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Evaluation of Post-Authorization Safety Studies in the First Cohort of EU Risk Management Plans at Time of Regulatory Approval

Thijs J. Giezen,[1,2] *Aukje K. Mantel-Teeuwisse*,[1,2] *Sabine M.J.M. Straus*,[1] *Toine C.G. Egberts*,[2,3] *Stella Blackburn*,[4] *Ingemar Persson*[4,5,6] and *Hubert G.M. Leufkens*[1,2,4]

1 Medicines Evaluation Board, The Hague, the Netherlands
2 Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Utrecht, the Netherlands
3 University Medical Center Utrecht, Department of Clinical Pharmacy, Utrecht, the Netherlands
4 European Medicines Agency, London, UK
5 Medical Products Agency, Uppsala, Sweden
6 Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

Abstract

Backgound: Since November 2005, an EU Risk Management Plan (EU-RMP) has had to be submitted as part of a marketing application for all new chemical entities in the EU. In the EU-RMP, the safety profile of the medicine has to be described and pharmacovigilance activities should be proposed to study further safety concerns during use of the drug in the real-world setting. These activities include, for example, collection of spontaneously reported adverse events and post-authorization safety studies (PASS). Since the submission of an EU-RMP is a relatively new requirement, there is limited knowledge on the quality and completeness of the study protocols of PASS at the time of approval and there are no data on the influence of certain drug characteristics on the proposed pharmacovigilance activities.

Objective: To examine the types of proposed pharmacovigilance activities in a sample of EU-RMPs, describe and evaluate the methodology of PASS, identify problems and propose remedies, and compare characteristics between biologicals and small molecules.

Methods: Eighteen EU-RMPs (nine for biologicals, nine for small molecules) given a positive decision regarding the marketing application by the Committee for Medicinal Products for Human Use between November 2005 and May 2007 were included in this descriptive cohort study. The EU-RMPs were selected over time and different therapeutic areas. Classification of the safety concerns ('important identified risks', 'important potential risks', 'important missing information' within the EU-RMP was studied. For PASS, data source (registry,

population-based database, sponsor-owned clinical trial database), source of study population to be included in PASS and comprehensiveness of study protocol (full protocol, limited protocol, study synopsis, short description, commitment without further information) were studied.

Results: Compared to small molecules, safety concerns for biologicals were less frequently classified as important identified risks (relative risk [RR] 0.6; 95% CI 0.3, 1.0) and more frequently as important missing information (RR 1.6; 95% CI 1.0, 2.7).

Forty-seven PASS were proposed; 31 for biologicals and 16 for small molecules. Compared with studies proposed in population-based databases (4 for biologicals, 8 for small molecules), studies in registries (18 for biologicals, 4 for small molecules) were more frequently proposed for biologicals than for small molecules (RR 2.5; 95% CI 1.1, 5.7). About 60% of the proposed PASS will include EU inhabitants. No full study protocols were submitted; 26% involved a limited study protocol, 33% a study synopsis, 37% a short description and 4% a commitment without further information.

Conclusion: Approximately 40% of the study proposals for PASS were classified as a short description or a commitment to perform a study without further information, precluding an adequate scientific assessment. Study ing non-EU populations may give rise to difficulties with generalizability of the results to the EU due to differences in patient characteristics, differences in the indication for the medicine and different healthcare systems. This study emphasizes the need for more complete study proposals to be submitted earlier on in the evaluation period and for the inclusion of EU inhabitants in PASS. In addition, differences in the characteristics between biologicals and small molecules, e.g. in the data source proposed, support the need for individualized tailored PASS depending on the type of drug.

Background

The first spontaneous reports suggesting an association between the use of tumour necrosis factor antagonists and the occurrence of tuberculosis occurred during use of the drug in the postmarketing setting; the occurrence of tuberculosis had not been identified in pre-approval randomized clinical trials.[1,2] A recent study has shown that approximately one of four biologicals approved in the US and/or the EU required a safety-related regulatory action, defined as written communications to healthcare professionals and 'black-box' warnings, after approval of the drug by the regulatory authorities.[3] This illustrates the need for safety data to be gathered throughout the life cycle of a medicine due to the known limitations of clinical trials in predicting safety in 'real-world' use.[4] Therefore, postmarketing data offer a valuable and necessary complement to pre-registration studies in continuously evaluating the benefit-risk balance of marketed drugs, especially with respect to safety.[5] A more proactive approach towards the identification and quantification of safety concerns after marketing was aimed for in the International Conference on Harmonisation (ICH) guideline on pharmacovigilance planning, which

Table I. Situations in which an EU-Risk Management Plan is needed for the marketing application in Europe[7,8]

