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A Cohort Study Exploring Determinants of Safety-Related Regulatory Actions for Biopharmaceuticals

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Abstract

Background: The characteristics of biopharmaceuticals may require a tailored approach to their safety management. However, information on what tools and methods are employed to assess the safety of biopharmaceuticals post-authorization is lacking.

Objective: This study investigates determinants that contribute to the post-authorization management of biopharmaceuticals.

Methods: A cohort study was performed including all centrally approved biopharmaceuticals for which a Direct Healthcare Professional Communication (DHPC) was issued during 1997–2009. Safety-related regulatory actions were defined as updates of the summary of product characteristics through type II variations. Determinants of these actions were identified based on publicly available data. Urgent variations, defined as variations accompanied by a DHPC, were compared with other, 'non-urgent', safety-related variations.

Results: We identified 133 variations relating to 15 products, 24 urgent and 109 other variations. For 55% of urgent variations, spontaneous reports were the sole source of regulatory action, post-approval studies accounted for 33%, and 12% were based on other sources or combinations of sources. For the non-urgent variations, spontaneous reports were the sole source for 36%, post-approval studies for 28%, and 36% were based on other sources or combinations. Overall, most variations included safety issues categorized as 'infections and infestations' (33.1%), 'general disorders and administration site conditions' (25.6%), and 'neoplasms' (14.3%).

Conclusion: Determinants of urgent and non-urgent safety-related regulatory actions of biopharmaceuticals are largely similar. Spontaneous reports are an important pillar for both urgent and non-urgent actions and remain an important tool in the post-authorization safety management of biopharmaceuticals.

Introduction

Biopharmaceuticals have been defined as 'pharmaceutical products consisting of (glyco)proteins and/or nucleic acids'.[1] They differ from small molecules in both structure and pharmacology.[2] These differences result in a distinctive pattern of adverse events that are observed for biopharmaceuticals.[3,4] The characteristics of biopharmaceuticals may require a different approach to their post-authorization management when compared with synthetic 'small molecules'. The nature of safety concerns for biopharmaceuticals at the time of regulatory approval differs from 'small molecules', resulting in different post-authorization requirements; safety concerns of biopharmaceuticals are more often addressed through post-authorization safety studies when compared with small molecules.[5] Previous studies have found differences in the nature and timing of post-authorization regulatory actions for biopharmaceuticals.[6,7] These studies focused on a relatively narrow set of severe regulatory actions, which may not reflect the full breadth of post-authorization management of these products. Furthermore, while these studies found differences in the nature of regulatory actions, they did not examine which data sources were the determinants for the initiation of these actions.

In the European Union (EU) multiple levels of regulatory actions exist in response to safety concerns associated with the use of medicinal products (figure 1).[8] All these measures in the pyramid of regulatory actions contribute to the safe and effective use of medicinal products. Regulatory actions may follow from safety signals arising from several data sources including spontaneous reports received from healthcare professionals, clinical trials, observational studies, animal studies and *in vitro* experiments.[9] Data of these sources are periodically evaluated through the provision of Periodic Safety Update Reports (PSURs) to regulatory agencies. These reports provide an update of the worldwide safety experience of a pharmaceutical. They contain data from spontaneous reports, an overview of cumulative data, safety data from studies and other relevant safety information.[8] Historically, spontaneous reports have been the main source of postmarketing surveillance.[9] Several studies have been performed to determine the data source for marketing authorization withdrawals.[10-13] Of 21 market withdrawals in France during 1998–2004, 19 (90%) included spontaneous reports and in 12 (57%) spontaneous reports were the sole source of data for the withdrawal. Only one (5%) withdrawal was based on randomized clinical trial (RCT) data.[13] A similar study performed in the UK found that of 11 withdrawals during 1999–2001, eight (73%) included spontaneous reports, two included RCT data and four (36%) included observational data.[12] These data accord with results of studies examining withdrawals from earlier periods.[10,11] However, all these studies focused on the most 'severe' actions and none specifically looked at sources of regulatory actions for biopharmaceuticals. Therefore we have performed an analysis on the determinants and nature of all safety-related

