any residual risk. Another difference with regard to medical devices is that the Risk Management Plan of a medicinal product needs to be reviewed and approved by regulatory authorities whereas the RMF or the PMS plan of a medical device are reviewed by the NB and do not require approval from the NCA. Contrary to what happens with medicinal products where the process goes through the EMA, or the designated NCA, in EU the medical devices do not need to be approved by the NCA. In EU, the new medical device application (if required) is performed by the NB; an entity that examines the medical device application to assure compliance with the EU regulation. If the device meets regulatory requirements, a CE is applied, and the medical device can be marketed throughout Europe (25).

Figure 3. Risk managements documents required for the market placement of a medical device compared with a medicinal product.



*It includes description of processes and metrics
**Does not include description of processes and metrics. This information is included in the Pharmacovigilance System Master File (PSMF)
Note: In EU some low risk (class I) medical devices may be "self certified" (without requiring a CE certficate from the NB) (117)

Recommendations for implementation of the PMS plan for medical devices

Most of the current PMS requirements are included in the Medical Device guidelines, and not in the current Medical Device Directive; this has led to enforcement challenges for the manufacturer's requirements. With the new regulation, the EU wanted to eliminate those challenges and at the same time provide instructions on how to build a more proactive PMS system (tables 6 and 7).

Based on the requirements described in the new regulation and the lessons learned from medicinal products, we would like to propose the following recommendations for implementation of the new legislation. We have designed a template for the PMS plan content (see tables 3 and 4). The PMS plan becomes a master file and consists of a PMS plan Core (table 5) and a PMS plan Supplement (table 6) containing different modules of PMS data. The Core document should describe the PMS system (routine PMS procedures, methodologies and activities that are being performed for all medical devices or group/family of medical devices) as well as the key performance indicators used to evaluate the effectiveness of the plan. The Supplement should describe the specific PMS activities, methodologies and procedures performed by the manufacturer for a particular medical device or family/group of medical devices. The PMS Plan shall also define the frequency of the PMS data review. The manufacturer should institute a system to assess all the PMS information with a specific frequency and implement the necessary actions to improve safety and performance of the product. The Core and the Supplement should have different review timelines: the PMS plan Core only describes the processes and does not require a continuous update of the content. The periodicity of renewal of the PMS plan Supplement should be consistent with the risk associated to the product, the innovative character of the device, and the level of clinical experience with the device. For example, as a general rule class IIb and class III medical devices should be reviewed on a yearly basis and class IIa on a bi-annual basis (Note: Class I devices still need a review, but it is a simplified PMS supplement that should be updated at least every 5 years).

The final approval of the PMS plan should be made by the PRRC. However, the PMS plan should also define who will review the PMS plan. We have learned in the drug era that the manufacturers should create an organizational model that ensures an efficient cross-functional review and senior management communication, and the systematic incorporation of patient and healthcare professional's input into the PMS workflow. Key individuals from the different departments such as Medical Safety, Clinical, Research & Development, Regulatory Affairs, Compliance and Quality Assurance should participate in the production of the Core and Supplemental PMS plan. The final review of the documents should be performed by a cross-functional senior management team.

Table 6. Suggested template: PMS plan Supplement

Product Overview		
Product Name(s) / Family		
Approved Indication(s)		
Population being treated		
Medical Device Risk Classification		
License partners (if applicable)		
Summary of safety concerns		
Safety Concern	**Hazard**	**Harm**
Important Identified Risks		
Important Potential Risks		
Missing information		
Risk minimization measures		
Inherent safety by design and construction		
Protective measures in the medical device itself or in the manufacturing process		
Training to users and/or information for safe and proper use.		
Conduct of a study		
Communication of a FSCA		
Additional PMS activities		
Activity	Rationale	
Plans for Post-Market Clinical Follow-up and Clinical Evaluation		
Summary of PMCF report (including registry review) and CER		
Safety Communications		
External and internal communication of safety concern**s**		
Annexes		
Training of Personnel Documents and Records		
References		

Table 7. Proposed Key Performance Indicators to measure effectiveness of PMS plan

Process	KPI	Type	
		Quality	Timeliness
1.- Case Processing	Expedited reporting on time	-	✓
	Periodic Reporting on time	-	✓
2.- Case Quality Review	Case Quality Review	✓	-
	Quality review of regulatory reports	✓	-
	Comments and Inquiries received from Competent Authority after the submission of a Regulatory Report	✓	-
3.- Periodic Search of Scientific Literature	Literature Search Review timeliness	-	✓
	Peer review of selected abstracts	✓	-
	Peer review of rejected abstracts	✓	-
4.- Aggregate Reports	PSUR submission timeliness to Competent Authorities	-	✓
	Comments and Inquiries received from Competent Authority after the submission of PSUR	✓	-
5.- Safety Communications	Safety Communications submitted on time	-	✓
	Comments and Inquiries from Competent Authorities, healthcare professionals or consumers received after the submission of the safety communications	✓	-
6.- Signal Detection	Signals detected on time; timely identification of safety issues	-	✓
	Signal evaluation and validation performed effectively; real signal?	✓	-
7.- Corrective Action	Corrective actions implemented on time	-	✓
	Corrective actions effectiveness	✓	-
8.-Risk Management	Risk Management File timely review; timely update of the risk management file	-	✓
	Rates of comments and inquiries from Competent Authorities (CA) by impact	✓	-

Prior to launch, the manufacturer shall incorporate the risk minimization measures. The actual PMS plan and the activities involved with it may also lead to risk minimization measures such as a change in the labeling, a design change or a material change. The new risk minimization measure will need to be documented in a consistent and timely manner across the other PMS documents (such as Risk Management and Periodic Safety Update Reports). This will be ensured by the use of the suggested modular approach (see table 6) for the PMS plan structure.

A program of appropriate PMS including post-market studies and registries is very important to detect and investigate risks associated with the use of marketed medical devices, and should be included in the Post-Market Clinical Follow-up (PMCF) plan. The plan describes methods for clinical data collection to confirm the safety and performance of a device throughout its lifetime; these methods may include post-market studies or registries as appropriate.

Post-market studies and registries provide information on "real world" use and are a component of PMS. The post-market studies can be sponsor-led (sponsored by the manufacturer) or Investigator Initiated Trials (IITs) which are any scientific study, other than a manufacturer-sponsored study, originated and proposed by a third-party investigator. Medical device registries can be sponsor-led or Health Authority mandated, and are designed for different purposes. They can offer valuable data on long-term effectiveness and safety of devices, or on the impact of factors such as surgical method, physician, hospital, and patient conditions (26).

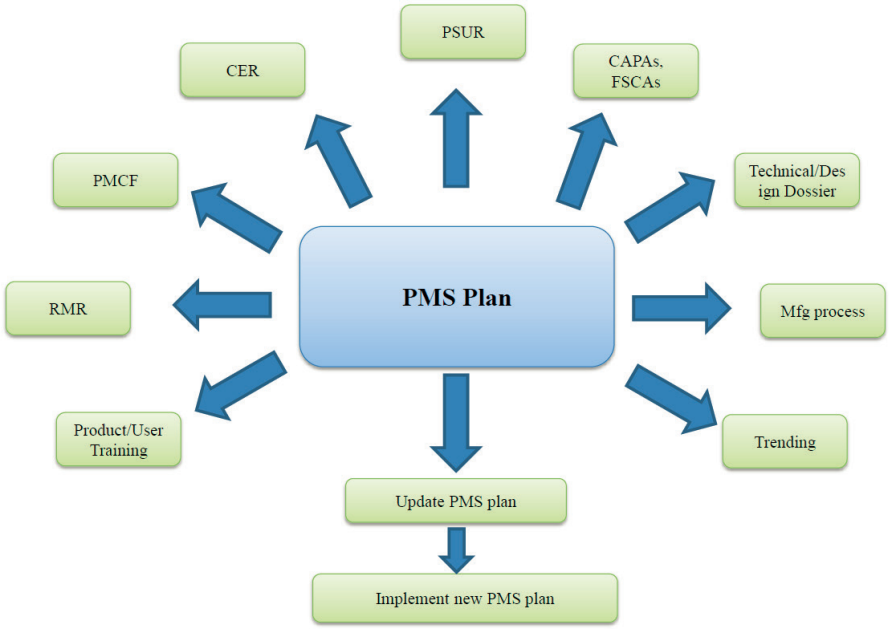
It is important to take into consideration that data from these studies and registries need to be used for continuous evaluation of the benefit-risk profile as well as for discovery of new indications of use. When the PMCF study is completed, there should be a final report with clear conclusions that will be included in the Periodic Safety Update Report (PSUR).