With the application for a new marketing authorization for new chemical entities, biosimilars, generic hybrid medicinal product where a safety concern requiring additional risk minimization activities has been identified with the reference medicinal product
With an application involving a significant change in marketing authorization (e.g. new dosage form, new route of administration or new manufacturing process for a biotechnologically-derived product) unless it has been agreed that submission is not required
On request from a competent authority
On the initiative of the marketing authorization applicant/marketing authorization holder

was recommended for adoption in the three ICH regions (EU, Japan and the US) in November 2004.[6] The ICH guideline on pharmacovigilance planning was adopted in the EU, including additional requirements, in November 2005 by the obligatory submission of an EU Risk Management Plan (EU-RMP) as part of the marketing application of innovative medicines (table I). In the EU-RMP, the safety profile of the medicine has to be described and pharmacovigilance activities should be proposed to study further safety concerns, i.e. the important identified and/or important potential risks and important missing information. What constitutes an important identified risk, an important potential risk or important missing information is defined as a risk that could impact the benefit-risk balance of the product or have implications for public health. The proposed pharmacovigilance activities can include spontaneous reporting, post-authorization safety studies (PASS) and clinical trials. The formalization of the post-authorization development plan for a medicine based on proactive pharmacovigilance is a new legal-based tool[7,9] and at the moment there is limited knowledge on the quality and completeness of the study protocols of PASS at the time of approval.

Therefore, the primary objective of the present study, as part of a quality review of EU-RMPs at the European Medicines Agency (EMEA), is to examine the type of pharmacovigilance activities in a sample of EU-RMPs, describe and evaluate the methodology of PASS as presented in the EU-RMPs at the time a positive decision regarding the marketing application is made by the Committee for Medicinal Products for Human Use (CHMP), identify problems with PASS and propose remedies.

To assess differences in the characteristics of EU-RMPs and PASS between different types of drugs, the drugs were classified into biologicals and small molecules. Biologicals and small molecules have different characteristics and, therefore, differ with respect to potential drug hazards. Potential drug hazards for biologicals include the complex production and purification process compared with small molecules, which are synthesized chemically; the high potential for the formation of antibodies, which is low for small molecules; and the limited predictability of preclinical studies to identify clinical consequences.[10-15] The major implications of changes to the production process of biologicals can be clearly illustrated by the increased incidence of pure red-cell aplasia in patients treated with a particular formulation of recombinant human epoetin (rHuEPO) in which human serum albumin was replaced by polysorbate 80 and glycine.[11,12] The change in product formulation increased the immunogenicity of the particular rHuEPO, which caused neutralizing antibodies, not only against rHuEPO but also against the endogenous erythropoietin.[11-14,16] The limited predictability of preclinical data for biologicals can be illustrated by the TeGenero trial in which healthy volunteers treated with the superagonist anti-CD28 monoclonal antibody TGN1412 developed a severe cytokine storm, which had not been predicted from preclinical trial data.[17] In addition, compared with small molecules, biologicals are often used in a specialized (hospital) setting so large population-based databases (which often mainly include general practitioner and public pharmacy data) are likely to contain limited or no information on biologicals. These differences may affect proposals for EU-RMPs and PASS; therefore, the secondary objective of the present study is to compare the type of pharmacovigilance activities and the methodology of PASS between biologicals and small molecules.

Methods

The EU-RMP

An EU-RMP (table I) consists of two parts. The first part consists of the safety specification and the pharmacovigilance plan. The safety specification aims to provide an overview of the results and possible limitations of the pre-registration studies, whilst the pharmacovigilance plan describes the proposed pharmacovigilance activities to further study the safety concerns. At the end of the safety specification, a summary of the important safety concerns is provided and this list is the basis for what needs to be discussed in the pharmacovigilance plan and the second part of the EU-RMP. A safety concern is defined in the Guideline on Risk Management Systems[8] as an 'important identified risk', 'important potential risk' or 'important missing information'. Safety concerns may be based on the expected safety concerns related to the characteristics of the drug or the unexpected safety concerns, not predictable by the characteristics of the drug but identified in the pre-registration studies or during the post-authorization activities. For each safety concern, pharmacovigilance activities encompassing both routine, e.g. collection of spontaneous reports of suspected adverse drug reactions, and additional activities, e.g. PASS, should be discussed.