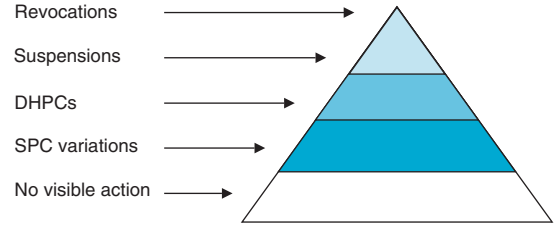

Fig. 1. Levels of regulatory actions. In many cases regulatory responses to safety issues result in additional information requests or risk mitigation activities that do not result in changes to the terms of marketing authorization. Some safety issues warrant changes to the SPC, which in urgent cases are accompanied by a DHPC. In case of severe safety issues, which changes the benefit-risk balance, regulators may decide to suspend the marketing authorization or even revoke it. **DHPC** = Direct Healthcare Professional Communication; **SPC** = Summary of Product Characteristics.

regulatory actions in a selection of biopharmaceuticals approved in the EU.

Materials and Methods

Data Collection

A retrospective cohort study was performed that included all biopharmaceuticals centrally approved in the EU for which a Direct Healthcare Professional Communication (DHPC) was issued between January 1995 and December 2009. All safety-related Summary of Product Characteristics (SPC) updates were collected that were implemented for these products, through so-called type II variations. Variations are changes to the terms of marketing authorization, including changes to the product labelling, to the production process or administrative changes. A type II variation is defined as ''a variation which is not an extension and which may have a significant impact on the quality, safety or efficacy of the medicinal product concerned''.[18] Type II variations always require prior approval of the competent authority, whereas type Ia and type Ib (minor) variations are notifications of changes that do not impact the product's quality, safety or efficacy and do not require formal approval. DHPCs were identified from the website of the Medicines Evaluation Board in the Netherlands. Type II variations were identified from European Public Assessment Reports (EPARs) that are publicly available from the European Medicines Agency website.[14] Products for which a non-safety-related DHPC was distributed, i.e. production shortages, etc., were excluded. For older variations that were not described in detail in the EPAR, updates of the SPC were analysed. SPCs were obtained from the community register of medicinal products of the European Commission.[15] Data were collected until 31 December 2009 or until the product was withdrawn from the European Market. Products were characterized according to the Anatomical Therapeutic Chemical (ATC) classification system.[16] Mechanistic classes were determined according to Giezen et al.[6]

Type of Regulatory Actions Included in the Study

Multiple changes could be introduced to the SPC through one type II variation. These changes could include the addition of newly identified adverse events, but also other changes, for example in treatment recommendations or the addition of warnings due to a lack of data, all of which were included in the analysis. All safety-related type II variations in the 'clinical particulars section' (sections 4.1–4.9) of the SPC were collected. An extensive description of the structure of SPCs can be obtained from the website of the European Commission.[17] All type II variations concerning other sections of the SPC were disregarded. 'Minor' adaptations to these SPC sections, for example textual changes not including new safety information, were also disregarded. All safety-related SPC variations introduced as part of extensions to the approved indication were excluded, unless specific mention was made that the variation included safety-related SPC changes based on post-authorization experience not associated with the extension dossier. Changes to the SPC resulting from the provision of long-term data were included. Changes to the SPC in sections 4.1–4.9 that were introduced as a means to expand treatment possibilities, without the introduction of new safety information, were excluded (e.g. shortened infusion, dose flexibility).

