ORIGINAL RESEARCH ARTICLE

Drug Saf 2012; 35 (4): 299-314
0114-5916/12/0004-0299/$49.95/0

Risk Minimization Activities of Centrally Authorized Products in the EU

A Descriptive Study

Inge M. Zomerdijk,[1,2] *Fakhredin A. Sayed-Tabatabaei,*[2] *Gianluca Trifirò,*[1,3] *Stella C.F. Blackburn,*[4] *Miriam C.J.M. Sturkenboom*[1] and *Sabine M.J.M. Straus*[1,2]

1 Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, the Netherlands
2 The Dutch Medicines Evaluation Board, Utrecht, the Netherlands
3 Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, Messina, Italy
4 European Medicines Agency, London, UK

Abstract

Background: Since the new legislation on risk management, which came into force in November 2005, an EU Risk Management Plan (EU-RMP) is a required part of the authorization dossier of innovative drugs licensed in the EU. The EU-RMP can include additional risk minimization activities (RMAs) to strengthen the benefit-risk balance of a drug. This study describes the additional RMAs of centrally authorized medicinal products authorized between 1 January 1995 and 1 January 2010.

Methods: The European Public Assessment Reports of all centrally authorized products were analysed to identify characteristics of the product (active substance, authorization date, Anatomical Therapeutic Chemical classification), the additional RMAs and the corresponding safety concerns (classified at Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class level).

Results: Additional RMAs were identified for 58 of the 391 active substances that were authorized as of 1 January 2010. The proportion of active substances with additional RMAs was 5% among those authorized before, and 29% among those approved after the new risk management legislation. Since the new legislation, blood products and antineoplastic and immunomodulating agents most often had additional RMAs. All active substances with additional RMAs required the provision of educational material, most frequently involving healthcare professionals (n = 57) and the patient (n = 31). Thirty-three active substances required additional RMAs on top of the provision of educational material, most frequently including patient monitoring and screening (n = 19).

Conclusions: The proactive pharmacovigilance approach is evolving and the number of products with additional RMAs is growing since the introduction

of the EU-RMP. The provision of educational material is the primary additional risk minimization strategy in the EU. The effect of additional RMA implementation has to be explored.

Introduction

The knowledge of the full benefit-risk balance of a medicinal product is limited at the time of licensing and can change after approval. For this reason, this balance requires continuous re-evaluation during the postmarketing phase when the product is used in clinical practice within a broader and more heterogeneous population compared with premarketing clinical trials.[1] The dynamics of the benefit-risk balance necessitates a lifecycle approach with continuous assessment and evaluation of the benefit-risk balance during the whole product lifecycle.[2] Proactive pharmacovigilance is part of the lifecycle approach aimed at early detection and minimization of risks, as stated in the strategic plans of the European Medicines Agency (EMA) and the US FDA.[3,4]

According to the current EU legislation, in force since November 2005, Marketing Authorization Applicants (MAAs) have to submit a detailed description of the risk management system as part of the application for drug licensing for innovative products.[5,6] For new chemical entities, biosimilar medicinal products and generics of substances for which a risk has been identified for the reference product, it is mandatory to submit an EU Risk Management Plan (EU-RMP).[7] Furthermore, an EU-RMP can be requested by regulatory authorities. An EU-RMP consists of a set of pharmacovigilance activities and interventions that are designed to identify, characterize, prevent or minimize risks during the lifecycle of a drug.[6] The EU-RMP aims to ensure that the benefits of a medicinal product exceed its risks to the largest possible extent, both at individual and population level.[7]

For all medicinal products, an EU-RMP includes routine risk minimization activities (RMAs) aiming to reduce the probability or severity of adverse drug reactions (e.g. precautions in the Summary of Product Characteristics [SmPC]). Some medicinal products, however, may carry risks that require an extra level of risk minimization, i.e. the *additional* RMAs. Examples of additional RMAs include the provision of educational material, implementation of a pregnancy prevention programme, or intensive monitoring of markers of potential harm, such as liver enzymes for the assessment of hepatic function.[7]

Since 2007, the FDA Amendments Act authorized the FDA to require risk evaluation and mitigation strategies (REMS) as part of the authorization documents in the US.[3] An REMS can include the following elements: a Medication Guide, a Communication Plan, Elements To Assure Safe Use (ETASU), an Implementation System and a Timetable for Submission of Assessments.[8] A notable difference between the EU and the US is that it is mandatory for the EU-RMPs to be included in the marketing authorization application for all new active substances and other required situations, while the FDA does not require REMS unless requested on a case-by-case basis. One of the specific challenges for the EU is the variation across countries and the national legislation that is often the main determinant of how additional RMAs are implemented. Since the implementation of the REMS, several studies have described the impact on patients, healthcare providers and health systems in the US.[9-11]

Only a few publications have reviewed EU-RMPs and data on additional RMAs specifically are even more limited.[12-16] To explore the implementation and effectiveness of additional RMAs in the EU, it is necessary to have an overview of the currently approved additional RMAs. The objective of the present study is to describe additional RMAs of medicinal products, which have been licensed through the central authorization procedure in the EU.

Methods

Drugs of Interest

Centrally authorized products (CAPs) were the medicinal products of interest in this study since information about these products is publicly available. Products authorized through the centralized procedure have a single application, evaluation and authorization, which is valid throughout the EU market. The centralized procedure was introduced when the EMA was established in January 1995.[17] Although the scope of the centralized procedure has been modified over time, the procedure included mainly products derived from biotechnology, officially designated orphan medicines, and those in the therapeutic areas of HIV, cancer, neurodegenerative diseases and diabetes mellitus, and other innovative products may apply for this procedure.[5,7] Other terms frequently used within the regulatory field are described in table I.

This cross-sectional study included all active substances authorized through the centralized procedure between 1 January 1995 and 1 January 2010, and which were still authorized as of 1 January 2010. Active substances withdrawn or suspended before 1 January 2010 (n = 31) could not be included in our study since limited data regarding these substances were available. Active substance was the basis for the analysis, i.e. substances that were the subject of multiple and/or generic applications and biosimilar medicinal products were only counted once.

Data Sources

For each CAP, the European Public Assessment Report (EPAR) is published on the website of the EMA (www.ema.europa.eu) once the medicinal product has a positive decision from the European Commission. The information in the EPAR is updated throughout the lifecycle of the drug, and changes to the original terms and conditions of the authorization (i.e. variations, safety specifications, specific obligations) are included.[21] Since November 2005, the EU-RMP is a mandatory part of the application dossier for drug licensing. The EU-RMP aims to strengthen the benefit-risk balance of a medicinal product by requiring the implementation of routine and additional pharmacovigilance and RMAs (table II). Summary information of the EU-RMP is reflected in the EPAR. For each active substance the following characteristics were extracted from the EPAR available as of 1 January 2010: product name(s), Anatomical Therapeutic Chemical (ATC) classification and marketing authorization date.