The second part of the EU-RMP consists of an evaluation of the need for risk minimization activities, and, if considered necessary, a risk minimization plan should also be provided.[7,9,18] The Guideline on Risk Management Systems for Medicinal Products for Human Use can be found in Volume 9A of *The Rules Governing Medicinal Products in the European Union*.[7] The template for EU-RMPs is described in annex C of this guideline.[19]

In the period November 2005 to May 2007, a total of 59 EU-RMPs (36 for small molecules and 23 for biologicals) were submitted as part of a new marketing application for centrally authorized products in Europe (not including line extensions). Of these, 18 EU-RMPs (nine biologicals [as defined by the EMEA[18]] and nine small molecules) were sampled and included in this descriptive cohort study. The sample of 18 EU-RMPs was selected over time and different therapeutic areas to obtain a comprehensive overview of EU-RMP practice. The EU-RMP or study protocol submitted in the final EU-RMP being part of the positive decision by the CHMP was included in the analysis. Information was obtained from EU-RMPs provided by the EMEA and from the European Public Assessment Reports, accessible via the EMEA website (www.emea.europa.eu).

Safety Concerns and Types of Pharmacovigilance Activities to Address them

Safety concerns were classified according to the EU Guideline on Risk Management Systems for Medicinal Products for Human Use[8] as important identified risks (adequate evidence of association with the medicinal product), important potential risks (there is a basis for suspicion of an association with the medicinal product but the association has not been confirmed) or important missing information, including populations not studied in the pre-authorization phase, which may form part of the target population post-authorization. 'Important' in this context means an identified risk, potential risk or missing information that could impact on the benefit-risk balance of the product or have implications for public health.[7]

The activities proposed to study safety concerns were classified as (1) routine pharmacovigilance; (2) PASS; (3) clinical trials; and (4) others. Routine pharmacovigilance, PASS and clinical trials were defined as laid down in Volume 9A of *The Rules Governing Medicinal Products in the European Union*.[7]

1. *Routine pharmacovigilance:* Pharmacovigilance activities that should be conducted for all medicinal products and include the submission of Periodic Safety Update Reports and reporting of spontaneous adverse events.
2. *PASS:* A pharmacoepidemiological study (non-interventional study) or a clinical trial (interventional study) carried out in accordance with the terms of the marketing authorization, conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product.

3. *Clinical trials:* Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s) and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal products with the objective of ascertaining its (their) safety and/or efficacy. An investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way that is different from the authorized form, or when used for an authorized indication or to gain further information about the authorized form.[7] Clinical trials that were specifically designed for identifying or quantifying a safety hazard relating to an authorized medicinal product were classified as PASS (2), and other clinical trials were classified as a clinical trial (3).
4. *Others:* Activities that could not be classified in one of the three previously described subgroups were classified as 'others' (4). An example of activities included in this group was a commitment to validate a new assay for antibodies.

Nature of Safety Concerns to be Addressed by Post-Authorization Safety Studies (PASS)

The nature of the safety concerns laid down in the safety specification to be addressed by PASS was classified at the System Organ Class (SOC) level according to the Medical Dictionary for Regulatory Activities (MedDRA), version 9.1. Special patient groups, for example children and hepatically impaired patients, are not included in MedDRA and were therefore classified as 'Special patient groups'. This was also done for safety concerns relating to the potential for off-label use, which was classified as 'Potential for off-label use'. Safety concerns that could not be classified according to MedDRA or the additional classification were classified as 'Others' and included, for example, 'Duration of protection and the need for a booster dose'.

Where several safety concerns belonging to different SOCs were included as one safety concern, both SOCs were counted; for example, misuse and abuse was classified in the SOCs 'Injury, poisoning and procedural complications' and 'Social circumstances', respectively.

PASS Methodology

The study protocols of the proposed PASS were evaluated by two assessors (TJG and AKM-T) to obtain information on study type, study design and data source (including target population).

Study Types

Study types were classified as comparative studies, non-comparative studies, background incidence studies and drug utilization studies. The primary aim of comparative (drug under study vs comparator) and non-comparative (no comparator group) studies was to evaluate safety. Both study types were therefore classified as safety studies. Background incidence studies were studies to investigate the background incidence of certain adverse events of interest in the target population and drug utilization studies evaluate how a medicinal product is marketed, prescribed and used in a population and how these factors influence the outcomes.[7] The classification of PASS was based on the provided primary objective of the PASS. PASS with more than one primary objective involving multiple study types were classified in all study types involved.

Study Designs

Study designs were classified as cohort studies (prospective or retrospective), case-control studies, cross-sectional studies, (extensions of) randomized clinical trials (RCTs), including large simple trials, and unknown. The (extensions of) RCTs are clinical trials that will be conducted after marketing of the drug, and can be classified as PASS, as previously described.

Data Sources and Target Population

Data sources were classified as large, population-based databases, registries or sponsor-owned clinical trial databases. Registries were defined as

data sources that include patients with a certain disease, condition or exposure and from which the data will be used for observational studies. Sponsor-owned clinical trial databases were defined as postmarketing (extensions of) clinical trials set up by the Marketing Authorization Holder. Information on the country/countries in which the study will be conducted was also collected.