Data Sources as Determinants of Variations

The determinants of the type II variations were identified from the EPAR text and SPC text. We defined four possible sources as determinants for type II variations: (i) spontaneous reports, which included cases that were added in the SPC as 'postmarketing experience' without any reference to clinical studies; (ii) post-authorization studies, which included data from clinical trials and other post-authorization studies, i.e. observational studies (both variations resulting from novel trial results and variations implemented based on a review of clinical trial data were included); (iii) analysis of the entire safety database, including variations for which multiple sources were quoted for a single issue; and (iv) other sources, including results from

animal studies, *in vitro* studies, information from other products in the class, literature reviews or the addition of important missing data to the SPC to harmonize it with the company's safety specification, the so-called 'core data sheet'. If a single variation included multiple safety issues based on different sources we classified them as 'combination of multiple data sources'.

Nature of the Events Included in the Type II Variations

To characterize the nature of the safety issues included in these type II variations, they were classified according to the System Organ Class (SOC). SOCs were identified using MedDRA® (Medical Dictionary for Regulatory Activities) [UK version 11.1]. If no SOC could be identified that matched the type II variation, a corresponding SOC was selected by consensus (HE and AMT).

Analysis

The distribution of determinants of 'urgent' variations, defined as variations accompanied by the distribution of a DHPC, was compared with other ('non-urgent') safety-related type II variations, i.e. variations that were not accompanied by a DHPC. For each type II variation a decision is taken by the Committee for Medical Products for Human Use (CHMP), this date was used to assess the timing of variations.[18]

For each variation, the SPC sections affected by the type II variation were recorded. In a subanalysis it was determined whether PSURs contributed to the initiation of the type II variation. PSUR contribution was defined as any reference to PSUR evaluations in the EPAR text, the SPC text and/or DHPC letter.

All data were entered into a database and were analysed using SPSS version 16 (SPSS Inc., Chicago, IL,USA). For all comparative analyses, p-values were calculated using 2-sided Fisher's exact tests. Multilevel logistic regression with a random intercept for each product was used to evaluate the association between PSUR exposure and 'urgent' and 'non-urgent' regulatory actions.

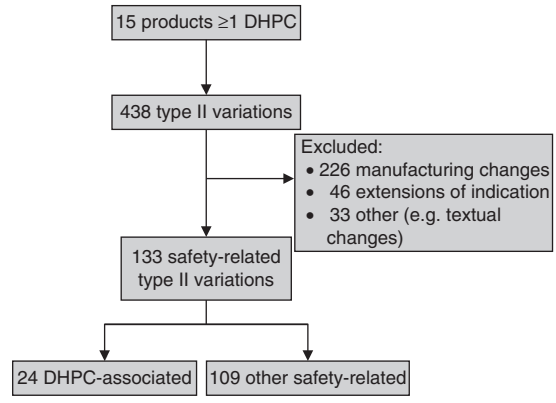

Fig. 2. Flowchart of type II variations included in the analysis. Twenty-six DHPCs were identified. One variation included information on two DHPCs. For one DHPC the corresponding type II variation could not be identified in the EPAR. **DHPC** = Direct Healthcare Professional Communication; **EPAR** = European Public Assessment Report.

Results

A total of 26 DHPCs were issued for 15 biopharmaceutical products during the study period. For one DHPC the corresponding type II variation could not be identified and one type II variation included information on two DHPCs. The final sample included 24 urgent variations and 109 other safety-related type II variations amounting to a total of 133 variations (table I and figure 2). During the study period two products were withdrawn from the EU market, Exubera (inhaled insulin) and Raptiva (efalizumab). The median follow-up per product was 7.8 years (range 3.5–12.8). Of the 133 type II variations included in the analysis, most concerned products in the classes of immunosuppressants 82 (61.7%) and antineoplastic agents 26 (19.5%). The remaining variations concerned antithrombotic agents, eight (6.0%); drugs for the treatment of bone diseases, six (4.5%); drugs used in diabetes mellitus, two (1.5%); and muscle relaxants, nine (6.8%) [table I].

A median of six variations were implemented for each product. Overall, the median time from regulatory authorization of a product to a decision on the variation was 1653 days (range 315–3949). This did not differ between urgent and other safety-related variations.