Identification of Additional Risk Minimization Activities (RMAs)

A marketing authorization consists of several parts. If additional RMAs are required, these conditions are laid down in Annexes II and IV of the marketing authorization. Annex IIB describes specific conditions and restrictions imposed on the Marketing Authorization Holder (MAH), and Annex IV is addressed to the national authorities of the member states and requires them to ensure that the MAH complies with the conditions or restrictions in their territory. The EMA publishes Annex IIB and IV within the EPAR if special conditions or restrictions have been required. Additional RMAs were considered to be the conditions and restrictions with respect to the safe and effective use of a medicinal product described in these Annexes. Annex IIC of the marketing authorization, which is also published in the EPAR, describes the specific obligations to be fulfilled by the MAH. To identify the active substances with additional RMAs, Annexes IIB and Annex IV within the EPAR of each active substance available as of 1 January 2010 were analysed. In addition, Annex IIC of all active substances has been reviewed for additional RMAs to account for the possibility that information might (erroneously) be included in Annex IIC. For active substances with additional RMAs, as identified from Annexes IIB, IIC and IV, the summary information of the EU-RMP was reviewed to obtain detailed information regarding corresponding safety concerns.

The identified additional RMAs were categorized into six groups, based on the aim and target group of the activity. The additional RMAs are described in table III. To explore the effect of the

Table I. Short description of terms frequently used within the regulatory field of medicines evaluation

Term	Description
ATC classification system	This drug classification system divides the active substances into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. The classification system is controlled by the WHO Collaborating Centre for Drug Statistics Methodology[18]
Annex IIB	The EMA publishes Annex IIB of the European Commission decision in the publicly available EPAR to present the conditions imposed on the MAH. Annex IIB includes the conditions or restrictions imposed on the MAH, with regard to the safe and effective use of the medicinal product which reflect the additional RMAs approved for the product[6]
Annex IIC	The EMA publishes Annex IIC of the European Commission decision in the publicly available EPAR to present the specific obligations to be fulfilled by the MAH. Specific obligations data to be submitted in the post-authorization phase are specific to marketing authorizations granted under exceptional circumstances due to limited efficacy and/or safety data available at the time of the CHMP opinion[6]
Annex IV	In addition to Annex IIB, the EMA may publish Annex IV of the European Commission decision. This is a decision addressed by the Commission to the national authorities of the EU member states and contains conditions or restrictions with regard to the safe and effective use of the medicinal product. Annex IV of the Commission decision requires the national authorities to ensure that the MAH implements the additional RMAs in their territory[6]
Biological medicinal product	Biological medicines are made by a living organism, such as a bacterium or yeast, and can consist of relatively small molecules such as human insulin or erythropoietin or complex molecules such as monoclonal antibodies[19]
Biosimilar medicinal product	A 'biosimilar' medicine is a biological medicine that is similar to another biological medicine (the 'biological reference medicine') that has already been authorized for use[19]
Centralized authorization procedure	The EMA is responsible for the centralized authorization procedure. It is a registration procedure for which a single application and evaluation, if positive, results in a single marketing authorization applicable to the whole EU. The centralized procedure includes mainly medicinal products derived from biotechnology, for officially designated 'orphan medicines', for those in certain therapeutic areas (HIV, cancer, neurodegenerative diseases, diabetes mellitus, immunosuppressive diseases and viral diseases) and is available for other innovative products[5]
CMDh	The CMDh is a co-ordination group of the EMA and examines questions relating to the marketing authorization of a medicinal product for human use in two or more Member States in accordance with the mutual recognition procedure or the decentralized procedure[6]
CHMP	The CHMP is the scientific Committee of the EMA and is responsible for providing the European Commission with a scientific opinion on the quality, safety and efficacy of the medicinal product, especially with regard to centralized authorization procedures. The members and alternates of the CHMP are nominated by the EU Member States, based on their individual expertise[5]
European Commission decision	In case of marketing application, the CHMP's opinion is transmitted to the European Commission, which gives a decision. If the decision is positive, the MAH can grant a marketing authorization[20]
EMA	The EMA is a decentralized body of the EU located in London and was established under Regulation 2309/93 EC to harmonize the work of national medicine regulatory bodies. It came into being in January 1995. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use[17]
EPAR	The scientific grounds for the CHMP opinion concerning the approval of a medicinal product are reflected in the EPAR, which includes the product information (Summary of Product Characteristics, labelling and package leaflet) for the medicine, details of the procedural steps taken during the assessment process and the CHMP Assessment Report with confidential parts removed. The EPAR of all centrally authorized products are published on the EMA website[21]
Generic medicinal products	Once the 10-year data protection of a medicinal product expires, another MAA can apply for a marketing authorization for a generic medicine. A generic medicinal product is equivalent to the original medicinal product, since the generic medicinal product contains the same active substances at the same concentration and has similar therapeutic efficacy and safety as the original medicinal product[5]
Lifecycle approach	The continuous evaluation and integration of drug safety and efficacy during the entire lifecycle of a drug. After approval when the drug is used within a broader population, benefit/risk assessment with post-authorization data is an ongoing activity[1,2]

Continued next page

Table I. Contd

Term	Description
Multiple applications	A term used when MAAs wish to obtain, either simultaneously or successively, more than one marketing authorization for a specific medicinal product, under different invented names[5]
Pharmacovigilance	Pharmacovigilance is defined by the WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem[22]
PhVWP	PhVWP is a working party of the CHMP, which provides recommendations to the CHMP on the safety of medicinal products and on the investigation of adverse reactions associated with medicinal products authorized in the EU and other issues relating to pharmacovigilance[23]
REMS	The FDA Amendments Act of 2007 has given the FDA the authority to require an REMS from MAAs to ensure that the benefits of a drug or biological product outweigh its risks. REMS contain an analysis of possible risks and measures to manage known or expected safety issues[3]
EU-RMP	The EU-RMP describes the risk management system of a medicinal product, which is a required part of certain applications for drug licensing. This requirement was part of the new legislation that came into force in November 2005 (table II). It is mandatory to submit an EU-RMP for new chemical entities, biosimilar medicinal products and generics of substances for which a risk has been identified for the reference product. Furthermore, it can be requested by regulatory authorities.[7,20] See table II for a further description of the EU-RMP
US FDA	The FDA is responsible for protecting public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics, products that emit radiation and tobacco products. In addition, the FDA is responsible for advancing public health by helping to speed innovations that make medicines and foods more effective, safer and more affordable, and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health[24]

ATC = Anatomical Therapeutic Chemical; **CHMP** = Committee for Medicinal Products for Human Use; **CMDh** = Co-ordination Group for Mutual Recognition and Decentralised Procedures – human; **EMA** = European Medicines Agency; **EPAR** = European Public Assessment Report; **EU-RMP** = EU Risk Management Plan; **MAAs** = Marketing Authorization Applicants; **MAH** = Marketing Authorization Holder; **PhVWP** = Pharmacovigilance working party. **REMS** = Risk Evaluation and Mitigation Strategy; **RMAs** = risk minimization activities.

introduction of the EU-RMP on the additional RMAs, the periods before and after the introduction of the new risk management legislation (1 November 2005) were analysed separately.