The results of PMS activities will have an impact on the PMS process during the device life cycle management. Some of the information from the PMS plan will be used to update other related PMS documents. A modular approach to structure the contents of the PMS plan may help to consistently update other PMS information. The output of the PMS plan could lead/affect different post-market documents (figure 4). For example, after the review of national registries (part of the PMCF up plan) the manufacturer may identify a new safety issue with the product that will affect different post-market documents: update of RMR, update of Clinical Evaluation Report (CER), new PSUR, development of Corrective And Preventive Actions (CAPAs), new training to the user, or submit a FSCA to the NCA.

To measure the effectiveness of the PMS plan, it is important to have adequate tools in place for each of the processes. Key Performance Indicators (KPIs) must be identified a priori when building the processes. Moreover, together with the KPIs it is essential to identify a threshold for each of the indicators to take action if this threshold is reached. Therefore, the key processes that need to be measured should be identified and the significant points of measurement that define the performance of the systems should be described in the PMS plan. These measures will help to

identify areas of improvement. In table 7 we propose different KPIs to monitor the performance of the PMS system, there should be KPIs for case processing, safety communications, PSURs, risk management, early detection of signals and implementation of corrective actions.

Figure 4. Output of the PMS plan.



DISCUSSION

This paper tries to provide implementation guidance to the medical device EU-regulation based on lessons learned from the medical product area. We have seen how vital it is to identify the risks in a timely manner for all stakeholders to be aware of the risks associated with medical devices. Stakeholders need to take appropriate corrective and preventive measures to improve patient outcome (3) resulting in a device that is safe and performs well.

We conclude that the PMS plan needs to include the identified risks, potential risks and missing information from the RMF. Next, safety evaluation tools (CER, PSUR, RMF) to find responses to unanswered questions and find more information regarding missing information should be implemented. The PMS plan should have clear objectives, a robust structure with specifications on data integrity, periodicity, and defined

responsibilities. We recommend a modular approach to structure the contents of the PMS plan which will facilitate consistent updating of other PMS information. The PMS plan should consist of a PMS plan Core and a PMS plan Supplement. The PMS plan Core document will describe the manufacturer's general PMS system and the PMS plan Supplement will describe the specific PMS activities performed by the manufacturer for a particular medical device or family/group of medical devices. Since we learned from the medicinal products area that a template is important, we proposed one. In addition to the template, another important aspect learned from the experience with medicinal products is the methodology used to include customer feedback and the organizational structure within the company. To deliver high-quality PMS plans, companies need to implement a system that includes cross functional review and takes into account the patient feedback received during the post-market phase. A difference with medicinal products is the fact that no filtering is implemented: we would recommend that the regulatory bodies develop product-specific guiding documents outlining how to perform the filtering of risks from the RMF to the PMS plan, and also provide guidance on the stakeholder responsibility in reviewing and approving the PMS plan.

Moreover, to ensure the success of the PMS plans, the manufacturers should first identify the key processes of the plan and define KPIs as well as the associated thresholds to take action. These indicators will help to measure the effectiveness of the plan.

In conclusion, the new EU MDR may positively impact medical device safety evaluations and calls for a more hands-on approach which does not only consist of spontaneous reporting but also include proactive methods to manage product-related risks with new safety evaluation tools such as the PMS plan. There are several questions regarding the implementation of the new EU medical device guideline and differences with medicinal products. This paper tries to review them and provide some guidance.

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ABBREVIATIONS

CAPA: Corrective And Preventive Action
CER: Clinical Evaluation Report
EU: European Union
FSCA: Field Safety Corrective Action
HCP: HealthCare Professional
KPI: Key Performance Indicator
MDR: Medical Device Regulation
NCA: National Competent Authority
NB: Notified Body
PASS: Post-Authorisation Safety Studies
PMCF: Post-Market Clinical Follow-Up
PMS: Post-Market Surveillance
PIP: Poly Implant Prothèse
PRAC: Pharmacovigilance Risk Assessment Committee
PRRC: Person Responsible for Regulatory Compliance
PSUR: Periodic Safety Update Report
PV Plan: Pharmacovigilance Plan
QA: Quality Assurance
RMA: Risk Minimization Activities
RMF: Risk Management File
RM Plan: Risk Management Plan
RMR: Risk Management Report
SOP: Standard Operating Procedure

Chapter 8

Summary of main findings and general discussion

R.D.C. Francisca
I.M. Zomerdijk
M.C.J.M. Sturkenboom
S.M.J.M. Straus

SUMMARY OF MAIN FINDINGS

This thesis encompasses studies intended to gain a deeper understanding of different aspects of additional risk minimisation measures (aRMMs), such as factors that determine the need for aRMMs and the role of aRMMs in the life cycle management of medicines.

We started this thesis with an overview of medicines with aRMMs at the time of authorisation between January 1st 2010 and December 31st 2015. As shown in **Chapter 2**, aRMMs were required for 70 of the 231 medicines (30%) approved during the study period. The proportion of medicines with aRMMs at the time of authorisation before the EU's pharmacovigilance legislation came into force (July 2012) was not significantly different than after with either Pearson's C^2 test or segmented Poisson regression analysis. With the latter analysis, we attempted to account for a delay in the potential effect of the legislation due to ongoing regulatory assessments. The medicines with aRMMs at the time of authorisation (n=70) most frequently concerned "Antineoplastic and immunomodulating agents" (n=20), followed by products targeted at "Blood and blood forming organs" (n=9), "Alimentary tract and metabolism" (n=7) and "Cardiovascular system" (n=7). An interesting finding in our study was that medicines with conditional marketing authorisation or authorisation under exceptional circumstances had aRMMs at authorisation more often than medicines with regular marketing authorisation (52% vs 28%). All aRMMs included the provision of educational materials. These materials were directed at healthcare professionals in 93% of medicines and at patients in 56%. There were 8 products (all licensed after 2012) that required other types of aRMMs in addition to educational materials: three pregnancy prevention programmes, two controlled access and four controlled distributions. One product required both a pregnancy prevention programme and a controlled distribution programme.

The need for aRMMs is evaluated on a case-by-case basis by regulatory authorities, and for each safety concern individually. Several factors are taken into account during this assessment, such as seriousness, severity and preventability of the risk as well as indication, route of administration, target population and health care setting for use of the medicine (1). Previous studies have shown heterogeneity in whether aRMMs are required as well in the type of aRMMs required across similar safety concerns (2). In **Chapter 3**, we provided an overview of the safety concerns with and without aRMMs of medicines authorised between January 1st 2010 and December 31st 2015. There were 3,588 total safety concerns for the medicines authorized during the study period, with a median 16 safety concerns (range 3-33) per medicine. There were 289 safety concerns (8%) that were addressed by aRMMs. Univariate analyses showed that the probability of aRMMs was increased for safety concerns that described

"Congenital, familial and genetic disorders", "Immune system disorders", "Eye disorders", "Injury, poisoning and procedural complications" and "Infections and infestations". Safety concerns that described populations not studied in clinical trials had a significantly decreased probability of aRMMs. In addition, there was a higher probability of aRMMs for safety concerns that were listed for medicines targeting the "Blood and blood forming organs", "Cardiovascular system" and "Sensory organs", as well as "Dermatologicals" and "Respiratory system". The probability of aRMMs was lower for "Antineoplastic and immunomodulatory agents", "Antiinfectives for systemic use" and medicines targeting the "Alimentary tract and metabolism". We anticipated that there would be an interaction between specific indication areas and medical conditions. We found eight combinations of indication area and medical condition for which the calculated probability of aRMMs was significantly higher than for other combinations of indication area and medical condition, and an additional 10 combinations in which all of the safety concerns were addressed with aRMMs. In a classification and regression tree analysis of our data, no discriminative ability could be learned from our data, possibly due to low numbers of safety concerns.

Adverse drug reactions (ADRs) are a source of considerable morbidity and mortality worldwide, and medication errors have been increasingly recognized as a common cause of preventable harm. In **chapter 4**, we focused on the medicines with medication error safety concerns in the RMP and provided an overview of the routine and additional risk minimisation measures to minimise the risk of medication error. Of the medicines authorized between January 1st 2010 and December 31st2017, 27% had at least one safety concern describing a medication error. In total, 103 medication error safety concerns were identified with "Drug administration error", "Product dosage form confusion" and "Product preparation error" being the most frequently listed. Routine risk minimisation measures for medication error safety concerns most often entailed the risk being addressed in the Summary of Product Characteristics sections 4.2 (Posology and administration), 4.4 (Warnings and Precautions) and 6.6 (Special precautions for disposal and other handling of the product). Of the 84 medicines with a medication error safety concern, 23 had aRMMs at the time of authorisation. The proportion of medication error safety concerns with aRMMs was higher than the proportion of non-medication error related safety concerns with aRMM (28.4% vs 7.5%), a sign that preventability plays a large role in the evaluation of the need for aRMMs. All medicines with aRMMs for medication error safety concerns required the provision of educational materials for healthcare professionals. Eight medicines also required the provision of educational materials for patients and four medicines required measures on top of the educational materials.