Table I. Characteristics of the products included in the study

ATC drug class	INN	Product name	Authorization date (EU) [dd/mm/yyyy]	Number of type II variations			Description of urgent safety issues	Date of approval of type II variation [dd/mm/yyyy]
				Urgent [n (%)]	Other [n (%)]	Total [n (%)]		
Antineoplastic agents	Rituximab	MabThera	2/6/1998	3 (12.5)	9 (8.3)	12 (9.0)	Progressive multifocal leukoencephalopathy	23/10/2008
							Progressive multifocal leukoencephalopathy	19/7/2007
							Deaths due to cytokine release syndrome	22/2/1999
Antineoplastic agents	Trastuzumab	Herceptin	28/8/2000	1 (4.2)	2 (1.8)	3 (2.3)	Cardiotoxicity in combination with anthracyclines	21/3/2002
Antineoplastic agents	Alemtuzumab	MabCampath	6/6/2001	1 (4.2)	2 (1.8)	3 (2.3)	Cases of death related to infections in chronic lymphoid leukaemia patients	18/10/2007
Antineoplastic agents	Bevacizumab	Avastin	12/1/2005	2 (8.3)	5 (4.6)	8 (5.3)	Tracheoesophageal fistula in limited disease small-cell lung cancer patients	20/9/2007
							Haemolytic anaemia in combination with higher doses of sunitinib	24/7/2008
Antithrombotic agents	Lepirudin	Refludan	13/3/1997	1 (4.2)	1 (0.9)	2 (1.5)	Fatal anaphylactic reactions	25/4/2003
Antithrombotic agents	Drotrecogin-α	Xigris	22/8/2002	1 (4.2)	5 (4.6)	6 (4.5)	Contraindication in paediatric use due to lack of efficacy	13/10/2005
Drugs for treatment of bone diseases	Dibotermin-α	InductOs	9/11/2002	3 (12.5)	4 (3.7)	6 (5.3)	Localised oedema following unlicensed use of the product in cervical spine fusion procedures	29/7/2004
							Formation of fluid collections (pseudocysts, localised oedema, implant site effusion) patients undergoing spine surgery	22/2/2007
							Exclude "reamed nail fixation" from the indication to use InductOs in open tibial fractures	24/4/2008
Drugs used in diabetes	Insulin human	Exubera	24/1/2006[a]	1 (4.2)	1 (0.9)	2 (1.5)	Primary lung carcinoma	30/5/2008
Immunosuppressants	Infliximab	Remicade	13/8/1999	3 (12.5)	28 (25.7)	31 (23.3)	Tuberculosis	29/3/2001
							Worsening heart failure, infections including tuberculosis	17/1/2002
							Hepatosplenic t-cell lymphoma	1/6/2006
Immunosuppressants	Etanercept	Enbrel	3/2/2000	2 (8.3)	19 (17.4)	21 (15.8)	Blood dyscrasia (pancytopenia, aplastic anaemia)	16/11/2000
							Serious infections and neutropenia in combination with kineret	23/1/2003

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Table I. Contd

ATC drug class	INN	Product name	Authorization date (EU) [dd/mm/yyyy]	Number of type II variations			Description of urgent safety issues	Date of approval of type II variation [dd/mm/yyyy]
				Urgent [n (%)]	Other [n (%)]	Total [n (%)]		
Immunosuppressants	Anakinra	Kineret	8/3/2002	1 (4.2)	3 (2.8)	4 (3.0)	Serious infections and neutropenia in combination with etanercept	23/1/2003
Immunosuppressants	Adalimumab	Humira	8/9/2003	1 (4.2)	14 (12.8)	15 (11.3)	Hepatosplenic t-cell lymphoma	26/6/2008
Immunosuppressants	Efalizumab	Raptiva	20/9/2004[a]	1 (4.2)	6 (5.5)	7 (5.3)	Progressive multifocal encephalopathy	23/10/2008
Immunosuppressants	Natalizumab	Tysabri	27/6/2006	2 (8.3)	2 (1.8)	4 (3.0)	Hepatic damage	24/4/2008
							Progressive multifocal leukoencephalopathy	25/9/2008
Muscle relaxants	Botulinum toxin type b	Neurobloc	8/3/2001	1 (4.2)	8 (7.3)	9 (6.8)	Muscle weakness, dysphagia, aspiration	22/2/2007
Total				**24 (100)**	**109 (100)**	**133 (100)**		

a Product withdrawn.