Safety Concerns

The safety concerns that required additional RMAs were analysed. The safety concerns addressed by additional RMAs were identified from either the summary information of the EU-RMP or Annexes IIB and IV. These safety concerns were classified based on System Organ Class (SOC) level according to the Medical Dictionary for Regulatory Activities (MedDRA®), version 13.0. Safety concerns including specific patient groups, e.g. paediatrics or HIV patients, were not included in the MedDRA® dictionary and could not be classified. Therefore, an additional class 'Special patients' was created to review this group separately. Other safety concerns that could not be classified according to the MedDRA® dictionary (e.g. the term 'long-term safety data') were classified as 'Not Elsewhere Classified' (NEC). If a MedDRA® preferred term was related to multiple SOCs, only the primary SOC was considered. A medically trained researcher (IZ) conducted categorization. In case of doubt, two additional researchers (GT and FS-T) performed an independent assessment. In case of discrepancy, a fourth expert (SS) arbitrated.

Results

As of 1 January 2010, 391 independent active substances were authorized in the EU through the centralized procedure (figure 1). For 58 active substances (15%), additional RMAs were identified either in Annex IIB (56 active substances) or Annex IIC (2 active substances), and for 43 of these 58 substances (74%) a Commission decision concerning the additional RMAs addressed to the Member States in Annex IV was identified. (see Appendix I). At the time of the analysis, 5% (11 out of 227) of the active substances, authorized before the new legislation, had additional

RMAs, while additional RMAs were identified for 29% (47 out of 164) of the active substances approved after the new legislation. Additional RMAs were most frequently agreed for active substances concerning 'alimentary tract and metabolism', 'anti-infectives for systemic use' and 'antineoplastic and immunomodulating agents' (figures 2a and b). This was not different for the two periods. In the period after the introduction of the new legislation 50% of the authorized blood products obtained additional RMAs, and 47% of the authorized antineoplastic and immunomodulating agents had additional RMAs.

Characteristics of Additional RMAs

All active substances with additional RMAs (n = 58) required, as a minimum, the provision of educational material (table IV). Educational material was always directed to healthcare professionals (e.g. Direct Healthcare Professional Communication, training programme, brochure), except for one substance (requiring only a patient card). Furthermore, for 53% of the active substances, provision of additional risk information to the patient, such as a leaflet or guide (n = 12), Patient Alert Card (n = 13) or both (n = 6), was part of the additional RMAs. Of the active substances with additional RMAs, educational material to the patient was required for all substances for the sensory organs (n = 2), for 4 out of 5 active substances aimed at treatment of the cardiovascular system, and for the majority of the antineoplastic and immunomodulating agents (16 out of 20). In contrast, none of the anti-infective products required the provision of educational material to the patient.

In addition to the provision of educational material, other types of additional RMAs were requested for 57% (33 out of 58) of substances (figures 2a and b). As shown in table IV, there were 19 active substances with a need for patient monitoring as an additional RMA. This patient monitoring was considered an additional RMA since it was identified from Annex IIB or IIC and not only described in the SmPC, in which case it would have been considered only routine risk minimization. The need for patient monitoring identified as additional RMAs included tuberculosis screening (n = 4), regular blood tests (n = 7) [e.g. International Normalized Ratio (INR),

Table II. Structure of the EU-RMP[7,12,13,20]

Part I	
Safety specification	Summarizes the safety profile of a medicinal product at a particular point in time of its lifecycle, including important identified risks, important potential risks and important missing information that could affect the benefit-risk balance of the medicinal product or have implications for public health. It helps to identify the needs for specific data collection and facilitates building of a pharmacovigilance plan and risk minimization plan
Pharmacovigilance plan	
Routine pharmacovigilance activities	Pharmacovigilance activities that should be conducted for each medicinal product to detect safety signals, including the reporting of suspected adverse drug reactions to regulatory authorities, submission of the Periodic Safety Update Report, and other activities as required under EU legislation
Additional pharmacovigilance activities	Activities designed for medicinal product with significant important or potential risks, or significant missing information, in order to detect safety information, e.g. post-authorization safety studies, clinical trials, monitoring ongoing studies, and registries
Part II	
Evaluation of the need for RMAs	Assessment of each safety concern as to whether any RMAs are needed beyond the pharmacovigilance plan, and whether routine RMAs will adequately address the safety concern
Risk minimization plan	
Routine RMAs	Warnings and information within the Summary of Product Characteristics and patient leaflet, and careful use of labelling and packaging, to reduce the probability of an adverse reaction occurring or its severity. The legal status of the product and the pack size are also considered to be routine RMAs
Additional RMAs	Activities that reduce the probability or severity of an adverse drug reaction, which go beyond those activities considered as routine. These include educational information for healthcare professionals or patients or through conditions or restrictions that control the use of the medicine or activities for monitoring patient status

EU-RMP = EU Risk Management Plan; **RMAs** = risk minimization activities.

Table III. Description of the additional risk minimization activities

Controlled distribution	Conditions and restrictions at drug distribution level. Distribution is controlled to ensure that certain conditions are met, e.g. medicine is only available in a qualified centre or after a special training programme
Informed consent/treatment initiation forms	Document that ensures the patient is fully informed of and understands the risk of the medicinal product
Patient monitoring/screening	The need for monitoring of the patient's health status prior or during treatment, e.g. liver function tests, regular blood tests. The need for patient monitoring is highly recommended in Annex IIB of the marketing authorization, educational material and SmPC, however, it cannot be legally enforced
Pregnancy prevention programme	A programme, which can contain various elements, that is designed to eliminate the risk of pregnancy during drug exposure
Provision of educational material	The provision of educational material in addition to the SmPC and patient leaflet about specific safety concerns (risks) of a drug and measures taken to reduce these concerns. Educational material could be designed for various target groups (healthcare professionals, patients, laboratories, patient associations, etc.). Examples of educational material types are Direct Healthcare Professional Communications, information brochures and specific training programmes. Various media types (written, audio, video) are possible
Registry	Patient registries to record results of tests, to ensure that the recommended conditions of use are being adhered to, and control access to a medicine. Regularly, registries are considered additional pharmacovigilance activities. However, patient registries act as additional RMAs when required for all users of that drug
Special packages/labels	Special packages (i.e. cool boxes) or additional labels (i.e. stickers for traceability of the product), which are required according to Annex IIB of the Commission decision, to ensure safe and effective drug use

SmPC = Summary of Product Characteristics.

haemoglobin or haematocrit], liver function monitoring (n = 6) and various others (n = 9). Active substances with additional need for patient monitoring were, in particular, interleukin inhibitors (n = 3), tumour necrosis factor-α (TNFα) inhibitors (n = 3), antihypertensives indicated for pulmonary arterial hypertension (PAH) [n = 3] and products acting on the nervous system (n = 4). Four of the seven anti-infective products with additional RMAs (all vaccines), required a special package or labelling to enable traceability of the batches. The five active substances that required a pregnancy prevention programme also required a controlled distribution system.