Registries were further categorized into (i) existing or newly set up registries; and (ii) ownership – registries owned by the pharmaceutical company or registries owned by other organizations, e.g. academia.

Comprehensiveness of PASS Study Protocols

Study protocols were classified as full study protocol, limited study protocol, study synopsis, (very) short description or a commitment (to perform the study) without further information. Study protocols were assessed based on the topics laid down in the Guideline for Good Pharmacoepidemiology Practice[20] and include objectives, study design, strategy and reasons for proposed design, study population, inclusion criteria, exclusion criteria, data source, health outcomes, potential confounders and effect modifiers, clear definition of health outcomes, exposure, selection criteria, comparison groups, study power, data analysis, description of quality assurance and quality control procedures, and limitations of the study.[20] A full study protocol contained 16 or 17 of the 17 topics; a limited study protocol contained between 11 and 15 of the 17 topics; a study synopsis contained between 6 and 10 topics; a (very) short description contained between 1 and 5 topics; and a commitment without further information did not contain any of the described topics.

Data Analysis

Proportions and relative risks (RR) with corresponding 95% confidence intervals (CI) were calculated to compare the classification of safety concerns and studies relating to biologicals and small molecules. SPSS version 14.0 was used (SPSS Inc, Chicago, IL, USA).

Results

The characteristics of the 18 products included (nine biologicals and nine small molecules) and the description of the included EU-RMPs are shown in table II and figure 1, respectively.

Classification of Safety Concerns and Pharmacovigilance Activities to Address them

A total of 169 safety concerns were included in the 18 safety specifications. These safety concerns consisted of 50 (29.6%) important identified risks, 73 (43.2%) important potential risks and 46 (27.2%) important missing information (table III). For biologicals, as compared with small molecules, safety concerns were less frequently classified as important identified risks (0.6; 95% CI 0.3,1.0) and more frequently as important missing information (RR 1.6; 95% CI 1.0, 2.7). Comparison of the important potential risks did not show a difference (RR 1.0; 95% CI 0.7, 1.5) between biologicals and small molecules. Safety concerns were more frequently classified as either an important potential risk or important missing information (RR 1.2; 95% CI 1.0, 1.5) for biologicals when compared with small molecules.

Routine pharmacovigilance was proposed to address more than 80% of all safety concerns. The major difference between biologicals and small molecules in pharmacovigilance activities to address safety concerns was the number of PASS and clinical trials proposed (table III).

Safety Concerns Addressed by Proposed PASS

PASS were frequently proposed to study 'Special patient groups' and 'General disorders and administration site conditions' (table IV). In addition, PASS were frequently proposed for safety concerns related to the SOCs 'Investigations', 'Infections and infestations', and 'Immune system disorders' for biologicals, and 'Psychiatric disorders' and 'Neoplasms, benign, malignant and unspecified (including cysts and polyps)' for small molecules.

Table II. Characteristics of the drugs included (www.emea.europa.eu)

Drug	Active substance	Indication	Date of positive decision CHMP
Biologicals			
Atryn®	Antithrombin α	Prophylaxis of venous thromboembolism in surgery of patients with congenital antithrombin deficiency	1 June 2006
Elaprase®	Idursulfase	Long-term treatment of patients with Hunter syndrome	18 October 2006
Gardasil®	Human papillomavirus vaccine (types 6, 11, 16, 18)	Prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3) and external genital warts (condyloma acuminata) causally related to human papillomavirus types 6, 11, 16 and 18	27 July 2006
Lucentis®	Ranibizumab	Neovascular (wet) age-related macular degeneration	16 November 2006
Myozyme®	Recombinant human alglucosidase α	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Pompe disease (acid α glycosidase deficiency)	26 January 2006
Orencia®	Abatacept	In combination with methotrexate, indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease modifying anti-rheumatic drugs, including at least one tumour necrosis factor inhibitor	19 March 2007
Preotact™	Parathyroid hormone	Osteoporosis in postmenopausal women at high risk of fractures	23 February 2006
Soliris®	Eculizumab	Paroxysmal nocturnal haemoglobinuria	27 April 2007
Tysabri®	Natalizumab	Single disease-modifying therapy in highly active relapsing-remitting multiple sclerosis for the following patient groups: patients with high disease activity despite treatment with interferon-β; or patients with rapidly evolving severe relapsing-remitting multiple sclerosis	27 April 2006
Small molecules			
Acomplia®	Rimonabant	As an adjunct to diet and exercise for the treatment of obese patients (BMI ≥30 kg/m^2) or overweight patients (BMI >27 kg/m^2) with associated risk factor(s), such as type 2 diabetes mellitus or dyslipidaemia	27 April 2006
Baraclude®	Entecavir	Chronic hepatitis B virus infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis	26 April 2006
Champix®	Varenicline	Smoking cessation in adults	27 July 2006
Circadin®	Melatonin	As monotherapy for the short-term treatment of primary insomnia characterized by poor quality of sleep in patients aged 55 years or over	27 April 2007
Competact®	Pioglitazone/ metformin	Type 2 diabetes patients, particularly overweight patients, who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone	1 June 2006
Invega®	Paliperidone	Schizophrenia	27 April 2007
Januvia®	Sitagliptin	Patients with type 2 diabetes to improve glycaemic control in combination with metformin when diet and exercise, plus metformin, do not provide adequate glycaemic control. For patients with type 2 diabetes in whom use of a PPAR agonist (i.e. a thiazolidinedione) is appropriate, Januvia® is indicated in combination with the PPAR agonist when diet and exercise plus the PPAR agonist alone do not provide adequate glycaemic control	24 January 2007
Sprycel®	Dasatinib	Adults with chronic-, accelerated- or blast-phase CML with resistance or intolerance to prior therapy, including imatinib and for adults with Philadelphia chromosome positive acute lymphoblastic leukaemia and lymphoid blast CML with resistance or intolerance to prior therapy	21 September 2006
Tygacil®	Tigecycline	Complicated skin and soft tissue infections; complicated intra-abdominal infections	23 February 2006