The need for aRMMs is evaluated at the time of authorisation, but it may change post-authorisation as new safety information becomes available during the life cycle. Newly identified risks or previously unknown aspect of known risks may require introduction of aRMMs for medicines previously authorised without. Conversely, aRMMs may be reduced or discontinued, for instance if their recommendations become part of clinical practice. In **Chapter 5**, we determined that the probability of introduction of aRMMs within 5- and 10-years post-authorisation for medicines authorised without aRMMs was 3.5% and 6.9% respectively. These probabilities are relatively low, particularly in light of the 465 of safety signals discussed by the Pharmacovigilance Risk Assessment Committee from its inception in July 2012 to the end of our study period (June 2018) (3). These findings imply a cautious approach by EU regulators at the time of authorisation. The probability of discontinuation of aRMMs within 5- and 10-years post-authorisation was 0.9% and 8.3% respectively. The probability of discontinuation is very low within 5 years post-authorisation but rises quickly, possibly reflecting the time necessary for collection of sufficient data on aRMM effectiveness.

Evaluation of effectiveness of risk minimisation measures is an integral part of the life cycle management of medicines, but is particularly important for medicines with aRMMs. Though they are intended to protect patients and aid healthcare professionals, aRMMs may pose a burden on the health care system, for example through administration time, and they may also have other unintended consequences, such as restricted patient access. Effectiveness evaluation is important to assess programme effectiveness and identify potential targets for improvement. In **Chapter 6**, we provided an overview of the methods utilised to evaluate the effectiveness of aRMMs. We identified 44 effectiveness studies for 35 medicines authorised with aRMMs between August 1st 2012 and December 31st 2017, and we could retrieve data on study characteristics for 38 studies. Effectiveness of aRMMs was most often evaluated through surveys (16 studies), followed by medical record review (11 studies). Most studies collected patient-level data (25 studies) only, while some studies were aimed at health care professionals (9 studies). There were four studies that combined the collection of patient-level data and data from health care professionals. The majority of studies (22 studies) focused on evaluating the effectiveness of the implementation of aRMMs (ie. process indicators), ranging from receipt of educational materials to adherence to recommended conditions for use; six studies evaluated adverse event data (outcome indicators) and nine studies evaluated both process and outcome indicators. Seven studies had been finalised and assessed by regulatory authorities. ARMMs were deemed effective in one study, while the remaining six studies were deemed inconclusive due to mixed concerns: two studies failed to reach achieve the pre-specified threshold of success, two

studies had methodological issues, one study was conducted outside the EU, one study showed poor but stable adherence to the risk minimisation program among healthcare professionals over a longer period of time.

Public health safety issues involving medical devices have led to initiatives to strengthen the post-marketing risk evaluation of medical devices and to move from passive-reactive post-marketing surveillance to more proactive life cycle management. The 2017 European Union Regulation (EU) 2017/745 on medical devices introduced the requirement of a post-market surveillance (PMS) plan, which shares features with the Risk Management Plan (RMP) of medicinal products. In **Chapter 7**, we provided recommendations for the implementation of PMS plans for medical devices based on lessons learnt from pharmacovigilance:

- There should be a centralised group consisting of experts from national competent authorities and notified bodies that should oversee medical device post-marketing surveillance and enforce completion of PMS commitments
- Implementation of a template to document post-approval commitments and making these commitments conditions to the marketing authorisation to ensure their enforced
- Development of a risk-based approach to include only risks that have an impact on the benefit risk balance
- Cross-functional review of the PMS plan and approval by the person responsible for regulatory compliance within the company

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GENERAL DISCUSSION AND CONCLUSIONS

Additional risk minimisation measures at the time of authorisation

The need for additional risk minimisation measures (aRMMs) is an important consideration during the authorisation process of medicines in the European Union. In **chapter 2**, we found that aRMMs were required at the time of authorisation for 30% of the new centrally approved medicines between 2010 and 2015. A study by Zomerdijk et al showed that 5% of the centrally approved medicines authorised between 1995 and 2005 required risk minimisation measures in addition to the product information. From 2005 to 2009, when the Risk Management Plan (RMP) become a mandatory part of the authorisation dossier of innovative medicines in Europe in 2005, 29% of the centrally approved medicines included in that study required aRMMs (1). Similarly, Rubino et al found that at the time of authorisation aRMMs were required for 26% of the non-generic medicines approved through the central procedure in the EU between 2006 and 2015 (2). It is important to note that although we included newly approved centrally authorised medicines in **chapter 2** similar to Zomerdijk et al and Rubino et al, each study applied slightly different selection criteria based on the type of application: we only included medicines for which a full dossier was submitted to the European Medicines Agency (EMA), while Rubino et al included all applications except generics. This potentially accounts for the differences between **chapter 2** and the study by Rubino et al. A study by Keddie et al included medicines for which the RMP was assessed between 2005 and 2011 by the British regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), of which 42% required aRMMs at the time of authorisation (3).The proportion of medicines approved with aRMMs in the EU is substantially higher than the proportion of medicines approved with Risk Evaluation and Mitigation Strategies (REMS), the United States (US) equivalent of aRMMs, namely 30% vs 13% (4). In comparison, aRMMs were required for 65% of the medicines authorised in Japan from 2013 to 2017. Notably, only 7% of medicines approved in the EU, Japan and the US had aRMMs/REMS in all three territories and an additional 24% had aRMMs/REMS in two of the three territories (5). Other studies have also shown regulatory thinking to differ in different countries/territories, particularly regarding safety-related topics, at least in part due to different healthcare systems and cultural differences (6-8)

Interestingly, the proportion of medicines with aRMMs/REMS at the time of authorisation in the US and Japan declined substantially in the years following the introduction of the RMP and the concept of aRMMs/REMS (4, 5, 9). In the US, this decline is partly explained by the Food and Drug Administration's (FDA) decision in 2011 that not every medication guide should be an element of a REMS. Medication guides are paper handouts with FDA-approved information regarding issues that are

particular to a drug or drug class. They are intended to help patients avoid serious adverse events, somewhat similar to patient educational materials in the EU. From the introduction of REMS until 2011, 60% of REMS only included a medication guide (9) This decline was not observed in the EU (1, 2), even though we expected that it would: the initial guidance documents written by the European Medicines' Agency (EMA) following the introduction of the RMP in 2005 required marketing authorisation applicants to justify why aRMMs were not required, potentially leading to more aRMMs than truly required. However, the proportion of medicines approved with aRMMs hasn't declined after the EU's pharmacovigilance legislation came into force in 2012. The guidance documents were updated into the Good Pharmacovigilance Practices (GVP) guidelines and justification for the need for aRMM at product level has become the standard. In **chapter 2**, we found no differences in the proportion of medicines with aRMMs at authorisation before and after the pharmacovigilance legislation came into force, even using interrupted time series analysis. Moreover, in the approval process of medicines in the US, the FDA's Division of Risk Management must justify why REMS aren't necessary. The justification why REMS aren't required was most often the ability of patients/caregivers and healthcare professionals to manage the risks (10). For 45 medicines approved in the US, EU and Japan between 2013 and 2017, Yasuoka et al showed that REMS were most often aimed at preventing risks whereas aRMMs in both the EU and Japan were most often aimed at mitigating risks (i.e., providing healthcare professionals and/or patients with additional information to improve management of risks) (5). For example, immune checkpoint inhibitors nivolumab, ipilimumab and pembrolizumab all require aRMMs in the EU to mitigate the risk of immune-mediated adverse events. No REMS are required for these medicines in the US.

In contrast to the findings by Yasuoka et al, we found in both **chapter 3** and **chapter 4** that there is increasing attention for preventable events in the EU. In **chapter 3**, we determined the probability of aRMMs for safety concerns of medicines approved between 2010 and 2015. We found that safety concerns in the System Organ Class "Injury, poisoning and procedural complications" as well as safety concerns describing "Congenital, familial and genetic disorders", "Immune system disorders", "Eye disorders" and "Infections and infestations" were more likely to have aRMMs than safety concerns in other System Organ Classes. Our findings are largely in line with other studies to have investigated the safety concerns of medicines with aRMMs in the EU as well as REMS in the US, where "Injury, poisoning and procedural complications" were also frequently addressed by aRMMs/REMS (1, 4, 5). Attention for preventable harm from medical errors has increased in the past two decades, with studies showing that medical errors are still a source of significant morbidity and mortality in the EU and worldwide (11-14). In **chapter 4**, we focused on medication

errors, which are a subset of medical errors and a High-Level Group Term under "Injury, poisoning and procedural complications". We showed that 27% of centrally authorised medicines in the EU have at least one safety concern related to medication errors, which are a subgroup of "Injury, poisoning and procedural complications". Furthermore, we also showed that safety concerns related to medication errors were almost four times more likely than non-medication error safety concerns to require aRMMs. Preventable harms such as risks arising from medication errors, off-label use and drug interactions are a logical target for risk minimisation: these risks may be prevented or minimised, either through dissemination of additional information or through other interventions aimed to change risk-taking behaviour. Several models and frameworks have been developed that address predicting behaviour and affecting behavioural change, as well as effective communication processes and diffusion of innovation. These models have been used successfully in other healthcare fields to analyse risk-taking behaviour and develop measures to change them (15, 16). Pharmaceutical companies and regulators should seek to apply these models and frameworks in the design and implementation of aRMMs, such as the Theory of Planned Behaviour to achieve the desired behavioural changes particularly regarding preventable harms (17).