Safety Concerns

We identified 268 safety concerns addressed by additional RMAs. The provision of educational material addressed 261 of the 268 identified safety concerns (97%) [table IV]. Products with additional RMAs most frequently contained safety concerns, for which additional RMAs were required, classified in SOCs 'general disorders and administration site conditions', 'investigations', 'infections and infestations', and 'injury, poisoning and procedural complications' (table V). Additional RMAs in addition to educational material were most often required for products with safety issues classified as hepatobiliary disorders (6 out of 7 active substances with hepatobiliary safety issues [86%]), for 83% of the active substances with congenital, familial and genetic safety concerns, for 60% of those with renal and urinary safety concerns and for 50% of those with safety concerns classified as metabolism and nutrition disorders. All safety concerns classified as 'congenital, familial and genetic disorders' were addressed by a pregnancy prevention programme. In addition, 67% of the safety concerns classified as 'infections and infestations' were addressed by the provision of educational material to the patient.

Discussion

To our knowledge, this is the first descriptive study aimed at exploring additional RMAs among CAPs in the EU. With the new legislation on risk management of 2005, the pharmacovigilance of medicines shifted from a largely reactive approach based on the spontaneous reports of suspected adverse drug reactions, to a continuous proactive lifecycle management. The EU-RMP is a roadmap

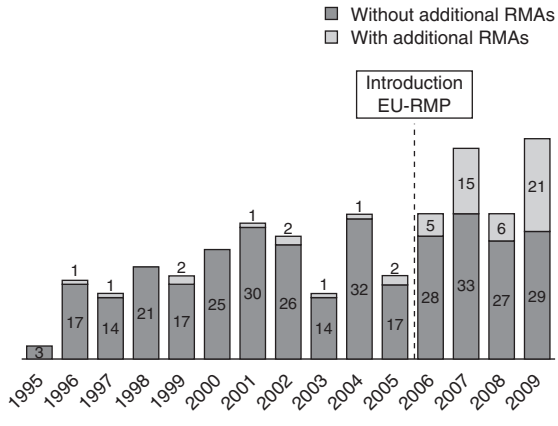

Fig. 1. Active substances with and without additional RMAs, stratified by year of authorization. **EU-RMP** = EU Risk Management Plan; **RMAs** = risk management activities.

that evolves as the benefit-risk profile becomes further defined and additional RMAs facilitate proactive measures to improve the benefit-risk balance.[15] It allows regulatory authorities to specify the conditions and restrictions necessary for the safe and effective use of the medicinal product as part of the marketing authorization. Before the new legislation this possibility did not exist.

We identified 58 (centrally authorized) active substances with additional RMAs. The proportion of active substances with additional RMAs authorized after the new legislation on risk management is substantially higher as compared to those authorized before the new legislation, 29% and 5% respectively. Comparing the period before and after the new legislation of 2005, the proportion of active substances with additional RMAs varied the most among antineoplastic and immunodulating agents. As of 1 January 2010, 9% of these products authorized before the new legislation included additional RMAs, compared to 47% of those that were approved afterwards. This increase is mainly due to the immunosupressants (including selective immunosuppressants, TNFα inhibitors and interleukin inhibitors). Of the immunosuppressants authorized before and after the new legislation, 2 out of 11, and 11 out of 12 had additional RMAs, respectively.

Although it was not specifically the subject of our analyses, it might be possible that the safety profile of newer products differs from older products, and additional RMAs might be more relevant for these newer products. We observed, however, no substantial changes over the years regarding the most commonly involved product classes of products with additional RMAs. In addition, the proposed additional RMAs of these products were not different, although the number of products with additional RMAs authorized before the new legislation was quite limited.

Since the adoption of legislation, the new proactive approach of pharmacovigilance has gained momentum, and there is increasing awareness of the available options to minimize risks, although we are still at the beginning of realizing the full potential of proactive pharmacovigilance.[15] The development towards more proactive pharmacovigilance with a risk management approach has created additional possibilities for active substances to obtain additional RMAs. In addition, according to the current Guideline on risk management systems, the MAH should justify that there is no need for additional RMAs, suggesting that additional RMAs are needed by default.[7] This might lead, on the one hand, to more proposals and, on the other hand, to fewer rejections of proposed additional RMAs by the regulators, causing excessive use. Another concern expressed is the use of inappropriate educational material for commercial interests instead of the intended use. Strict monitoring of the additional RMAs should prevent this. Provisions in the new pharmacovigilance legislation that are to be implemented in July 2012 require monitoring the outcome of additional RMAs, which might limit this risk in the near future.

Educational Material

Provision of educational material is the predominant strategy in the EU to reduce the probability or severity of an adverse drug reaction. All active substances with additional RMAs required the provision of educational material, which was used to address 97% of the safety concerns. This might be explained by the fact that provision of educational material is a relatively easy risk minimization strategy, i.e. not complicated to produce

and simple to implement. In the EU, because different healthcare systems are in place, a certain level of flexibility seems important to facilitate national implementation. For this reason, often only key elements to be included in a certain type of educational material are agreed on at EU level.