BMI = body mass index; **CHMP** = Committee for Medicinal Products for Human Use; **CIN** = cervical intraepithelial neoplasia; **CML** = chronic myeloid leukaemia; **PPAR** = peroxisome proliferator-activated receptor; **VIN** = vulvar intraepithelial neoplasia.

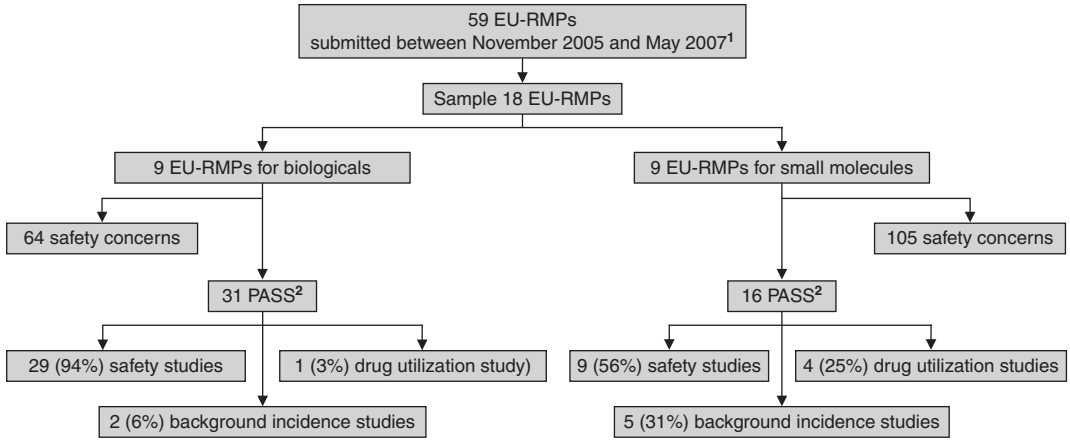

Fig. 1. Inclusion and characteristics of the EU-Risk Management Plans (EU-RMPs). **1**. These included 36 EU-RMPs for small molecules and 23 EU-RMPs for biologicals. **2**. The total number of study types proposed exceeds 47 because of multiple study types proposed in one study.

PASS Methodology

In the sample of 18 EU-RMPs, a total of 47 PASS were proposed – 31 for biologicals and 16 for small molecules (figure 1).

Study Types

Comparison of the number of safety studies (29 for biologicals vs 9 for small molecules) with the number of background incidence and drug utilization studies (3 for biologicals vs 9 for small molecules) [figure 1] showed that PASS were more frequently classified as safety studies for biologicals compared with small molecules (RR 1.7; 95% CI 1.1, 2.6).

Study Designs

The study designs proposed were cohort design (n = 35), nested case-control design (n = 5), RCT (n = 3), extension of RCT (n = 8) and in one case the study design could not be established. All (extensions of) RCTs were open-label studies. No cross-sectional studies were proposed. Of the 35 cohort studies, 24 were prospective, 10 were retrospective and 1 study was not classifiable on the data given.

Data Source and Target Population

The data source used differed between biologicals and small molecules. For biologicals, 18 (58%) of the studies were proposed in registries and four (13%) in large population-based databases. For small molecules, four (25%) of the studies were proposed in registries and eight (50%) in large population-based databases. A comparison of the number of studies proposed in registries with the number of studies proposed in large population-based databases showed that compared with small molecules, studies for biologicals are more often proposed in registries (RR 2.5; 95% CI 1.1, 5.7). Nine (29%) of the studies proposed for biologicals and two (13%) of the studies proposed for small molecules will be conducted in sponsor-owned clinical trial databases. For two PASS proposed for small molecules, the data source was unknown. All cohort studies proposed in registries had a prospective nature.