The need for aRMMs at the time of authorisation is determined on a case-by-case basis. In fact, GVP Module XVI states that each safety concern needs to be considered individually to select the most appropriate risk minimisation measure. In addition to preventability of the adverse event, the GVP also advises to take into account the seriousness and severity of the adverse event as well as indication, route of administration, target population and healthcare setting of the medicine (18). In **Chapter 3**, we attempted to investigate how these factors influenced the need for aRMMs and whether strong predictors for the need for aRMMs could be identified that could be utilised to build a prediction model. However, no predictors could be identified using classification and regression trees, a form of machine learning. We found substantial heterogeneity in the safety concerns with aRMMs at authorisation by System Organ Class, RMP category and the medicines' Anatomical Therapeutic Chemical (ATC) classification. In our analyses, we used RMP category as a proxy for the strength of the association and ATC classification as a proxy for indication. In addition to these factors, it also important to consider risks in the context of the expected benefits of the medicine. Moreover, new categories of complex medicines such as anti-body drug conjugates, may present new safety issues or uncertainties that may require aRMMs (19). Moving to more standardised assessments of the need for aRMMs may not be feasible.

Additional risk minimisation measures in the post-authorisation phase

The requirement of aRMMs may change during the medicine life cycle as new safety information becomes available. New risks or new aspects of known risks may be identified that may not be sufficiently minimised through routine measures. New information may also show that aRMM recommendations/actions have become integrated in clinical practice or even that the risk to be minimised is no longer applicable or may be sufficiently minimised by routine measures alone. Finally, aRMMs can be adapted to improve effectiveness or reduce the burden on the healthcare system. ARMMs may therefore be introduced, strengthened, altered, reduced or discontinued during the life cycle of medicines.

In **chapter 5**, we investigated the probability of introduction of aRMMs for medicines authorised without aRMMs and the probability of discontinuation of aRMMs for medicines with aRMMs at authorisation. We found that the probability of introduction of aRMMs within 5- and 10-years post-authorisation for medicines authorised without aRMMs was low (3.5% and 6.9% respectively). Safety signals arising from spontaneous reporting were an important source of data for the majority of the medicines for which aRMMs were introduced in our study. The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) discussed 465 safety signals since its inception in July 2012 to the end of our study period, of which only 2% led to changes to the RMP (20-22). Importantly, changes to the RMP do not necessarily mean introduction of aRMMs, but might also mean that the risk was included in the safety specification for further evaluation. PRAC has a wide array of options to deal with arising safety signals. Although it would be interesting to investigate which factors contribute to the conclusion that aRMMs were necessary post-authorisation, the low number of medicines for which aRMMs were introduced post-authorisation in **chapter 5** precluded meaningful assessment. It is also important to note that Direct Healthcare Professional Communications (DHPC) are included as a type of aRMM in the GVP Module XVI and have a prominent place in the post-authorisation risk minimisation strategy of medicines in Europe (18, 23, 24). DHPCs differ from the other aRMMs, which we have focused on in this thesis, since DHPCs have a much broader scope of use (eg. communication of quality issues, withdrawals, contraindications, etc.) and have a one-off/once off mode of action. They are often used when important safety information becomes available that must be shared with healthcare professionals immediately, either because some form of action is required or to raise awareness of an important risk. As an example, for strontium ranelate (approved for the treatment of osteoporosis in 2004), data became available in 2013 indicating an increased risk of cardiovascular events which led to restrictions in the indication of strontium ranelate in order to minimise exposure to strontium ranelate in high-risk groups. Two DHPCs were issued to inform prescribers of the restricted indications and contra-indications (25).

ARMMs may also be introduced post-authorisation based on new data from clinical trials, e.g., for new indications (26). As an example, dapagliflozin was approved for the treatment of type 2 diabetes mellitus in 2012 without aRMMs. In 2018, a new indication was sought for the treatment of type 1 diabetes mellitus patients in adjunct to insulin treatment. The risk of diabetic ketoacidosis in type 1 diabetes mellitus patients had already been recognised previously and additional risk minimisation measures had been used during the pivotal studies supporting the application for the indication: study participants were received training and printed materials as well as a ketone meter to facilitate timely recognition of early ketoacidosis (27-30). The indication was approved with the requirement of aRMMs (eg. educational materials to facilitate the early recognition of ketoacidosis).

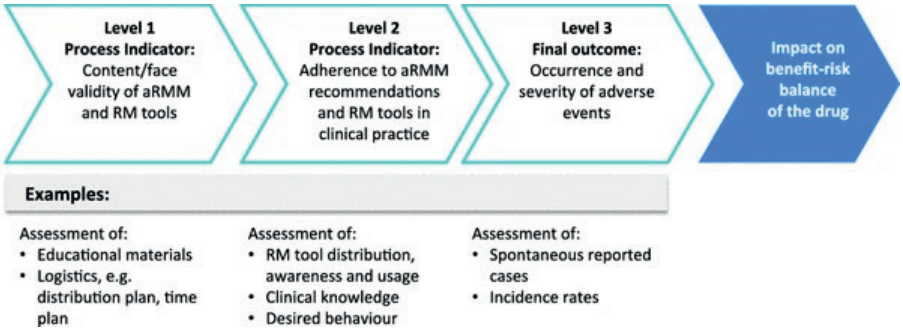
The probability of discontinuation of aRMMs within the first 5 years post-authorisation was very low (0.9%) and increased to 8.3% within 10 years post-authorisation. This might reflect that time is needed to gather sufficient safety data justifying discontinuation of aRMMs. Although we've shown in **chapter 5** that time is correlated to the discontinuation of aRMMs, it would be interesting to investigate if there might also be an association between post-authorisation exposure and discontinuation of aRMMs. In our study, aRMMs were discontinued for only four medicines, precluding a meaningful assessment. In addition, GVP Module XVI emphasised the possibility of discontinuation of aRMMs only following an update in 2017. Since then, several aRMMs have been reduced or discontinued, such as the educational materials for healthcare professionals for tumour necrosis factor alpha inhibitors while the educational materials for patients remain present.

Effectiveness evaluation

Effectiveness evaluation was at the basis of the discontinuation of aRMMs for only one of the four medicines for which aRMMs were discontinued in **chapter 5**. The data source supporting the discontinuation could not be identified for two other medicines. This was unexpected, particularly in light of the importance of evaluation of effectiveness of regulatory interventions in general and risk minimisation measures in particular in the life cycle management of medicines. Moreover, there has been a breath of studies published in which the effectiveness of risk minimisation interventions for specific medicines or active substances were investigated (31-64). That these studies have been published is positive, as publication of study results increases transparency and offers the possibility for all stakeholders to reflect on best practices and opportunities for improvement. As an example, multiple stakeholders from pharmaceutical industry, academia and regulatory agencies teamed up to study the quality of reporting of effectiveness evaluation studies. The result of their efforts was the development of the RIMES statement, a checklist to assess the quality of effectiveness evaluation studies (65).

Following effectiveness evaluation, regulators may conclude that aRMMs should be continued, improved, augmented, reduced or discontinued. In **chapter 6**, we investigated how effectiveness was evaluated specifically for medicines with aRMMs at authorisation between 2012 and 2017. We found that 56% of the medicines had at least one study to evaluate effectiveness of aRMMs. Our findings are largely in line with the results of several recently published (systematic) reviews of effectiveness evaluation studies of risk minimisation measures in the EU (66-70). First, although the methods used to evaluate effectiveness are heterogenous, the majority of effectiveness evaluations focus on the process of implementation of aRMMs. Several frameworks, devised for effectiveness evaluation, break down the implementation of aRMMs into several steps: whether the aRMMs reach the intended target audience, what knowledge is retained from the aRMMs and whether aRMMs affect clinical actions such as prescribing/dispensing behaviours (18, 71-73). These steps, termed process indicators, are most often the focus of effectiveness evaluations, with 31 of 37 studies included in chapter 6 evaluating at least one process indicator. See figure 1 for a visual representation of the evaluation steps of aRMMs.