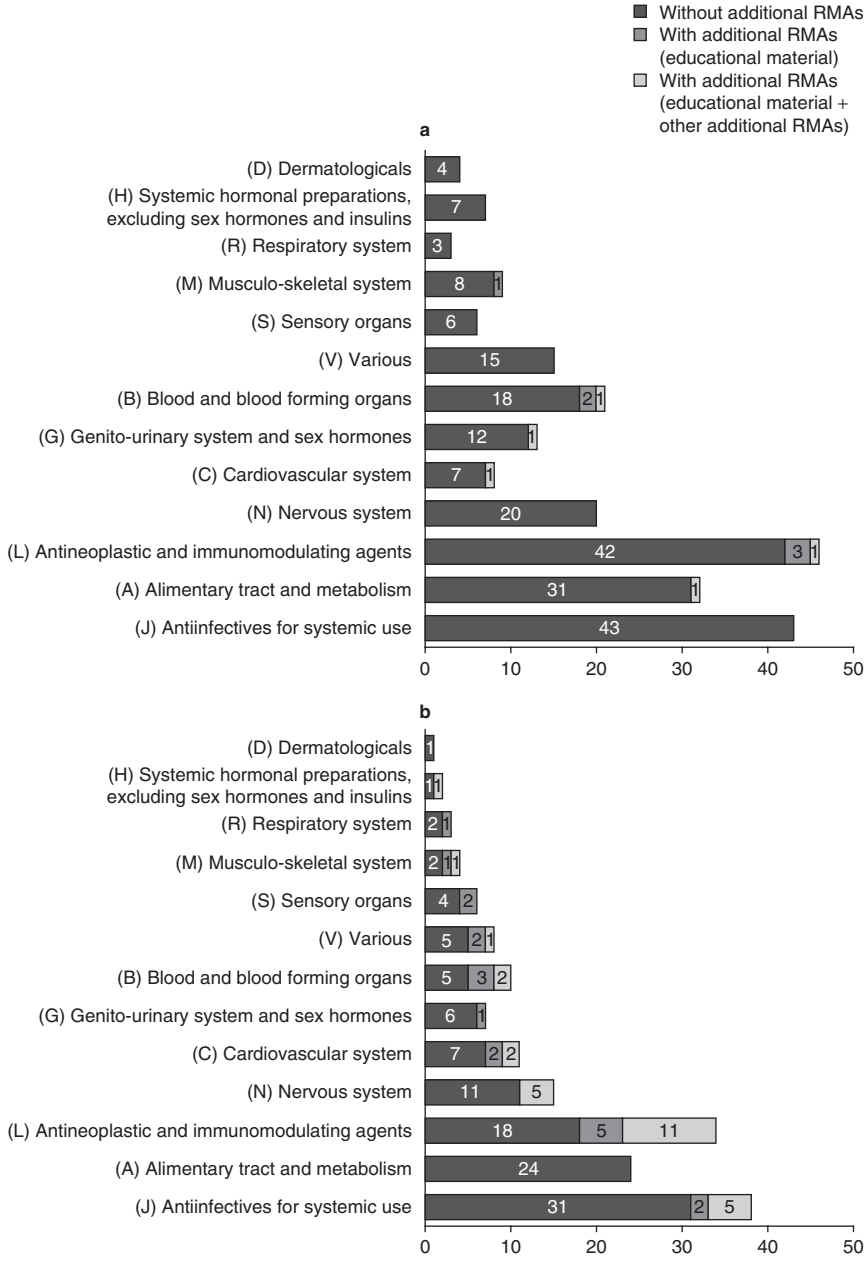

Fig. 2. (**a**) Distribution of active substances authorized before the new legislation on risk management according to ATC classification system (n = 227). (**b**) Distribution of active substances authorized after the new legislation on risk management according to ATC classification system (n = 164). **ATC** = Anatomical Therapeutic Chemical; **RMAs** = risk management activities.

Table IV. Overview of additional RMAs classified by risk minimization type

Additional risk minimization activity	Active substance authorized before new legislation [n = 11] (%)	Active substance authorized after new legislation [n = 47] (%)	Active substance[a]	Safety concerns addressed by additional RMAs [n = 268]
Provision of educational material – total	11 (100)	47 (100)	All active substances with additional RMAs (Appendix I)	261
To healthcare professionals[b]	11 (100)	46 (98)		251
To the patient	8 (73)	23 (49)		94
Patient monitoring/ screening	2 (18)	17 (36)	Agomelatine, Ambrisentan, *Bosentan,* Caffeine, Canakinumab, Capsaicin, Certolizumab, ChondroCelect®, Deferasirox, Golimumab, Hydroxycarbamide, *Infliximab,* Mecasermin, Methoxypolyethylene glycol-epoetin beta, Micafungin, Olanzapine, Rilonacept, Sitaxentan, Ustekinumab	43
Controlled distribution	3 (27)	7 (15)	5-aminolevulinic acid hydrochloride, Ambrisentan, *Bosentan,* Caffeine, ChondroCelect®, Eculizumab, Lenalidomide, *Miglustat, Sildenafil*, Sitaxentan	52
Pregnancy prevention programme	1 (9)	4 (9)	Ambrisentan, *Bosentan,* Lenalidomide, Thalidomide, Sitaxentan	5
Special packages/ labels (e.g. stickers, cool boxes)	1 (9)	6 (13)	Fentanyl citrate, *Moroctocog alfa*, Pandemic influenza vaccines (Celvapan®, Focetria® and Pandemrix®), Pneumococcal polysaccharide conjugate vaccine, Epoetin alfa	8
Others[c]	NA	6 (13)	ChondroCelect®, Clofarabine, Fentanyl citrate, Methoxypolyethylene glycol-epoetin beta, Rinolacept, Thalidomide	17

a Italicized drug names were authorized before the legislation of 2005 came into effect.

b Prescribers, pharmacists, nurses.

c Informed consent for the patient (n = 1), registry (n = 1), retesting of the antibody status in a reference laboratory (n = 1), single-source distribution (n = 1), systematic return of used and unused nasal spray solutions (n = 1), treatment initiation form (n = 1).

NA = not applicable; **RMAs** = risk minimization activities.

However, at the same time, the lack of a standardized approach complicates implementation for member states and MAHs, might hamper evaluation of its effectiveness and may cause confusion for patients. In addition, educational material may be interpreted by healthcare professionals, due to, for example, glossy appearance, as promotional and may not have been appreciated as risk minimization. An overload of educational material may result in a less effective risk minimization or have a deterrent effect.[25,26]

Although different legal bases to minimize risks are in force in the US, educational material is also the strategy of choice in the approved REMS. This is in line with our findings regarding the EU. As of June 2010, nearly all (119 of the 123) products with approved REMS listed on the FDA website included at least a medication guide for the patient, and 25% of the REMS included a communication plan for the healthcare professional.[26,27] In the EU, a patient leaflet is provided routinely, whilst in the US, a medication guide for patients is only required if requested according to the REMS.[28] In the EU, the provision of educational material as additional RMA was always aimed at healthcare professionals and at patients in 54% of instances, in addition to the standard patient information leaflet.

In our study, 33 active substances in the EU required measures in addition to the provision of

educational material, and the need for patient monitoring was the second most frequently identified additional RMA. Little consistency in additional RMAs across similar safety concerns was identified in this study, except for 'teratogenicity', which in all cases was addressed with a pregnancy prevention programme, and 'hepatobiliary disorders', which, in four of the seven active substances, was addressed with patient monitoring or screening. This lack of consistency can partly be explained by the case-by-case consideration of each safety concern.[7] This emphasizes that the need for additional RMAs can be very drug specific.