Twelve (26%) of the 47 PASS proposed will be conducted in the EU population, 15 (32%) in the non-EU population (mainly US) and 17 (36%) in a multinational setting, including the EU. For three studies (6%), this information could not be ascertained.

Further specification of the 22 studies proposed in registries showed that this involved 10 (45%) existing registries and 11 (50%) newly initiated registries. For one study (4.5%), this information could not be retrieved. The pharmaceutical industry owned 11 (50%) of the registries and other institutions owned 9 (41%) of the

Table III. Safety concerns and how these are intended to be addressed [n (%)]

Safety concern	Safety concerns	Addressed by routine pharmacovigilance	Addressed by post-authorization safety studies	Addressed by clinical trials	Others
Biologicals	64	52 (81)	52 (81)	16 (25)	2 (3)
Important identified risks	13 (20)	12 (92)	11 (85)	4 (31)	1 (8)
Important potential risks	28 (44)	21 (75)	21 (75)	9 (32)	1 (4)
Important missing information	23 (36)	19 (83)	20 (87)	3 (13)	
Small molecules	105	89 (85)	14 (13)	53 (50)	6 (6)
Important identified risks	37 (35)	33 (89)	3 (8)	20 (54)	
Important potential risks	45 (43)	37 (82)	6 (13)	18 (40)	4 (9)
Important missing information	23 (22)	19 (83)	5 (22)	15 (65)	2 (9)

registries. For two registries (9%), this information could not be retrieved. In total, 10 of the 11 registries owned by the pharmaceutical industry were newly initiated and all nine registries owned by other organizations already existed.

Comprehensiveness of PASS Study Protocols

None of the 46 PASS (one background incidence study was excluded since this study was part of the EU-RMP but had already been conducted before licence approval) had a full study protocol at the time of a positive decision by the CHMP. A limited protocol was submitted for 12 (26%) of the 46 PASS, 15 (33%) had a study synopsis, 17 (37%) had a (very) short description and two (4%) had a commitment to perform a study without further information. Topics most frequently missing from the submitted study protocols were strategy and reasons for proposed design (discussed in 2 protocols); limitations of the study (in 2 protocols); description of quality assurance and quality control procedures (in 4 protocols); potential confounders and effect

Table IV. Classification of the most frequently reported safety concerns, by System Organ Class (SOC) [n (%)]

SOC	Safety concerns – PASS biologicals (n = 52[a])	Safety concerns – total biologicals (n = 64[a])	Safety concerns – PASS small molecules (n = 14[a])	Safety concerns – total small molecules (n = 105[a])
Special patient groups	15 (28.8)	18 (28.1)	4 (28.6)	24 (22.9)
General disorders and administration site conditions	6 (11.5)	8 (12.5)	1 (7.1)	8 (7.6)
Investigations	6 (11.5)	8 (12.5)		7 (6.7)
Infections and infestations	5 (9.6)	6 (9.4)	1 (7.1)	5 (4.8)
Immune system disorders	4 (7.7)	5 (7.8)		2 (1.9)
Nervous system disorders		1 (1.6)		11 (10.5)
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	3 (5.8)	3 (4.7)	2 (14.3)	5 (4.8)
Psychiatric disorders			4 (28.6)	6 (5.7)
Cardiac disorders	1 (1.9)	1 (1.6)	1 (7.1)	4 (3.8)
Injury, poisoning and procedural complications	4 (7.7)	6 (9.4)		4 (3.8)
Others	10 (19.2)	10 (15.6)	3 (21.4)	35 (33.3)

a Sum of the columns exceeds the total number of safety concerns due to safety concerns including multiple safety issues categorized in different SOCs.

PASS = post-authorization safety studies.

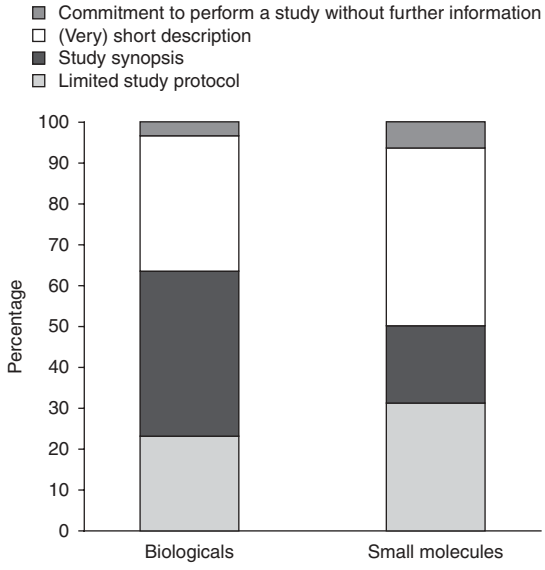

Fig. 2. Comprehensiveness of the study protocols submitted.