Figure 1: Evaluation steps of additional risk minimisation measures (from Zomerdijk et al (74))



The two most frequently used methods to evaluate aRMM implementation are surveys and drug utilisation studies. This wasn't unexpected, given that a study by Zomerdijk et al showed that 36% of the key elements of aRMMs aimed at knowledge change and 57% aimed at behavioural change (74). Surveys offer a relatively cost-effective and fast way to collect data on every step of the implementation process, from distribution of materials to self-reported actions. Surveys are the primary method to evaluate knowledge, and may also help identify enablers and barriers to implementing aRMMs. However, surveys also have challenges. Particularly, recruitment of participants can be difficult and lead to problems with validity of the results, for instance when lagging recruitment leads to either small sample sizes or unrepresentative samples or selection bias. The sampling methods in aRMM

effectiveness evaluations have been shown to be heterogeneous, when they are described at all (75). Additionally, surveys may also be susceptible to misclassification or information bias, as well as social desirability bias (69, 76, 77).

Conversely, drug utilisation studies (DUS) are an excellent method to assess behaviour. Particularly when conducted in electronic healthcare databases, DUS give information of medicine use and aRMM effectiveness in the real-world setting. Moreover, these studies can also be combined with outcome assessments, such as incidence rates. However, DUS also have challenges. First, the type of behaviour that must be evaluated must also be captured in the database. For example, in the case of teratogenicity and sodium valproate, the educational materials for patients advise women of childbearing potential to use contraception. If contraception is defined as an oral anticontraceptive or intrauterine device, then the behaviour of interest (i.e., use of contraception) is likely to be captured in an electronic healthcare database (EHD). If contraception is defined as the use of condoms, then the behaviour of interest will not be captured in an EHD. A study by Zomerdijk et al shows that only 37% of the key elements that aimed at a behavioural change was eligible for assessment in electronic healthcare databases (74). Second, exposure to a medicine in a single database may be too low to achieve sufficient sample size for meaningful interpretation of the results, for instance for very rare diseases. Conducting studies in multiple databases might remedy the issue, but differences between databases make the process more laborious and might make interpretation of results more challenging if substantial differences exist between the databases. Moreover, conducting multiple database studies could be fairly costly, though conducting a field study is probably costlier and may not lead to analysis of real-world data. Marketing authorisation holders may also leverage other available data sources: for instance, drug and/or disease registries with exposure information, such as those available for haemophilia, pregnancy exposures and medication errors (78-81). Data availability is probably one of the most important drivers of the heterogeneity in in methodology of effectiveness evaluation studies. Third, DUS offer no potential explanation on why aRMMs may not be effective, such as information on enablers and barriers of their implementation. For example, the desired behavioural change may not be achieved if the educational tools under evaluation are too complex for their intended target audience despite readability testing, particularly for older patients or those with low literacy, or they may not offer actionable insights (50, 82, 83). Moreover, patient/caregiver and healthcare professional preferences should be considered when selecting educational tools as well as when evaluating the effectiveness of the risk management program (84-86). Evaluation of process indicators should ideally therefore evaluate multiple process indicators, as was the case for the aRMMs introduced for sodium valproate containing medicines following the referral procedure in 2014 (87, 88).

Outcome indicators were measured for 15 of 37 studies in **Chapter 6**, in which we studied only medicines with aRMMs at the time of authorisation. In other reviews of effectiveness evaluation studies, outcome indicators were studies predominantly for medicines for which aRMMs become required after authorisation (66, 67, 70). This is not unexpected, as evaluation of the effect of aRMMs on specific outcome measures such as incidence rates of adverse drug reactions is easier to interpret due to the availability of an adequate comparison group (i.e., before the aRMMs were introduced) (89). For medicines with aRMMs at the time of authorisation, finding an adequate control group is challenging. Direct comparisons of incidence rates in the real-world setting with adverse event rates in the clinical trial setting may not be valid due to critical differences between the real-world users of a medicine and the study population of the trials. Methods to improve the validity of these comparisons should be further evaluated, such as the method devised by Hampp et al or other forms of quantitative bias analysis (90, 91).

Importantly, a threshold for success was pre-defined for only 29% of the studies included in **chapter 6**. All of these studies were survey studies and their pre-defined thresholds for success were heterogenous, with some studies setting a target of 70% correct answers given per person and other studies designating key questions. The heterogeneity might in part be caused by different study objectives (i.e., assessing knowledge alone versus assessing both receipt and knowledge) and by the key messages that patients and/or healthcare professionals should retain knowledge from. For surveys, a standardized approach should be feasible: to minimise the burden on the target population, the survey should only contain relevant/important questions.

For DUS and other studies, thresholds for success should also be pre-defined based on the context of the risk to be minimised and the goal of the aRMMs (e.g., prevention of an adverse event or improving management of an adverse event). Since so few studies have set a threshold, there is little to know insight in the best practices or ideal threshold values.

Future perspectives

Since their introduction in 2005 in the EU, aRMMs have evolved as experience with their use has accumulated. This evolution is best illustrated by the updates to the GVP modules V and XVI in 2014 and 2017, as well as the ongoing revisions to module XVI that is expected to be finalised early 2022. Despite the evolution of aRMMs, many opportunities still exist to improve the effectiveness of aRMMs.

The most important way to improve the effectiveness of aRMMs would be to improve their integration in daily clinical practice through expanding distribution modalities, aRMM formats and content. First, most aRMMs are currently based on a paper

hand-off which conveys the safety information and recommendations for safe and effective use of the medicines at the time of reading and can be stored for future reference. This approach theoretically ensures that the aRMMs are also accessible for healthcare professionals and patients that don't have access to electronic medical records, internet or smartphones. However, it also has some limitations as accessibility of paper-based aRMM depends on distribution, receipt and storage of paper-based materials. Moreover, healthcare professionals have to recognise paper-based aRMMs as regulatory approved communications containing important safety information. For patients, access to aRMMs also depends on their healthcare professionals' compliance with and distribution of patient-targeted aRMMs. Exceptions are patient information cards or patient alert cards that are included in the packaging as part of the product information. While aRMMs have been shown to reach around 60% of healthcare professionals and 50-80% of patients/caregivers, this means that a substantial proportion of healthcare professionals and patients do not receive the aRMMs (67). Other aRMMs formats and methods of delivery in addition to paper-based aRMMs should therefore be leveraged to improve aRMM distribution/receipt.

In some countries, like the Netherlands, marketing authorisation holders are, in addition to paper-based educational materials also expected to provide a website from where the materials can be accessed electronically (i.e., in PDF format). However, there are other potential methods of delivery and formats that may be more difficult to achieve, but may be expected to more effectively improve adherence to aRMMs and thus their effectiveness.

The first and most important possible method of delivery that comes to mind is integration of the aRMMs into electronic medical records and electronic prescription systems, so materials become available at the time of prescription or during periodic treatment review. Such an integration might be challenging, since there are many diverse electronic medical records systems, each with different levels of customisation by healthcare professionals and healthcare institutions. However, integration would have an added benefit of reducing the time and effort required for healthcare professionals to be aware of and use aRMMs. Integration would thus facilitate adherence, for example if checklists and/or risk acknowledgement forms are embedded in the software or if printing a prescription automatically leads to printing patient-targeted educational materials.

The second possible method of delivery and aRMM formats are web and app platforms, where the safety information and recommendations are embedded in the platform, i.e. not only available as a PDF or word file. These platforms offer

opportunities to incorporate the safety information and recommendations in the aRMMs in different ways, such as instructive or educational videos. Moreover, these platforms can be made interactive by quizzing patients/caregivers and/or healthcare professionals while they access the safety information and recommendations, and they can be invited to perform (short) surveys to assess effectiveness of the aRMMs. In the Netherlands, the marketing authorisation holder of ipilimumab previously developed such an interactive website, which unfortunately is no longer available. Moreover, an app platform has already been developed to facilitate reporting of adverse drug reactions under the WEB-RADR project, which launched in 2014. The outputs of the WEB-RADR project, including research into factors that may influence the use of such an app to receive safety information, can be used to develop app platforms to share safety information and recommendations from aRMMs (92).

Another important consideration to improve the effectiveness of aRMMs, is the sender of the information. The current pharmaceutical legislation places the responsibility for drafting and distribution of safety information such as aRMMs (including DHPCs) with the marketing authorisation holder, with oversight and coordination from regulators. However, healthcare professionals trust safety information more when it is issued by an independent source, such as a regulator or healthcare professionals' scientific societies, rather than the pharmaceutical company (93). For aRMMs, including DHPCs, it should either be emphasised that the information has been approved by regulators or regulators should be designated as official senders of the safety information. Moreover, healthcare professionals' scientific societies should be involved in the distribution of the safety information on the short term and inclusion of the safety information in guidelines on the long term.

In general, studies have shown that healthcare professional across different specialties and different countries have different preferences when it comes to receiving safety information (94). These preferences range from the sources of information, such as reference books or guidelines, to the method of delivery (i.e. electronic vs hardcopy). These preferences should be considered when distributing aRMMs where possible.