ATC = Anatomical Therapeutic Chemical; **EU** = European Union; **INN** = International Nonproprietary Name.

Data sources could be identified for 132 of the variations. Spontaneous reports were the only mentioned data source in 52 (39%) of the type II variations (figure 3). Post-authorization studies were the sole determinant for 39 (30%) of the variations. Including the variations that were based on multiple data sources, spontaneous reports contributed to 85 (65%) of the variations and postmarketing studies contributed to 66 (50%) of the variations. The distribution of determinants was not significantly different between the urgent and the other safety-related type II variations (table II).

The relative contribution of post-approval studies was smaller for monoclonal antibodies when compared with all other products (table II). The sample comprised for a large part of variations associated with products that can be categorized in the ATC class 'immunosuppressants', but no significant difference in the distribution of determinants of regulatory actions was found (table II). No individual product changed the distribution of determinants of regulatory action.

Overall, most variations included issues that were categorized in the SOCs 'infections and infestations' (33.1%), 'general disorders and administration site conditions' (25.6%), 'neoplasms' (14.3%), 'blood and lymphatic system disorders' (13.5%), and 'nervous system disorders' (12.8%). Urgent variations less often included safety issues from the SOC 'nervous system disorders' compared with other variations (0% vs 15.6%, $p = 0.04$). Otherwise, the distribution of adverse events was not significantly different for urgent versus other safety-related type II variations.

The large proportion of variations in the 'general disorders and administration site conditions' ($n = 34$) was mostly due to inclusion of information about interactions, eight (24%); lack of effect in specific patient populations, eight (24%); and infusion reactions, seven (21%). Overall, three (2.3%) variations were classified as 'injury, poisoning and procedural complications, of these, two related to dosing-related safety issues and one to excretion of a drug in mother's milk in an animal study.

Overall, 59 (45%) variations introduced multiple changes to the SPC (median 2, range 2–8). Urgent variations less often included multiple

safety issues compared with other safety-related type II variations, 6 (25%) vs 53 (49%) [p = 0.04]. Variations often led to changes to multiple sections of the SPC. Most variations included at least changes to section 4.8 of the SPC ('undesirable effects'). This was the case for 91.6% of the urgent variations and 78.0% of the other safety-related variations (p = 0.13). Urgent variations more often included changes to SPC section 4.4 (Special Warnings and Precautions for Use) than other safety-related type II variations (95.8% vs 58.7%, p < 0.01). No significant difference was found for other sections of the SPC.

In subanalyses we evaluated the role of PSURs in the initiation of regulatory actions. Overall we found a reference to PSUR evaluations in 50 (38%) of all type II variations (figure 4). PSURs contributed more often to type II variations based on spontaneous reports, but less to variations based on postmarketing studies (table II). A total of 90 variations included adaptations to either sections 4.3 (Contraindications) or 4.4 (Special Warnings and Precautions for Use); 28 (31%) of these variations referred to PSURs. In 28 variations, changes were introduced only to section 4.8 (Undesirable Effects) of the SPC. In 17 of these (61%), reference was made to PSUR evaluations.