modifiers (in 8 protocols); and clear defined health outcomes (in 11 protocols). Study protocols were generally more complete for biologicals than for small molecules, as shown by the fact that a limited study protocol or study synopsis (63% for biologicals vs 50% for small molecules) seemed to be submitted more frequently than a (very) short description or a commitment to perform a study without further information (37% for biologicals vs 50% for small molecules) [RR 1.3; 95% CI 0.7, 2.2] (figure 2).

Discussion

This first review on the types of pharmacovigilance activities and the methodology of PASS in a sample of EU-RMPs provides valuable information on current EU-RMP practice and is important to help identify problems with EU-RMPs/PASS at this early phase of EU-RMP practice, along with a focus on possible remedial actions. It was shown that more than 80% of the safety concerns will be addressed by routine pharmacovigilance, including spontaneous reporting of suspected adverse drug reactions. Spontaneous reporting has an important function in the detection of new, rare and/or serious adverse events; however, certain limitations exist, including under-reporting and a difficult causality assessment.[15,21,22] 25% of the safety concerns for biologicals and 50% of the safety concerns for small molecules will be addressed by additional (extensions of) clinical trials. Extensions of clinical trials are a relatively uncomplicated method to follow patients over a longer period of time. However, limitations of clinical trials include a homogenous population and they are often underpowered to detect rare adverse events.[23] PASS offer an important new tool to actively study safety concerns in the real-world setting. However, as shown by the present study, certain problems have been identified related to PASS, which need to be improved in the future. It was shown that no full study protocols had been submitted at the point of a positive decision, that 26% had submitted a limited study protocol, 33% a study synopsis and 37% a (very) short description. A commitment to perform a study without further information involved 4% of the PASS. The limited availability of full/limited study protocols and study synopses during the decision-making process is of major concern since this precludes a proper scientific assessment by the regulatory authorities. Although some protocols were requested to be provided post-authorization, not having at least a study synopsis during decision making makes it impossible to assess the likelihood of the PASS providing the necessary safety information, which is counterintuitive to the spirit of proactive risk management practice. In addition, the lack of a protocol makes it impossible to assess the feasibility of the proposed PASS during decision making, which increases the risk that the required safety information will not be forthcoming. The Guideline on Risk Management Systems[8] states that additional pharmacovigilance activities should be designed and conducted according to the Guidelines for Good Pharmacoepidemiological Practice and that protocols (draft or otherwise) for any formal study should be provided. In addition, in Annex C to this guideline (the template for the EU-RMP) it is stated that full study protocols should be annexed to the EU-RMP; however, Annex C was adopted by the CHMP in September 2006 and was therefore not available for a large part of this study period.[7] Although requested in

the guideline, it might be difficult for marketing applicants to submit study proposals early in the application cycle since regulators often request different approaches from those suggested by the applicant, ask for PASS late in the evaluation process or identify new safety concerns during the evaluation process when additional data are provided in the applicants' responses to questions. In addition, the proposed indication (and hence the target population) may change during the evaluation procedure. Ideally, marketing authorization applicants and regulators should have active discussions on PASS early in the evaluation process or prior to the first submission of the dossier to the regulatory authorities by way of scientific advice. If the submission of study protocols is not feasible during the decision making process, clear timelines should be set by which full study protocols should be submitted as part of the post-approval commitments.

At the moment of a positive decision by the CHMP, the information on the safety profile of biologicals is more limited than that of small molecules, in part due to the specific characteristics of biologicals, e.g. the limited predictability of preclinical data to clinical data.[10,14] This finding reinforces the need for more active pharmacovigilance of biologicals to obtain information on the potential risks and missing information. This was supported by the 31 PASS proposed for biologicals compared with the 16 PASS for small molecules and the significantly higher overall number of safety studies for biologicals. However, this might also be (partly) due to the fact that three of the biologicals included have an orphan designation compared with one small molecule. It is known that clinical trials for orphan drugs include fewer patients compared with drugs with no orphan designation,[24] resulting in limited knowledge on the safety profile. In addition, differences were found between biologicals and small molecules in the type of safety concerns, the type of PASS and the data source used. These findings support the need for individualized tailored PASS, depending on the type of product.

The studies will include EU inhabitants in about 60% of the proposed studies, and about one-third of the studies will include non-EU inhabitants, mainly from the US. Extrapolation of non-EU results to the European patient population may be affected by differences in patient characteristics, differences in the indication for the medicine and different healthcare systems. In addition, it might be that a drug for which the EU-RMP proposes studies in the non-EU countries, has not yet been approved by the country in which the study is proposed. If the marketing application will not be granted in the non-EU countries, the postmarketing studies proposed will not be conducted.