In addition to other aRMM formats and methods of delivery, the content of educational materials is another potential area of improvement. Currently, the content of educational materials for patients is agreed between pharmaceutical companies and regulators (i.e., by well-educated people with a scientific background) to be uniformly distributed to all patients. However, patients have different levels of (health) literacy and studies have shown medicines' safety information (medication guides, risk management plan summaries) to be too complex and difficult to understand (82, 95). User testing of educational materials aimed at patients could

improve the effectiveness of aRMMs by ensuring that the materials are easy to understand for everyone, even patients with low literacy. Supplementary materials can be considered for those with high literacy seeking further knowledge.

ARMMs might be more effective if healthcare professionals would be more familiar with the concept and applications. There should be more attention on and academic training in pharmacovigilance, in particular adverse event reporting and risk minimisation including aRMMs (96). This should be the case during graduation and specialty training for both medical doctors and (hospital) pharmacists, but other important healthcare professionals involved in the prescription or dispensing of medicines should not be overlooked (i.e., specialised nurses, physician assistants, pharmacy assistants).

Importantly, regulators should be involved more often in drafting national or European treatment guidelines, as they will often have insights from data not yet published in scientific literature. This could in turn lead to the inclusion of the safety information and recommendations of aRMMs in the guideline. Herein lies the responsibility for both regulators and scientific associations to seek this discourse.

Conclusion

ARMMs are a crucial part of the life cycle management of medicines approved in the EU, with one in three new medicines requiring aRMMs at authorisation. The need for aRMMs is determined on a case-by-case basis and many independent factors are considered. There is an emphasis on mitigating preventable harms, particularly medication errors are four times more likely to be addressed by aRMMs. ARMMs have evolved over time since their introduction, as stakeholders gain more knowledge regarding how to design and implement tailored and effective risk management programs. Regulators and pharmaceutical companies should adopt best practices from related inter-disciplinary fields like pharmaceutical sciences, regulatory science and implementation science. Effectiveness evaluation remains key to identify successful aRMMs and potential areas for improvement. More research is needed on robust methods to evaluate effectiveness particularly of medicines with aRMMs at authorisation, as well as on defining success of aRMMs.

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Chapter 9

Nederlandse samenvatting van de belangrijkste bevindingen

R.D.C. Francisca
I.M. Zomerdijk
M.C.J.M. Sturkenboom
S.M.J.M. Straus

Dit proefschrift omvat studies die bedoeld zijn om een dieper inzicht te krijgen in verschillende aspecten van aanvullende risicominimalisatie maatregelen (aRMMs), zoals factoren die de noodzaak van aRMMs bepalen en de rol van aRMMs in het levenscyclusbeheer van geneesmiddelen.

We zijn dit proefschrift begonnen met een overzicht van geneesmiddelen met aRMMs op het moment van toelating tussen 1 januari 2010 en 31 december 2015. Zoals we hebben laten zien in **Hoofdstuk 2** waren aRMMs vereist voor 70 van de 231 geneesmiddelen (30%) die tijdens de onderzoeksperiode waren goedgekeurd. Het aandeel geneesmiddelen met aRMMs op het moment van goedkeuring voordat de EU-wetgeving inzake geneesmiddelenbewaking van kracht werd (juli 2012) was niet significant anders dan daarna met ofwel de Pearson's X^2-test of gesegmenteerde Poisson-regressieanalyse. Met de laatste analyse hebben we geprobeerd rekening te houden met een vertraging in het mogelijke effect van de wetgeving als gevolg van lopende beoordelingen door regelgevende instanties. De geneesmiddelen met aRMMs op het moment van toelating (n=70) hadden het vaakst betrekking op "Antineoplastische en immunomodulerende middelen" (n=20), gevolgd door producten gericht op "Bloed en bloedvormende organen" (n=9), stofwisseling" (n=7) en "Cardiovasculair systeem" (n=7). Een interessante bevinding in ons onderzoek was dat geneesmiddelen met een voorwaardelijke handelsvergunning of een vergunning onder uitzonderlijke omstandigheden vaker aRMMs hadden bij de vergunning dan geneesmiddelen met een reguliere handelsvergunning (52% vs 28%). Alle aRMMs omvatten het verstrekken van educatief materiaal. Deze materialen waren in 93% van de geneesmiddelen gericht op beroepsbeoefenaren in de gezondheidszorg en in 56% op patiënten. Er waren 8 producten (allemaal goedgekeurd na 2012) waarvoor naast educatief materiaal ook andere soorten aRMMs nodig waren: drie zwangerschapspreventieprogramma's, twee gecontroleerde toegang en vier gecontroleerde distributies. Eén product vereiste zowel een zwangerschapspreventieprogramma als een gecontroleerd distributieprogramma.

De behoefte aan aRMMs wordt per geval beoordeeld door regelgevende instanties en voor elk risico afzonderlijk. Tijdens deze beoordeling wordt rekening gehouden met verschillende factoren, zoals ernst, intensiteit en vermijdbaarheid van het risico, evenals indicatie, toedieningsweg, doelgroep en gezondheidszorgomgeving voor gebruik van het geneesmiddel (1). Eerdere studies hebben heterogeniteit aangetoond in de vraag of aRMMs vereist zijn voor vergelijkbare risico's evenals in het type aRMMs dat vereist is (2). In hoofdstuk 3 hebben we een overzicht gegeven van de risico's met en zonder aRMMs van geneesmiddelen die tussen 1 januari 2010 en 31 december 2015 zijn goedgekeurd. Er waren in totaal 3.588 risico's voor de

geneesmiddelen die waren goedgekeurd tijdens de onderzoeksperiode, met een mediaan 16 risico's (bereik 3-33) per geneesmiddel. Er waren 289 risico's (8%) die werden aangepakt door aRMMs. Univariate analyses toonden aan dat de kans op aRMMs verhoogd was voor risico's die beschreven werden als "Aangeboren, familiale en genetische aandoeningen", "Immuunsysteemaandoeningen", "Oogaandoeningen", "Verwondingen, intoxicaties en procedurele complicaties" en "Infecties en parasitaire aandoeningen". Zorgen over de veiligheid die populaties beschreven die niet in klinische onderzoeken waren onderzocht, hadden een significant verminderde kans op aRMMs. Bovendien was er een grotere kans op aRMMs vanwege risico's die werden vermeld voor geneesmiddelen die gericht zijn op de "Bloed en bloedvormende organen", "Cardiovasculair systeem" en "Zintuiglijke organen", evenals "Dermatologie" en "Ademhalingssysteem". De kans op aRMMs was lager voor 'Antineoplastische en immunomodulerende middelen', 'Anti-infectiemiddelen voor systemisch gebruik' en geneesmiddelen die gericht zijn op 'Het spijsverteringskanaal en het metabolisme'. We verwachtten dat er een wisselwerking zou zijn tussen specifieke indicatiegebieden en medische aandoeningen. We vonden acht combinaties van indicatiegebied en medische aandoening waarvoor de berekende kans op aRMMs significant hoger was dan voor andere combinaties van indicatiegebied en medische aandoening, en nog eens 10 combinaties waarin alle risico's werden aangepakt met aRMMs. In een classificatie- en regressieboomanalyse van onze gegevens kon geen onderscheidingsvermogen worden gevonden in onze gegevens, mogelijk vanwege het lage aantal risico's.

Bijwerkingen (ADR's) zijn wereldwijd een bron van aanzienlijke morbiditeit en mortaliteit, en medicatiefouten worden steeds meer erkend als een veelvoorkomende oorzaak van vermijdbare schade. In **Hoofdstuk 4** hebben we ons gericht op de geneesmiddelen met risico's door medicatiefouten in het RMP en hebben we een overzicht gegeven van de routinematige en aanvullende risicominimalisatie maatregelen om het risico op medicatiefouten te minimaliseren. Van de geneesmiddelen die tussen 1 januari 2010 en 31 december 2017 zijn goedgekeurd, had 27% ten minste één risico dat een medicatiefout beschreef. In totaal werden 103 risico's met betrekking tot medicatiefouten geïdentificeerd, waarbij "Drugstoedieningsfout", "Verwarring productdoseringsvorm" en "Productbereidingsfout" de meest voorkomende zijn. Routinematige risicominimalisatie maatregelen voor risico's door medicatiefouten hielden meestal in dat het risico wordt behandeld in de samenvattingen van de productkenmerken, rubrieken 4.2 (Dosering en toediening), 4.4 (Waarschuwingen en voorzorgsmaatregelen) en 6.6 (Speciale voorzorgsmaatregelen voor het verwijderen en andere hantering van het product). Van de 84 geneesmiddelen met een risico door een medicatiefout, hadden er 23 een aRMM op het moment van toelating. Het aandeel risico's door medicatiefouten met aRMMs was hoger dan het aandeel

niet-medicatiefoutengerelateerde risico's met aRMM (28,4% vs. 7,5%), een teken dat vermijdbaarheid een grote rol speelt bij de evaluatie van de behoefte aan aRMMs. Voor alle geneesmiddelen met aRMMs voor risico's door medicatiefouten was het verstrekken van educatief materiaal voor beroepsbeoefenaren in de gezondheidszorg vereist. Acht geneesmiddelen vereisten ook het verstrekken van voorlichtingsmateriaal voor patiënten en vier geneesmiddelen vereisten maatregelen bovenop het voorlichtingsmateriaal.