Discussion

Although urgent regulatory actions such as withdrawals and DHPCs generate a lot of attention in a wider public, much of the effort of regulators and pharmaceutical companies is aimed at improving the safe and effective use of medicines through less visible activities such as SPC updates. Overall, spontaneous reports contributed to the majority of post-authorization regulatory actions. When looking specifically at urgent actions, 55% included only spontaneous reports, which is comparable with what was previously reported for drug withdrawals that included mainly small molecules (36–57%).[10,12,13] A previous study found an important role of studies in the post-approval safety management of newly approved biopharmaceuticals.[5] Our study demonstrates that the spontaneous reporting system remains an essential part of the pharmacovigilance of biopharmaceuticals, both for urgent and non-urgent safety concerns. Increasing the awareness of the distinct adverse event profile observed for biopharmaceuticals can help healthcare professionals in recognizing adverse events.

Where other studies made a distinction between post-authorization studies, i.e. randomized controlled trials, non-randomized trials and observational studies, we limited our analysis to what was cited in the EPAR.[10,12,13] For the majority of the variations, the EPAR did not provide any details on the nature of the post-authorization study. For both urgent and non-urgent actions, we found a larger contribution of post-authorization studies than was previously reported.[10,12,13] This may be partly due to the fact that our study is more recent. In November 2005, new European regulations came into effect that mandated stricter

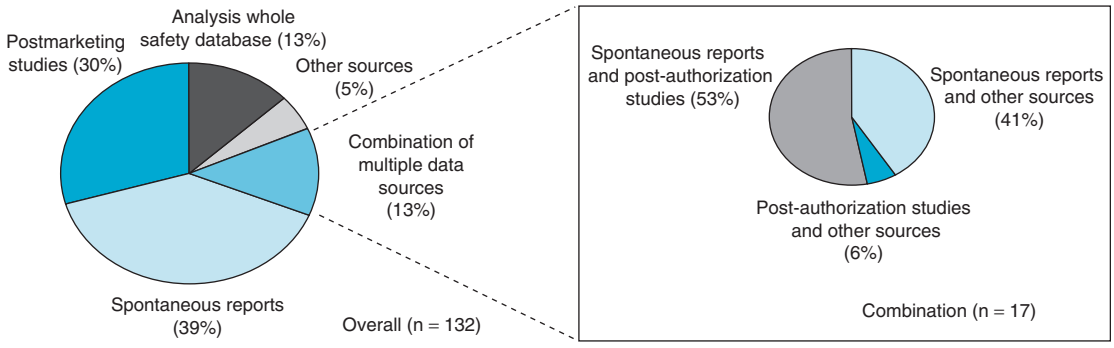

Fig. 3. Information source for type II variations included in the study, including the distribution of information sources for variations based on a combination of sources.

Table II. Sources of regulatory actions split out in several subgroups

	Spontaneous reports [n (%)]	p-Value[a]	Post-approval studies [n (%)]	p-Value[a]	Analysis of whole safety database [n (%)]	p-Value[a]	Other [n (%)]	p-Value[a]	Combination [n (%)]	p-Value[a]
Urgency										
Urgent (n = 24)	13 (55)	0.112	8 (33)	0.630	2 (8)	0.737	0 (0)	0.349	1 (4)	0.308
Other (n = 109)[b]	39 (36)		31 (29)		15 (14)		7 (6)		16 (15)	
Mechanistic class										
Monoclonal antibodies (n = 83)	37 (45)	0.141	19 (23)	0.047*	10 (12)	0.790	3 (4)	0.423	14 (17)	0.106
All other (n = 49)	15 (31)		20 (41)		7 (14)		4 (8)		3 (6)	
ATC class										
Immunosuppressants (n = 81)	31 (38)	0.855	21 (26)	0.327	12 (15)	0.595	4 (5)	1.000	13 (16)	0.194
All other (n = 51)	21 (41)		18 (35)		5 (10)		3 (6)		4 (8)	
PSUR involvement										
PSUR involvement (n = 49)	27 (55)	0.006*	6 (12)	0.001*	7 (14)	0.790	1 (2)	0.258	8 (16)	0.424
No PSUR involvement (n = 83)	25 (30)		33 (40)		10 (12)		6 (7)		9 (11)	

a p-Values were tested for significance using the 2-sided Fisher's exact test at an α-level of 0.05.

b For one non-urgent safety issue the source could not be identified.

