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DRUG SAFETY

Comparing safety information of biosimilars with their originators: a cross-sectional analysis of European risk management plans

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Keywords biosimilar, EMA, regulatory, risk management plan, safety profile

BACKGROUND AND AIMS

Biosimilars have been available in the European Union (EU) since 2006. However, their uptake in routine care is heterogeneous across countries. The aim of the present study was to compare the safety information of biosimilars and their originators based on the information in the European risk management plan (RMP).

METHODS

A cross-sectional analysis on publicly available regulatory documents (RMPs and Summaries of Product Characteristics) of biosimilars and corresponding originators up to 1 November 2015 was performed. The safety concerns were extracted and merged into general safety concerns, and clinical relevance was assessed. The frequency of safety concerns and the representation of these safety concerns per general safety concern were assessed by either comparing RMPs of biosimilars and originators (if available for both) or comparing RMPs with the Summary of Product Characteristics of the originator.

RESULTS

Nineteen biosimilars and six originators were included. Overall, 55 general safety concerns (12 low, 21 medium and 22 highly clinically relevant) were identified. For all active substances, except for infliximab, no or only one difference was found in the listed general safety concerns. Comparison of regulatory documents for infliximab identified three medium clinically relevant general safety concerns more for infliximab biosimilars and two general safety concerns more for its originator.

CONCLUSION

Based on publicly available information filed for regulatory purposes, no substantial differences were observed in the reporting of safety information for biosimilars and related originators. A direct comparison between biosimilars and related originators through formal postmarketing studies is needed to evaluate specific safety issues emerging during the products' life cycle.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- In the European Union, a biosimilar should be compared with its originator through a comparability exercise to demonstrate 'biosimilarity' before receiving a marketing authorization.
- However, prescribers and patients remain sceptical about using biosimilars instead of originators because of doubts about differential safety profiles compared with the originators.
- The European risk management plan (RMP) is available for biosimilars and contains relevant safety information on the product, with a characterization of potential and identified risks.

WHAT THIS STUDY ADDS

- A safety information comparison of biosimilars and related originators reported in publicly available regulatory documents (RMP, and the 'Procedural steps taken and scientific information after authorization' document or SmPC) was undertaken.
- No substantial differences were observed in the reporting of safety information on most biosimilars and related originators. Some differences were found between infliximab biosimilars and their originators, but only one was considered a highly clinically relevant safety issue.

Introduction

A biological medicinal product is one whose active substance is made by or derived from a living organism. They are often used to treat severe diseases, considering indications from hormonal deficiencies to cancer [1–5]. Their importance can also be perceived in the rise of research and design expenditures for biologicals by pharmaceutical companies [4].

While the manufacturing process for small molecule drugs relies on predictable synthetic chemical processes, biological medicinal products are produced in living cell cultures. Owing to the complexity of the production process, it is hard to produce identical batches for biological medicinal products. Nevertheless, lot-to-lot variations do not necessarily translate into clinically relevant differences among batches [6]. Their biological nature, however, may result in the triggering of an immunogenic effect more frequently than with small molecules [7, 8]. Moreover, to understand the difficulty in predicting the immunogenic potential of a biological medicinal product, it is important to note that the manufacturing process itself depends on a variety of parameters that may influence the immunogenicity. Such parameters include the cell line, growth media and conditions, as well as the post-translational modification of the biomolecule [3].

In October 2005, the European Medicines Agency (EMA) released a guideline for the production of a specific type of biological medicinal product, so-called biosimilars [9]. Biosimilars are officially approved as similar products to a biopharmaceutical originator, which often share the same International Nonproprietary Name (INN) [10, 11]. This indicates that biosimilars and originators contain the same active substance and therefore exert the same therapeutic effect [11]. In the European Union (EU), a biosimilar should be compared with its originator through a comparability exercise to demonstrate 'biosimilarity' [12]. Subsequently, the clinical efficacy for one indication may be extrapolated to (all) other indications for which the originator is authorized after a case-by-case evaluation [13–15].