De behoefte aan aRMMs wordt beoordeeld op het moment van autorisatie, maar dit kan na de autorisatie veranderen naarmate er nieuwe veiligheidsinformatie beschikbaar komt tijdens de levenscyclus. Nieuw geïdentificeerde risico's of voorheen onbekende aspecten van bekende risico's kunnen de invoering van aRMMs vereisen voor geneesmiddelen die eerder zijn goedgekeurd zonder. Omgekeerd kunnen aRMMs worden verminderd of stopgezet, bijvoorbeeld als hun aanbevelingen onderdeel worden van de klinische praktijk. In **Hoofdstuk 5** hebben we vastgesteld dat de kans op introductie van aRMMs binnen 5 en 10 jaar na toelating voor geneesmiddelen die zijn goedgekeurd zonder aRMMs respectievelijk 3,5% en 6,9% was. Deze kansen zijn relatief laag, met name in het licht van de 465 veiligheidssignalen die zijn besproken door het Pharmacovigilance Risk Assessment Committee (PRAC) vanaf het begin in juli 2012 tot het einde van onze onderzoeksperiode (juni 2018) (3). Deze bevindingen impliceren een voorzichtige benadering door EU-regelgevers op het moment van autorisatie. De kans op stopzetting van aRMMs binnen 5 en 10 jaar na toelating was respectievelijk 0,9% en 8,3%. De kans op stopzetting is zeer laag binnen 5 jaar na vergunningverlening, maar neemt snel toe, mogelijk als gevolg van de tijd die nodig is voor het verzamelen van voldoende gegevens over de effectiviteit van aRMM.

Evaluatie van de effectiviteit van risicominimalisatie maatregelen is een integraal onderdeel van het levenscyclusbeheer van geneesmiddelen, maar is vooral belangrijk voor geneesmiddelen met aRMMs. Hoewel ze bedoeld zijn om patiënten te beschermen en beroepsbeoefenaren in de gezondheidszorg te helpen, kunnen aRMMs een belasting vormen voor het gezondheidszorgsysteem, bijvoorbeeld door de administratietijd, en kunnen ze ook andere onbedoelde gevolgen hebben, zoals beperkte toegang voor patiënten. Evaluatie van de effectiviteit is belangrijk om de effectiviteit van het programma te beoordelen en mogelijke doelen voor verbetering te identificeren. In **Hoofdstuk 6** hebben we een overzicht gegeven van de methoden die zijn gebruikt om de effectiviteit van aRMMs te evalueren. We hebben tussen 1 augustus 2012 en 31 december 2017 44 effectiviteitsstudies geïdentificeerd voor 35 geneesmiddelen die zijn goedgekeurd met aRMMs, en we konden gegevens over onderzoekskenmerken verzamelen voor 38 studies. De effectiviteit van aRMMs werd het vaakst geëvalueerd door middel van enquêtes (16

onderzoeken), gevolgd door beoordeling van medische dossiers (11 onderzoeken). De meeste onderzoeken verzamelden alleen gegevens op patiëntniveau (25 onderzoeken), terwijl sommige onderzoeken waren gericht op beroepsbeoefenaren in de gezondheidszorg (9 onderzoeken). Er waren vier onderzoeken die het verzamelen van gegevens op patiëntniveau en gegevens van beroepsbeoefenaren in de gezondheidszorg combineerden. De meeste onderzoeken (22 onderzoeken) waren gericht op het evalueren van de effectiviteit van de implementatie van aRMMs (dwz procesindicatoren), variërend van het ontvangen van educatief materiaal tot het naleven van de aanbevolen gebruiksvoorwaarden; zes studies evalueerden gegevens over ongewenste voorvallen (uitkomstindicatoren) en negen studies evalueerden zowel proces- als uitkomstindicatoren. Zeven studies waren afgerond en beoordeeld door regelgevende instanties. ARMMs werden in één onderzoek als effectief beschouwd, terwijl de overige zes onderzoeken vanwege gemengde zorgen als niet overtuigend werden beschouwd: twee onderzoeken bereikten de vooraf gespecificeerde succesdrempel niet, twee onderzoeken hadden methodologische problemen, één onderzoek werd buiten de EU uitgevoerd, één studie toonde een slechte maar stabiele therapietrouw aan het risicominimalisatieprogramma onder beroepsbeoefenaren in de gezondheidszorg over een langere periode.

Veiligheidskwesties op het gebied van de volksgezondheid waarbij medische hulpmiddelen betrokken zijn, hebben geleid tot initiatieven om de risico-evaluatie van medische hulpmiddelen na het in de handel brengen te versterken en over te stappen van passief-reactief toezicht na het op de markt brengen naar een meer proactief levenscyclusbeheer. De 2017-verordening van de Europese Unie (EU) 2017/745 betreffende medische hulpmiddelen introduceerde de eis van een plan voor post-market surveillance (PMS), dat dezelfde kenmerken heeft als het Risk Management Plan (RMP) van geneesmiddelen. In **Hoofdstuk 7** hebben we aanbevelingen gedaan voor de implementatie van PMS-plannen voor medische hulpmiddelen op basis van lessen die zijn getrokken uit geneesmiddelenbewaking:

- Er moet een gecentraliseerde groep zijn die bestaat uit deskundigen van nationale bevoegde autoriteiten en aangemelde instanties die toezicht moeten houden op de post-marketingbewaking van medische hulpmiddelen en de naleving van PMS-verplichtingen moeten afdwingen
- Implementatie van een sjabloon om verbintenissen na goedkeuring te documenteren en deze verbintenissen voorwaarden te stellen aan de vergunning voor het in de handel brengen om ervoor te zorgen dat ze worden gehandhaafd
- Ontwikkeling van een op risico's gebaseerde benadering om alleen risico's op te nemen die van invloed zijn op de baten-risicoverhouding
- Functie-overschrijdende beoordeling van het PMS-plan en goedkeuring door de persoon die verantwoordelijk is voor de naleving van de regelgeving binnen het bedrijf.

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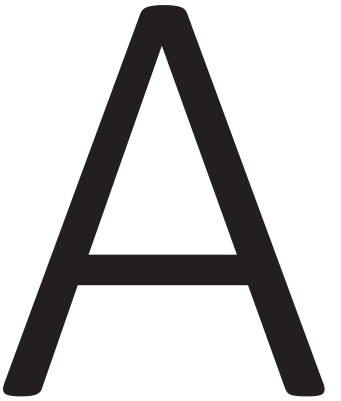
Appendices



DANKWOORD

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Liefs,

Remy

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PHD PORTFOLIO

Research skills

2015-2019 Master of Science in Health Science, specialisation in Pharmaco-epidemiology
Netherlands Institute of Health Sciences, Rotterdam, the Netherlands

Oral presentations

2021 Wetenschapsdag College ter Beoordeling van Geneesmiddelen, Utrecht, Netherlands
Introduction or discontinuation of additional risk minimisation measures of medicines during the life cycle of medicines in Europe

2019 Research seminar Clinical Pharmacology Group Erasmus Medical Centre, Rotterdam, Netherlands
Additionele risicominimalisatiemaatregelen in de levenscyclus van medicijnen

2019 International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Philadelphia, Netherlands
Introduction or discontinuation of additional risk authorised measures of medicines authorised in the European Union: a cohort study

2019 Drug Information Association training, Amsterdam, Netherlands
Additional risk minimisation measures of medicines authorised in the EU

2017 Research seminar Clinical Pharmacology Group Erasmus Medical Centre, Rotterdam, Netherlands
The European Union Risk Management Plan

Poster presentations

2018 34th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Prague, Czech Republic
Association of ischaemic colitis with triptans' treatment: A nested case-control study in the UK using THIN

2017 33rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Montreal, Canada
The safety concerns of medicinal products with additional risk minimisation measures

2017	33rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Montreal, Canada *The safety concerns of medicinal products licensed in the European Union*
2016	32nd International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Dublin, Ireland *Impact of the 2012 European pharmacovigilance legislation on required additional risk minimization measures*
2016	32nd International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Dublin, Ireland *Evaluating the effectiveness of additional risk minimization measures: a descriptive study*

Courses, Seminars and Workshops

2019	Erasmus Medical Centre courses in Basic and Advanced Microsoft Excel
2017	Scientific Integrity Course, Erasmus Medical Centre, Rotterdam, Netherlands
2017	Biomedical English Writing and Communication, Erasmus Medical Centre, Rotterdam, Netherlands
2017	Basic R course, Erasmus Medical Centre, Rotterdam, Netherlands
2016-2019	Pre-conference courses on epidemiology, Annual International Conferences on Pharmacoepidemiology and Therapeutic Risk Management
2015	Erasmus Medical Centre courses in Endnote and Systematic literature review in Pubmed and Other Databases
2015-2019	Weekly research seminars in pharmacoepidemiology, department of Medical Informatics, Erasmus Medical Centre, Rotterdam, Netherlands