ATC = Anatomical Therapeutic Chemical; **PSUR** = Periodic Safety Update Report.

and more proactive risk management of pharmaceuticals. This has resulted in the mandatory provision of risk management plans (RMPs) in which a detailed description of the safety profile of a product is given along with all steps taken to address any outstanding safety concerns and a description of risk-minimization activities.[8] For biopharmaceuticals, more often post-approval studies were requested, which could lead to a relatively large contribution of these studies in their post-authorization safety management.[5] A first study evaluating the effectiveness of RMPs found that, thus far, the influence of RMPs on the initiation of safety-related regulatory actions is modest at best.[19] Still, the introduction of RMPs is but one aspect of a more proactive attitude towards risk management that may have resulted in a different utilization of methods to assess the post-authorization safety of medicinal products, when compared with older studies. Our sample consisted for a large part of products used in the field of rheumatology, a field in which disease and treatment registries have collected data for many years.[20] However, the distribution of sources for SPC changes was not significantly different for immunosuppressants. SPC changes of monoclonal antibodies were less often based on results of studies. Further research is warranted to explain these results.

Previous studies found that in many cases several data sources are relevant for the assessment of a safety issue and they are often combined to provide evidence for safety withdrawals.[10,12,13] Our study was different in the unit of analysis, i.e. type II variations, rather than safety issues. The consequence is that our analysis is limited to those safety issues that were deemed relevant and sufficiently proven to include in the SPC. Non-urgent variations more often included multiple safety issues and therefore more often multiple sources were cited. Urgent regulatory actions on the other hand often follow suspected adverse drug reactions that may have such a large impact on patient safety that it will require immediate action, which does not allow time for extensive follow up, for example through performing additional studies.

Most of the type II variations in our analysis included safety issues from 'general disorders'

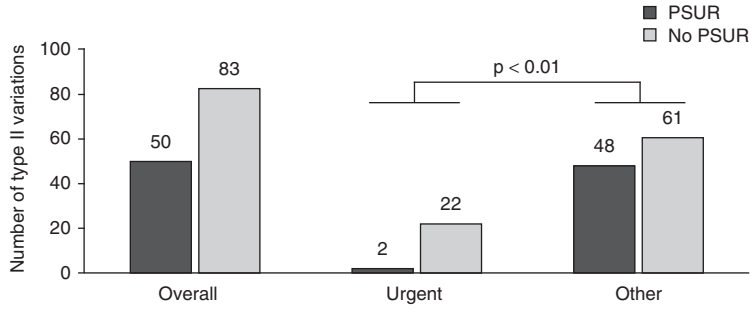

Fig. 4. Type II variations in which any reference was made to PSUR evaluations: urgent vs other safety-related type II variations. **PSUR** = Periodic Safety Update Report.

and 'administration site conditions', 'infections and infestations', 'blood and lymphatic system disorders' and 'neoplasms'. These results agree with previous studies that included urgent safety issues only.[6] They differ from the results obtained from a study that analysed all DHPCs for all approved medicines in the Netherlands, which found that the most common system organ classes were 'cardiac disorders', 'injury, poisoning and procedural complications' and 'general disorders and administration site conditions'.[7] These differences may be due to structural differences between biopharmaceuticals and small molecules. This seems likely since the toxicity of biopharmaceuticals is mostly a result of exaggerated and/or off target pharmacology and they do not form pharmacologically or toxicologically active metabolites.[21] Indeed, our sample did not include any type II variations due to toxicity. The large contribution of 'general disorders and administration site conditions' can in part be explained by the fact that biopharmaceuticals are mostly administered intravenously or subcutaneously, which may lead to administration site disorders. Also, 'lack of effect' was classified in this SOC, which accounted for a substantial part of the variations included in this category. Although anti-inflammatory and antineoplastic agents account for a large part of our sample, they did not appear to have influenced the outcome. Still, the number of variations in our study was limited and it will be of interest see how these results compare with type II variations from a randomly selected group of biopharmaceuticals or small molecules. Overall, our results suggest that the pharmacovigilance strategy for biopharmaceuticals does not lead to a different distribution in the determinants of regulatory actions.