Strengths and Limitations of the Study

Only CAPs were included in this study, which limits the generalizability of our findings. Active substances authorized through other procedures could also have additional RMAs since the Guideline on risk management systems applies to all medicinal products.[7] However, additional RMAs are most likely for innovative, complex and technically advanced products, which are generally authorized through the centralized procedure. In view of the type of products authorized through other procedures, e.g. generic medicinal products, very few others would have additional RMAs. One well known example is the pregnancy prevention programme for isotretinoin, which aims to reduce the risk of teratogenicity.[29]

From our cross-sectional analysis it cannot be concluded if an active substance had additional RMAs at the time of initial marketing authorization, or whether these were obtained during post-authorization. The EU-RMP is not designed as 'on-off', but rather as a continuous process amended as the experience grows and the benefit-risk profile

Table V. Safety concerns of the active substances with additional RMAs classified by SOC

SOC	Active substances with additional RMAs [n = 58]	Active substances with additional RMAs on top of educational material [n = 33] (57%)[a]
General disorders and administration site conditions	21	7 (33)
Injury, poisoning and procedural complications	19	6 (32)
Investigations	18	8 (44)
Infections and infestations	14	5 (36)
Blood and lymphatic system disorders	11	5 (45)
Immune system disorders	10	1 (10)
Special patient group	10	2 (20)
Nervous system disorders	10	5 (50)
Neoplasms benign, malignant and unspecified	9	3 (33)
Vascular disorders	9	2 (22)
Cardiac disorders	8	2 (25)
Metabolism and nutrition disorders	8	4 (50)
Surgical and medical procedures	8	2 (25)
Hepatobiliary disorders	7	6 (86)
Congenital, familial and genetic disorders	6	5 (83)
Musculoskeletal and connective tissue disorders	5	2 (40)
Renal and urinary disorders	5	3 (60)
Skin and subcutaneous tissue disorders	5	0 (0)
Pregnancy, puerperium and perinatal conditions	5	1 (20)
Other SOCs[b]	21	7 (33)

a Percentage of all active substances with additional RMAs.

b Includes SOCs not elsewhere classified and SOCs with n < 5 safety concerns (Ear and labyrinth disorders; Eye disorders; Gastrointestinal disorders; Psychiatric disorders; Reproductive system and breast disorders; Respiratory, thoracic and mediastinal disorders).

RMAs = risk minimization activities; **SOC** = System Organ Class.

of the drug further evolves.[15] The EPAR can be appropriately adapted during the lifecycle of the drug, with only the most recent version published. The exact timing of additional RMAs coming into force is therefore difficult to assess from publicly available data. This information might be specifically relevant for the active substances authorized before the new legislation on risk management came into force, and which required additional RMAs during the lifecycle.

The EPAR of some products contained discrepancies regarding information on additional RMAs. Differences between Annex IIB and the summary information of the EU-RMP were observed, in which either of these two documents contained extra additional RMAs. Furthermore, difficulties with the difference between pharmacovigilance activities and additional RMAs were observed in these documents. In some instances, pharmacovigilance activities, such as close monitoring of the safety issue in the Periodic Safety Update Report or long-term safety and effectiveness studies, were presented as additional RMAs. The aim of pharmacovigilance activities essentially differs from additional RMAs; while the former aims to study postmarketing safety concerns, the latter aims to reduce the probability of an adverse drug reaction. The discrepancies can easily be explained by a change in the characteristics of EU-RMPs, and the quality of the corresponding summary information of the EU-RMPs and Annexes IIB over time (improvements from learning and interventions), which will reduce the chance of such misclassification in future. The quality of the first EPARs can explain the two active substances with additional RMAs described in Annex IIC instead of Annex IIB. We might have missed active substances with additional RMAs, of which details regarding additional RMAs were lacking in the EPAR. We agree, in line with previous studies, that the quality of the publicly available information regarding additional RMAs should be improved.[12,13] A possible solution might be to provide a periodic overview of the required additional RMAs, including changes over time and updates of the EU-RMP regarding both additional pharmacovigilance and additional RMAs.

Giezen et al.[13] evaluated post-authorization safety studies (PASS) as part of the EU-RMP. The authors observed limited availability of full/partial study protocols of the PASS, precluding a scientific assessment of these studies at the time of regulatory approval. In line with previous findings, also in our study, limited availability of comprehensive information concerning additional RMAs precluded an in-depth description of the additional RMAs and corresponding risks. Although all stakeholders, including healthcare professionals, theoretically have full access to product information (including Annex IIB) and public assessment reports of the CAPs via the EMA website, it is a challenge to find information and instructions regarding the additional RMAs, e.g. which medicinal products require special obligations or restrictions and the type of measures involved. More transparency and easier access to information concerning additional RMAs, the corresponding risks and the evaluation of the need for additional RMAs may enhance awareness of the role that these activities have in clinical practice and might facilitate implementation at national level. Equal critical points were identified by Frau et al.[12] The authors identified limited transparency as one of the main issues that influence adequate implementation of EU-RMPs. We agree with the authors that better access to pharmacovigilance activities and doctor and patient programmes is needed to improve the effect of the additional RMAs.

Implications

Since 2005, the growing experience on the EU-RMP and additional RMAs has led to a better understanding of the possibilities and challenges of this proactive approach. The EU-RMP offers knowledge gain regarding the drug's benefit-risk profile and possibilities to ensure safe drug use during the product lifecycle. The new pharmacovigilance legislation that will come into force mid-2012 will further broaden the opportunities. There will be major changes to existing processes in the member states, EMA and MAHs with regard to evaluation of risks associated with medicinal products. In addition, the framework on

how the EU takes harmonized regulatory action on drug safety should be implemented in July 2012.[30]

The full opportunities offered by the EU-RMP are only beginning to be appreciated, and challenges concerning the implementation and assessment of the effectiveness of additional RMAs will need to be further addressed. Actual implementation of the additional RMAs takes place at national level and has to take into account national requirements, e.g. health systems, language and health beliefs. This national phase allows the realization of better-fitting programmes and better compliance of healthcare professionals and patients, which in turn might positively influence the effects of additional RMAs. Additional RMAs put an extra burden on the system and should therefore not only be carefully drafted and monitored, but also only be requested if added value of the benefit-risk balance is to be expected. It is in the interest of patients, healthcare professionals, industry and regulators that the least harm and maximum benefit results from using a medicine, and to avoid unnecessary, inefficient measures.

Recommendations in the new pharmacovigilance legislation offer opportunities to better address the limitations of the current guidance since it requires the EMA, member states and MAHs to monitor the outcome of additional RMAs.[31,32] Knowledge regarding the effectiveness of additional RMAs will impact the drafting and implementation of additional RMAs and will, in future, lead to improved benefit-risk balance and increased patient safety. Currently, there is limited knowledge available regarding the effectiveness of additional RMAs.[33-39] In view of the new pharmacovigilance legislation, methods to evaluate the implementation and effectiveness of additional RMAs need to be developed. In addition, it will be relevant to study the implementation of the additional RMAs and have a closer look at the differences across countries and the influences on individual patient safety.

Conclusions

This study describes the additional RMAs of CAPs that are required to be implemented when the drug has been, or will be, marketed in an EU member state. The risk management approach is developing and the number of products with additional RMAs is growing after the introduction of the EU-RMP. Almost one-third of the recent CAPs required additional RMAs, which emphasized the need for evaluation of these measures. Future research should explore the effects of additional RMA implementation in the minimization of risks associated with drug therapies in the EU at both patient and population level.

Acknowledgements

No sources of funding were used to conduct this study or prepare this manuscript. Stella Blackburn was the lead author of the risk management guideline and is responsible for risk management policy at the EMA. Miriam Sturkenboom is heading a research group that conducts unconditional research on the safety and effects of drugs for several pharmaceutical companies (AstraZeneca, Pfizer, Eli Lilly), none of which is related to this current research. Inge Zomerdijk, Fakhredin Sayed-Tabatabaei, Gianluca Trifirò and Sabine Straus have no conflicts of interest that are directly relevant to the content of this study.