With the introduction of biosimilars into the European market, more resources may be available to allocate to national healthcare services for innovative interventions [14, 16, 17]. Patterns of biosimilar use in Europe vary widely between countries, although a growth in their uptake has been documented recently, especially for filgrastim and epoetin alfa [18–20]. However, clinicians remain sceptical about using biosimilars instead of originators in naïve patients, as well as about substituting an originator with its biosimilar in patients already successfully treated [14, 16, 21–23]. The cautiousness is also seen in the United States, where they have been struggling for a framework themselves [24]. Efforts to communicate evidence on biosimilars in order to overcome information gaps led the EMA to publish an information guide for healthcare professionals, to provide them with reference information on the science and regulation underpinning the use of biosimilar medicines. This document clarifies that 10 years of clinical experience with biosimilars has shown them to be as safe and effective in all their approved indications as other biological medicines [25]. Barriers identified for the low uptake of biosimilars include the lack of comparative effectiveness and safety data in the real-world setting, the potential difference in immunogenicity, and uncertainty about data extrapolation to other indications [14, 26].

The available safety data reported in the documents filed for regulatory purposes at the EMA represent an important source of evidence. The European risk management plan (RMP) contains relevant safety information for each specific product, with a characterization of potential and identified risks alike, including data from real-life data. It represents an overview of a product's safety profile, being systematically updated, and could therefore provide an early indication of differential safety profiles between originators and related biosimilars.

The present study aimed to compare the consistency of safety information reported in the RMP of biosimilars with that available for their originators through publicly available regulatory documents.

Methods

Study design and setting

A cross-sectional analysis was conducted on publicly available documents (of biosimilars and their originators) filed for regulatory purposes at EMA level. The biosimilars

considered for inclusion in the analysis should have been authorized via the EMA centralized procedure during the timeframe 1 January 2005 to 30 October 2015. The corresponding originators were indicated in the European public assessment report (EPAR) for each biosimilar.

Data sources

A safety concern was defined as an 'identified risk', a 'potential risk' or 'missing information' listed in the summary of the RMP, and in the documents published after authorization called 'Procedural steps taken and scientific information after authorization' (see Box 1 for further details).

Box 1

Regulatory milestones and documents aimed at improving transparency and safety information for the biological medicinal products.

May 2004:	All biologically derived drugs need to be authorized through the centralized procedure.
Oct 2005:	The guidelines for biosimilar marketing authorization are effective.
June 2006 – Sept 2015:	Product-specific scientific guidelines have been established for recombinant human insulin, somatropin, recombinant granulocyte colony-stimulating factor, recombinant erythropoietins, monoclonal antibodies and recombinant follicle-stimulating hormone.
July 2012:	The establishment of the Pharmacovigilance Risk Assessment Committee (PRAC), which assesses all aspects of the risk management of medicines for human use. One of the responsibilities of the PRAC is to support the marketing authorization holder (MAH) with evaluating the safety profile of their product by preparing recommendations on potential risks and the ascertainment of them.
Dec 2012:	All marketing authorization applications for biosimilars need to include a risk management plan (RMP).
Mar 2014:	The EMA publishes the summaries of RMPs of centrally authorized drugs.

The Summary of Product Characteristics (SmPC) is a document in which medicinal product information collected through the course of authorization is summarized, containing: pharmaceutical quantitative and qualitative information; efficacy data; safety issues; pharmacological properties and particulars; and MAH information

The RMP is a document in which the safety profile of a drug is reflected, and presents the actions that the MAH will take to improve the safety profile. In the RMP, the safety concerns of drugs are categorized as 'identified risks', 'potential risks' or 'missing information'.

- *Identified risks*: Established adverse events that have been reported significantly during clinical trials or after marketing authorization.
- *Potential risks*: Expected risks based on the mechanism of action, but have not been reported significantly during clinical trials or after marketing authorization.
- *Missing information*: Lacking information about the effect on specific types of patient populations. Examples of missing information include populations not studied or where there is a high likelihood of off-label use. Specific types of population can range from patients from certain age groups to patients with comorbidities.

The document 'Procedural steps taken and scientific information after authorization' contains the outcomes of safety profile evaluations and other important information acquired about the drug during its life cycle (e.g. changes in the manufacturing process).