Other

2018	Supervising master's thesis project of Emna Baba titled "Alterations to additional risk minimisation measures in the post-marketing phase for EU authorized medicines"

CURRICULUM VITAE

Personalia

Naam:	Francisca-Pieterman
Voornamen:	Reynold Daniel Crisanto
Roepnaam:	Remy
Geboortedatum:	30 mei 1986
Geboorteplaats:	Willemstad, Curaçao
Nationaliteit:	Nederlands
Burgerlijke staat:	Gehuwd
Adres:	Tijkenweg 263
Postcode:	3195 XV
Woonplaats:	Pernis Rotterdam
Mobiel nummer:	06 – 43 80 19 78
Emailadres:	frans_rem@hotmail.com

Opleiding

Augustus 2015 – augustus 2019	Master of Science in Health Sciences
	Netherlands Institute for Health Sciences (NIHES)/ European Programme in Pharmacovigilance and Pharmacoepidemiology (EU2P)
	Onderzoeksrichting: Pharmacoepidemiology
September 2004 – juli 2013	Erasmus Universiteit te Rotterdam
	Geneeskunde oude stijl
September 1998 – juli 2004	Christelijke Scholengemeenschap Zandvliet
	VWO Gymnasium
	Profiel Natuur en Gezondheid met Grieks en Latijn

Cursussen

Januari 2020	Advanced Life Support
	IJsselland Ziekenhuis, Capelle a/d IJssel
December 2019	Fundamental Critical Care Support
	OSG, Houten

Werkervaring

Augustus 2020 – heden	Sint Franciscus Gasthuis en Vlietland, Rotterdam Functie: arts in opleiding tot specialist Interne Geneeskunde
Mei 2020 – juli 2020	IJsselland Ziekenhuis, Capelle a/d IJssel Functie: arts in opleiding tot specialist Interne Geneeskunde
Januari 2020 – april 2020	IJsselland Ziekenhuis, Capelle a/d IJssel Functie: arts niet in opleiding tot specialist voor de maatschap Interne Geneeskunde en Maag-, Darm- en Leverziekten Takenpakket: zaalwerkzaamheden voor de afdelingen Interne Geneeskunde, Maag-, Darm- en Leverziekten en Longziekten. Tevens opvang van patiënten op de Spoedeisende Hulp, Eerste Hart Hulp en Cardiac Care Unit.
Augustus 2015 - heden	Erasmus Medisch Centrum, afd. Medische Informatica Functie: PhD student farmacovigilantie Onderwerp: additionele risicominimalisatiemaatregelen
Augustus 2015 – juli 2019	College ter Beoordeling Geneesmiddelen (CBG) Functie: beoordelaar Geneesmiddelenbewaking Takenpakket: beoordeling van observationele studies, periodieke veiligheidsrapportages, (wijzigingen in) risicomanagementplannen en Samenvatting van Product Karakteristieken, tevens signaaldetectie en -validatie
Augustus 2013 – juli 2015	Maasstad Ziekenhuis Rotterdam Functie: arts niet in opleiding tot specialist voor de maatschap Interne Geneeskunde, Longziekten en Maag-, Darm- en Leverziekten Takenpakket: zaalwerkzaamheden voor de afdelingen Interne Geneeskunde, Maag-, Darm- en Leverziekten, Longziekten en Cardiologie. Tevens opvang van patiënten op de Spoedeisende Hulp, Eerste Hart Hulp/Cardiac Care Unit en Intensive Care

Augustus 2012 – januari 2014	Sport and Event Security Functie: medical steward Takenpakket: verlening van eerste hulp bij wedstrijden van Feyenoord Rotterdam en andere evenementen
2012 – 2013	MediGo Uitzendbureau Functie: doktersassistent op oproepbasis Takenpakket: telefonische triage en afspraken maken, herhaalrecepten en postverwerking
2008 – 2012	Erasmus MC-locatie Daniël Functie: medisch student, verpleegafdeling Radiotherapie en Nucleaire Geneeskunde Takenpakket: ondersteuning in de verpleging en basispatiëntenzorg en bijvullen van verpleegartikelen.
2006 – 2008	Erasmus Universiteit te Rotterdam Functie: student ambassadeur voor de opleiding Geneeskunde Takenpakket: voorlichting geven op open dagen, meeloopdagen en opleidingsbeurzen.

Publicaties

2022	Sultana J, Crisafulli S, Almas M, Antonazzo IC, Baan E, Bartolini C, et al. Overview of the European post-authorisation study register post-authorization studies performed in Europe from September 2010 to December 2018. Pharmacoepidemiology and drug safety. 2022.
2021	Francisca RDC, Baba E, Hoeve CE, Zomerdijk IM, Sturkenboom M, Straus S. Introduction or Discontinuation of Additional Risk Minimisation Measures During the Life Cycle of Medicines in Europe. Drug safety. 2021;44(1):63-72.

2020	Hoeve CE, Francisca RDC, Zomerdijk I, Sturkenboom M, Straus S. Description of the Risk Management of Medication Errors for Centrally Authorised Products in the European Union. Drug safety. 2020;43(1):45-55.
2019	Pane J, Francisca RDC, Verhamme KMC, Orozco M, Viroux H, Rebollo I, et al. EU postmarket surveillance plans for medical devices. Pharmacoepidemiology and drug safety. 2019;28(9):1155-65.
2018	Francisca RDC, Zomerdijk IM, Sturkenboom M, Straus S. Measuring the impact of the 2012 European pharmacovigilance legislation on additional risk minimization measures. Expert opinion on drug safety. 2018;17(10):975-82.

Neventaken

Juli 2021 – heden	Geneesmiddelencommissie Sint Franciscus Gasthuis en Vlietland
April 2021 – heden	Roostering assistentengroep Interne Geneeskunde Sint Franciscus Gasthuis en Vlietland
Maart 2020 – Juli 2020	Roostering assistentengroep Interne Geneeskunde IJsselland Ziekenhuis
2016 – 2019	Tennisvereniging Laatjeskaai Verenigingscompetitieleider (VCL) en Verenigingstoernooileider (VTL), covoorzitter Wedstrijd- en Jeugdcommissie en afgevaardigde van de Wedstrijdcommissie in het Bestuur Taken: organiseren van tennis gerelateerde activiteiten voor senior- en juniorleden, begeleiden van de KNLTB-competities op de vereniging en het organiseren van het KNLTB-toernooi voor amateurs op de vereniging
2007 – 2008	Erasmus Universiteit te Rotterdam, faculteit der Geneeskunde Bestuurslid Stichting Reductiebureau Remedi, commissaris syllabi

	Taken: verkoop van boeken en syllabi tijdens openingstijden van de winkel en het onderhouden van communicatie met het opleidingsinstituut van de faculteit Geneeskunde over de aanlevering van syllabi en readers.
2007 – 2007	Tennisvereniging Breekpunt te Den Haag Secretaris van het bestuur Taken: afhandelen van de post en de ledenadministratie.
2000 – 2004	Christelijk Scholengemeenschap Zandvliet Hoofdredacteur van de schoolkrant en lid van het dagelijks bestuur van de leerlingenvereniging.

Computervaardigheden

Word, Excel, Powerpoint, Outlook, SPSS, R

Hobby's

Tennis, lezen, schrijven, muziek luisteren en zingen.

ABOUT THE AUTHOR

Reynold Francisca, nicknamed Remy, was born on May 30th 1986 in Willemstad, Curaçao. He lived on Curaçao until 1997, when he moved to the Hague in the Netherlands. He attended secondary school at the Zandvliet College, which he graduated in 2004, and preceded to attend the Erasmus University in Rotterdam to study Medicine in the same year. He graduated Medicine in 2013, after which he began working as a physician at the Maasstad hospital in Rotterdam on the Internal Medicine, Gastroenterology, Pulmonology and Cardiology departments as well as the Emergency Room and the Intensive Care Unit. Following two very instructive years, Remy successfully applied to become a doctoral researcher at the Erasmus Medical Centre department of Medical Informatics under the supervision of professor Miriam Sturkenboom and doctors Sabine Straus and Inge Zomerdijk. There, he performed the research which was previously described in this thesis. In 2020, Reynold began his training to become an internist. He worked briefly at the IJsselland hospital before transferring to the Sint Franciscus Hospital to complete the non-teaching hospital portion of his training. He will be transferring to the Erasmus Medical Centre shortly before his PhD defense to complete the rest of his training.

Remy lives in Rotterdam with husband Johan Pieterman, whom he married in July of 2017. They foster a beautiful daughter, Liùsaîdh (Lucy), since January 2019.