Appendix

Appendix 1. Centrally authorized active substances presenting additional Risk Minimization Activities in the European Public Assessment Report at 1 January 2010

Active substance	Product name	Anatomical Therapeutic Chemical classification code	Date of issue of marketing authorization	Annex
5-Aminolevulinic acid hydrochloride	Gliolan®	L01XD04	7 Sep 2007	IIB + IV
Abatacept	Orencia®	L04AA24	21 May 2007	IIB
Adalimumab	Humira®	L04AB04	8 Sep 2003	IIB

Continued next page

Appendix 1. Contd

Active substance	Product name	Anatomical Therapeutic Chemical classification code	Date of issue of marketing authorization	Annex
Agomelatine	Thymanax®, Valdoxan®	N06AX22	19 Feb 2009	IIB + IV
Alemtuzumab	MabCampath®	L01XC04	6 Jul 2001	IIB + IV
Ambrisentan	Volibris®	C02KX02	21 Apr 2008	IIB + IV
Anidulatungin	Ecalta®	J02AX06	20 Sep 2007	IIB
Bosentan	Tracleer®	C02KX01	15 May 2002	IIB + IV
Caffeine citrate	Nymusa®	N06BC01	2 Jul 2009	IIB + IV
Canakinumab	Ilaris®	L04AC08	23 Oct 2009	IIB + IV
Capsaicin	Qutenza® (Transacin)	N01BX04	15 May 2009	IIB
Certolizumab	Cimzia®	L04AB05	01 Oct 2009	IIB + IV
Characterized viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins	ChondroCelect®	M09AX02	05 Oct 2009	IIB + IV
Clofarabine	Evoltra®	L01BB06	29 May 2006	IIC
Deferasirox	Exjade®	V03AC03	28 Aug 2006	IIB + IV
Degarelix	Firmagon®	L02BX02	17 Feb 2009	IIB + IV
Dronedarone	Multaq®	C01BD07	26 Nov 2009	IIB + IV
Eculizumab	Soliris®	L04AA25	20 Jun 2007	IIB + IV
Efavirenz/emtricitabine/tenofovir disoproxil	Atripla®	J05AR06	13 Dec 2007	IIB
Epoetin alfa	Abseamed®, Binocrit®, Epoetin alfa Hexal®	B03XA01	28 Aug 2007	IIB + IV
Epoetin zeta	Retacrit®, Silapo®	B03XA01	18 Dec 2007	IIB + IV
Eptacog alfa (activated)	NovoSeven®	B02BD08	23 Feb 1996	IIB + IV
Eptotermin alfa	Opgenra®	M05BC02	19 Feb 2009	IIB + IV
Fentanyl citrate	Instanyl®	N02AB03	20 Jul 2009	IIB + IV
Gadoversetamide	OptiMARK®	V08CA06	23 Jul 2007	IIB
Golimumab	Simponi®	L04AB06	01 Oct 2009	IIB + IV
Hydroxycarbamide	Siklos®	L01XX05	29 Jun 2007	IIB + IV
Indacaterol	Hirobriz Breezhaler®, Onbrez Breezhaler®, Oslif Breezhaler®	R03AC18	30 Nov 2009	IIB
Infliximab	Remicade®	L04AB02	13 Aug 1999	IIB + IV
Lasofoxifene	Fablyn®	G03XC03	24 Feb 2009	IIB + IV
Lenalidomide	Revlimid®	L04AX04	14 Jun 2007	IIB + IV
Mecasermin	Increlex®	H01AC03	3 Aug 2007	IIB + IV
Methoxy polyethylene glycol-epoetin beta	Mircera®	B03XA03	20 Jul 2007	IIB + IV
Micafungin (as sodium salt)	Mycamine®	J02AX05	25 Apr 2008	IIB + IV
Miglustat	Zavesca®	A16AX06	20 Nov 2002	IIC
Moroctocog alfa	ReFacto AF®	B02BD02	13 Apr 1999	IIB + IV
Natalizumab	Tysabri®	L04AA23	27 Jun 2006	IIB + IV
Nilotinib	Tasigna®	L01XE08	19 Nov 2007	IIB + IV
Nonacog alfa	BeneFIX®	B02BD09	27 Aug 1997	IIB
Olanzapine (as pamoate monohydrate)	Zypadhera®	N05AH03	19 Nov 2008	IIB + IV
Pandemic influenza vaccine	Celvapan®	J07BB01	04 Mar 2009	IIB
Pandemic influenza vaccine	Focetria®	J07BB02	02 May 2007	IIB

Continued next page

Appendix 1. Contd

Active substance	Product name	Anatomical Therapeutic Chemical classification code	Date of issue of marketing authorization	Annex
Pandemic influenza vaccine	Pandemrix®	J07BB02	20 May 2008	IIB
Pegaptanib sodium	Macugen®	S01LA03	31 Jan 2006	IIB + IV
Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)	Prevenar 13®	J07AL02	9 Dec 2009	IIB
Porfimer sodium	PhotoBarr®	L01XD01	25 Mar 2004	IIB + IV
Prasugrel	Efient®	B01AC22	25 Feb 2009	IIB + IV
Ranibizumab	Lucentis®	S01LA04	22 Jan 2007	IIB + IV
Ranolazine	Ranexa® (Latixa)	C01EB18	9 Jul 2008	IIB + IV
Rilonacept	Arcalyst®	L04AC08	23 Oct 2009	IIB + IV
Romiplostim	Nplate®	B02BX04	4 Feb 2009	IIB + IV
Sevelamer carbonate	Renvela®	V03AE02	10 Jun 2009	IIB + IV
Sildenafil	Revatio®	G04BE03	28 Oct 2005	IIB + IV
Sitaxentan	Thelin®	C02KX03	10 Aug 2006	IIB
Thalidomide	Thalidomide Celgene®	L04AX02	16 Apr 2008	IIB + IV
Tocilizumab	RoActemra®	L04AC07	16 Jan 2009	IIB + IV
Ustekinumab	Stelara®	L04AC05	16 Jan 2009	IIB + IV
Zoledronic acid	Aclasta®	M05BA08	15 Apr 2005	IIB + IV