In a subanalysis we examined the role of PSUR reporting in the post-authorization safety management of biopharmaceuticals. Although PSURs contribute to the initiation of many regulatory actions, their role was limited when we looked specifically at urgent actions. This could imply that PSUR reporting has a more important role in detecting non-urgent safety issues. This is supported by the fact that the contribution of PSUR reporting was larger in variations including only changes to section 4.8, when compared with variations concerning sections 4.3 and 4.4. An earlier study evaluating a statistical detection method for the identification of safety signals in the European pharmacovigilance database EudraVigilance reported that PSURs were the source of 64% of a selection of serious adverse drug reactions.[22] Their study included a sample of all centrally approved products and was limited to products that met predefined seriousness criteria. Our results were based on EPARs that provided only limited information on the possible roles of PSURs in the initiation of regulatory actions. Therefore, it is possible that this has led to an underestimation of the role of PSURs in post-authorization activities.

Although our results imply that PSURs do not have a great role in detecting urgent safety signals, the aim of PSUR reporting is to provide an overview of all relevant safety information,

rather than to expeditiously detect emerging safety issues. This is supported by our finding that urgent actions more often included a single safety issue than non-urgent variations. Future research into the role of PSURs should include detailed analysis of the outcome of PSUR evaluations.

How can these results contribute to improving the management of the post-authorization of biopharmaceuticals? Regulatory decisions are at the end of a process involving data from various sources, many different drivers and other, less tangible, factors.[23] The process is often criticized for not being transparent and drug regulation a 'black art'.[24,25] The past years have seen many developments to improve and rationalize pharmacovigilance both in methods to generate data and in legislation to ensure the collection of such data.[26] Despite improvements in the methods applied in pharmacovigilance, weighing benefits and risks of pharmaceuticals is still far from standardized and relies greatly on subjective judgement.[27] In December 2010 new European legislation has been adopted that aims to improve pharmacovigilance in the EU.[28] This will create more transparency of procedures and a new scientific committee to deal with matters of pharmacovigilance. The question remains how this will influence the post-authorization management of medicinal products, including biopharmaceuticals. How will all these measures lead to a system that is transparent, predictive and rooted in science?

We fully recognize the limitations of using type II variations as a proxy for the whole pyramid of regulatory activities. The determinants we included were limited to those included in the EPAR and other determinants may be relevant to assess pharmacovigilance activities, including patient characteristics, disease severity or the prevalence of adverse events. However, this study provides an example of how the effects of regulatory requirements can be visualized. Regulation is usually created to address specific issues, but may have unforeseen and/or unintended effects.[29] With ever-increasing costs in the development of medicinal products it is necessary that regulatory requirements are effective in attaining their intended purpose. However, evaluations of regulatory requirements in published literature are scarce. For example, the current concept of PSUR reporting was adopted globally in 1996, but since then the results of their use has not been thoroughly evaluated.[30] As regulators increasingly realise that a more consistent and transparent approach is needed in regulatory science, studies such as ours can contribute to evaluate the outcome of regulatory measures that are aimed at improving drug safety.

Conclusions

Determinants of urgent regulatory actions of biopharmaceuticals did not significantly differ from those of other, less urgent, safety-related regulatory actions. The comprehensive updates of the worldwide safety experience of a biopharmaceutical provided in PSURs appear to be less pivotal when it comes to urgent safety-related regulatory actions. Spontaneous reports continue to be an important pillar for both urgent and non-urgent actions. In the advent of the implementation of the new European pharmacovigilance legislation, where PSURs, spontaneous reporting systems and proactive RMPs are important building blocks, continuous and critical evaluation of the individual contribution to successful safety management of each of these tools is needed.

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