In this study, reviewing the most recent study protocol submitted in the final EU-RMP, being part of the CHMP decision-making process, can be considered a limitation since study protocols can be amended after marketing by submission of a more extensive study protocol and/or availability of new safety data. Inclusion of study protocols submitted up to the date of a positive decision will, however, provide insight into the data on which the decision by the CHMP was based. In addition, this resulted in comparable information between drugs.

The EU-RMPs included for biologicals and small molecules were sampled over time (November 2005–May 2007) and different therapeutic areas. It can be debated whether the selected EU-RMPs are a good representation of the population of biologicals and small molecules (e.g. with regard to the indication of the drugs) and if there has been a change in the characteristics of EU-RMPs over time (improvement from learning and interventions). However, a closer look at the number of products approved in the different Anatomical Therapeutic Chemical (ATC) classes in relation to the number of products included in this study showed that for most of the ATC classes in which three or more products are approved, between 21% and 45% of the products are included in this study. This does not apply to the ATC classes 'Genito-Urinary System and Sex Hormones' and 'Various', in which three products were approved, of which none were included in this study. This might influence the generalizability of our study and can be considered a limitation. However, in general it can be concluded that, based on the ATC classification, the sample of EU-RMPs included in this

study is representative of the other EU-RMPs submitted as part of an initial marketing application. Although learning over time will improve the quality of EU-RMPs, the sampling has resulted in the inclusion of a range of different therapeutic areas over time, for which the results found show a good overview of current practice, which has a positive impact on the generalizability of the results found in this study. Finally, it should be noted that parts of the information used in this study are not available in the public domain.

The limited availability of full/limited study protocols and study synopses at the time of a positive decision by the CHMP is of concern since this precludes a proper scientific assessment of the feasibility and value of the study. Discussion of the study protocols between the marketing authorization applicant and the regulatory authorities at an early stage in the application cycle is encouraged since this will facilitate assessment and might improve the quality and feasibility of the proposed studies. In some cases, the number of patients who will be treated is difficult to calculate, depending on, for example, reimbursement of the drug, indications approved in different countries (for non-EU studies) and uptake by clinicians in daily clinical practice. Although uncertainties will remain, adequate sample size calculations will provide important information on the power of the study and are therefore highly recommended. The potential problems encountered with the exclusion of EU inhabitants in about one-third of the PASS proposed should be taken into consideration, both by the pharmaceutical industry and the regulatory authorities, and pharmaceutical companies are encouraged to include EU inhabitants.

Large population-based databases and registries are an important tool for PASS. However, the marketing authorization applicant is advised to clearly assess the validity of a data source. In addition, it would be very useful if the marketing authorization applicant provided information as to the rationale of using the proposed data source. In addition, it should be emphasized that data from healthcare systems on exposed individuals should be accessible in order to build registries for clinical follow-up.

The results of this study will add to EMEA activities to improve the approval procedures, achieve a more timely and rapid regulatory review of the protocols of PASS, have an earlier interaction with the marketing authorization applicant and to consult the proper expertise, e.g. in pharmacoepidemiology. The new initiative to facilitate networking between competence centres in pharmacoepidemiological research and for coordinating data resources in the EU might further improve proactive pharmacovigilance in the EU. This network is being developed under the lead of the EMEA (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; www.encepp.eu)[25] and can be used in future by all relevant stakeholders involved.

In future, as part of the quality review of EU-RMPs at the EMEA, it will be relevant to follow-up the proposed PASS included within the present study, and to have a closer look at the status of the study and possible amendments to the study protocol at a later stage. In addition, it will be very interesting to study the effect of EU-RMPs on patient safety and the early identification of postmarketing safety problems.

Conclusions

This study showed that EU-RMP practice should be further improved by means of the submission of more complete study protocols at the moment of a positive decision by the CHMP, since at the moment of regulatory approval, 40% of the study proposals were classified as a short description or a commitment without further information, precluding an adequate scientific assessment. Problems might be expected based on the inclusion of non-EU inhabitants with regard to differences in patient characteristics, differences in the indication for the medicine and different healthcare systems. Inclusion of EU inhabitants in PASS is therefore highly recommended. In addition, differences in the characteristics between biologicals and small molecules, e.g. in the safety problems to be encountered and the data source proposed, support the need for individualized tailored PASS depending on the type of drug.

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Correspondence: Dr *Aukje K. Mantel-Teeuwisse*, Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, P.O. Box 80082, 3508 TB Utrecht, the Netherlands. E-mail: a.k.mantel@uu.nl