References

1. Eichler HG, Pignatti F, Flamion B, et al. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nat Rev Drug Discov 2008 Oct; 7 (10): 818-26
2. Vandenbroucke JP, Psaty BM. Benefits and risks of drug treatments: how to combine the best evidence on benefits with the best data about adverse effects. JAMA 2008 Nov 26; 300 (20): 2417-9
3. Meyer BM. The Food and Drug Administration Amendments Act of 2007: drug safety and health-system pharmacy implications. Am J Health Syst Pharm 2009 Dec 15; 66 (24 Suppl. 7): S3-5
4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonised tripartite guideline: pharmacovigilance planning (E2E). November 2004 [online]. Available from URL: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf [Accessed 2010 Apr 15]
5. European Commission. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [online]. Available from URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2004R0726:20090706:EN:PDF [Accessed 2010 Jul 30]
6. European Commission. Directive 2001/83/EC of the European Parliament and of the Council, as amended, on the Community code relating to medicinal products for human use [online]. Available from URL: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_cons/dir2001_83_cons_20081230_en.pdf [Accessed 2010 Jul 24]
7. Committee for Medicinal Products for Human Use. Guideline on risk management systems for medicinal products for human use. November 2005 [online]. Available from URL: http://web.invima.gov.co/portal/documents/BVSalud/IVC/anexo5emeagrmsmp.pdf [Accessed 2012 Jan 16]
8. Food and Drug Administration. Guidance for industry: format and content of proposed risk evaluation and mitigation strategies (REMS), REMS assessments, and proposed REMS modifications. Draft guidance, 2009 Sept [online]. Available from URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf [Accessed 2010 Jun 30]
9. American Pharmacists Association. White paper on designing a risk evaluation and mitigation strategies (REMS) system to optimize the balance of patient access, medication safety, and impact on the health care system. J Am Pharm Assoc 2009 Nov-Dec; 49 (6): 729-43
10. Shane R. Risk evaluation and mitigation strategies: impact on patients, health care providers, and health systems. Am J Health Syst Pharm 2009 Dec 15; 66 (24 Suppl. 7): S6-12
11. Stubbings J, Joshi RA, Hoffman JM. Risk evaluation and mitigation strategies: challenges and opportunities for health-system pharmacists. Am J Health Syst Pharm 2010 Sep 15; 67 (18): 1547-54
12. Frau S, Font Pous M, Luppino MR, et al. Risk Management Plans: are they a tool for improving drug safety? Eur J Clin Pharmacol 2010 Jun 25; 66 (8): 785-90
13. Giezen TJ, Mantel-Teeuwisse AK, Straus SM, et al. Evaluation of post-authorization safety studies in the first

cohort of EU risk management plans at time of regulatory approval. Drug Saf 2009; 32 (12): 1175-87

14. Arana A, Allen S, Burkowitz J, et al. Infliximab paediatric Crohn's disease educational plan: a European, cross-sectional, multicentre evaluation. Drug Saf 2010 Jun 1; 33 (6): 489-501
15. Raine J, Wise L, Blackburn S, et al. European perspective on risk management and drug safety. Clin Pharmacol Ther 2011 May; 89 (5): 650-4
16. Key C, Mulchrone B, Wai K. The value of reviewing existing EU risk management plans. RAJ Pharma 2010 Feb [online]. Available from URL: http://www.quintiles.com/elements/media/inthenews/reviewing-existing-risk-management-plans.pdf [Accessed 2012 Jan 16]
17. Herxheimer A. The European Medicines Evaluation Agency. BMJ 1996 Feb 17; 312 (7028): 394
18. WHO Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) index with Defined Daily Doses (DDDs) [online]. Available from URL: http://www.whocc.no/atc_ddd_index/ [Accessed 2010 May 15]
19. European Medicines Agency. Guideline on similar biological medicinal products. October 2005 [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf [Accessed 2010 Aug 4]
20. European Commission. Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2003_63/dir_2003_63_en.pdf [Accessed 2010 Apr 24]
21. European Medicines Agency. CHMP: overview [online]. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000095.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028c7a [Accessed 2010 Jul 30]
22. World Health Organisation. The importance of pharmacovigilance: safety monitoring of medicinal products. 2002 [online]. Available from URL: http:// http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf [Accessed 2010 Sep 10]
23. European Medicines Agency. Guideline on legal status for the supply to the patient of centrally authorised medicinal products [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004885.pdf [Accessed 2010 May 27]
24. Food and Drug Administration. What we do [online]. Available from URL: http://www.fda.gov/AboutFDA/WhatWeDo/default.htm [Accessed 2010 Jul 12]
25. Hirst C, Cook S, Dai W, et al. A call for international harmonization in therapeutic risk management. Pharmacoepidemiol Drug Saf 2006 Dec; 15 (12): 839-49; discussion 50-1
26. Traynor K. Stakeholders urge overhaul of REMS programs: standardization, better access, less paperwork sought. Am J Health Syst Pharm 2010 Sep 1; 67 (17): 1397-8
27. Food and Drug Administration. Approved Risk Evaluation and Mitigation Strategies (REMS) [online]. Available from URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm [Accessed 2010 Jun 9]
28. Dowlat H. The importance and impact of the EU RMP and US REMS to risk-benefit assessments. Regulatory Rapporteur 2011; 8 (2): 20-3
29. Mitchell AA, Van Bennekom CM, Louik C. A pregnancy-prevention program in women of childbearing age receiving isotretinoin. N Engl J Med 1995 Jul 13; 333 (2): 101-6
30. Waller P. Getting to grips with the new European Union pharmacovigilance legislation. Pharmacoepidemiol Drug Saf 2011 May; 20 (5): 544-9
31. European Commission. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human us [online]. Available from URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF [Accessed 2011 May 30]
32. European Commission. Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products [online]. Available from URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF [Accessed 2011 May 30]
33. Shin J, Cheetham TC, Wong L, et al. The impact of the iPLEDGE program on isotretinoin fetal exposure in an integrated health care system. J Am Acad Dermatol 2011; 65 (6): 1117-25
34. Miller D, Bennett L, Hollis K, et al. A patient follow-up survey programme for alosetron: assessing compliance to and effectiveness of the risk management programme. Aliment Pharmacol Ther 2006 Sep 1; 24 (5): 869-78
35. Brinker A, Kornegay C, Nourjah P. Trends in adherence to a revised risk management program designed to decrease or eliminate isotretinoin-exposed pregnancies: evaluation of the accutane SMART program. Arch Dermatol 2005 May; 141 (5): 563-9
36. Crijns HJ, Straus SM, Gispen-de Wied C, et al. Compliance with pregnancy prevention programmes of isotretinoin in Europe: a systematic review. Br J Dermatol 2011 Feb; 164 (2): 238-44
37. Chang L, Tong K, Ameen V. Ischemic colitis and complications of constipation associated with the use of alosetron under a risk management plan: clinical characteristics, outcomes, and incidences. Am J Gastroenterol 2010 Apr; 105 (4): 866-75
38. Hollis K, Calingaert N, Price M, et al. Tysabri TOUCH Prescriber Program Risk Management Program RiskMAP [poster]. Presented at the 26th International Conference on Pharmacoepidemiology & Therapeutic Risk Management. 2010 Aug 19-22; Brighton
39. Castaneda C, Zeldis J, Freeman J, et al. RevAssist®: a comprehensive risk minimization programme for preventing fetal exposure to lenalidomide. Drug Saf 2008; 31 (9): 743-52

Correspondence: *Inge M. Zomerdijk*, MSc, Department of Medical Informatics, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands.
E-mail: i.zomerdijk@erasmusmc.nl