When the RMP of an originator was not publicly available (i.e. those originators authorized through the mutual recognition procedure or decentralized procedure), the Summary of Product Characteristics (SmPC) was used. We assumed that sections 4.4 (Special warnings and special precautions for use) to 4.8 (Undesirable effects) of the SmPC should have contained all information on safety concerns, as reported in the RMP [27].

The SmPCs were obtained from the electronic Medicines Compendium (eMC) [28]. The eMC is a licensed database of product information (SmPCs and patient information leaflets) for medicines registered in the UK. The documents available on the eMC are originally approved by the EMA and the UK Medicines and Healthcare Products Regulatory Agency (MHRA), so they can be considered generalizable to the EU member states.

Data analysis

Two principal comparisons were carried out: (i) RMP biosimilar–RMP originator (whenever the RMP was available for both of them); (ii) RMP biosimilar–SmPC originator (in cases where the RMP of the originator was not available). The heterogeneity in the descriptions of safety concerns across regulatory documents was harmonized by grouping similar and related single safety concerns into a unique general safety concern favouring the highest possible homogeneity across different types of events (see Appendix I for more details). No analyses were performed on the basis for the original classification (i.e. 'identified risk', 'potential risk' or 'missing information'), because safety concerns may evolve over time, e.g. are considered a potential risk at the time of approval of the originator and later on become an identified risk.

The originator was compared with its registered biosimilars on a *qualitative level* (i.e. based on the presence or absence of a general safety concern) and on a *quantitative level* (i.e. counting the various safety concerns contained for

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each general safety concern). To evaluate the clinical relevance of safety issues, the general safety concerns were classified as low, medium or high clinical relevance by two of the authors separately (L.R.A.L. and F.T.); disagreements were resolved by discussion, and consensus was eventually sought with a third author (F.R.). Overall, the criteria adopted for categorizing clinical relevance were as follows: (i) nonspecific terms that described nonspecific and broad safety issues (e.g. *long-term use*, *interaction with other drugs*), medication errors and safety in specific patient populations (e.g. *use in pregnancy)* were classified as issues of low clinical relevance; (ii) less specific, reversible and nonfatal general safety concerns were classified as issues of medium clinical relevance (e.g. *splenic complications*, *lack of efficacy*, *immunogenicity*); (iii) life-threatening, unexpected and irreversible general safety concerns were classified as issues of high clinical relevance (e.g. *neoplasms*, *diabetes*, *interstitial lung disease*).

A third comparison – i.e. SmPC biosimilar *vs*. SmPC originator – was performed as a sensitivity analysis revealing if essential differences specified as Medical Dictionary for Regulatory Activities (MedDRA) terms had been missed in the previous comparisons.

The descriptive analyses of the study were conducted using Microsoft Excel, to calculate the cumulative numbers of safety concerns, general safety concerns and related percentages.

Results

A total of 25 biological medicinal products (19 biosimilars and six originators) were included in the analysis (Table 1). Overall, seven different types of active substances (as INNs) were included. Epoetin-zeta (Silapo and Retacrit) demonstrated biosimilarity to Eprex (epoetin-alfa), and so were included in the comparison as biosimilars of epoetin-alfa. The first biosimilar was approved in April 2006 (Omnitrope, somatropin), the last in September 2014 (Accofil, filgrastim; and Abasaglar, insulin glargine). The summary of the RMP was retrieved for all biosimilars and two originators (Remicade, infliximab and Lantus, insulin glargine). For the remaining four originators (Genotropin, somatropin; Neupogen, filgrastim; Eprex, epoetin alfa; and Gonal-f, follitropin-alfa), the SmPC was used for the comparison.

Overall, 142 safety concerns were retrieved, corresponding to 55 general safety concerns (Table 2). The degree of clinical relevance was classified consistently by the authors for 49 general safety concerns, while for the remaining six general safety concerns consensus was reached after discussion. Twenty-two (40%) general safety concerns were classified as being of high clinical relevance, 21 (38%) of medium clinical relevance and 12 (22%) of low clinical relevance. Somatropin presented the largest proportion of highly clinically relevant general safety concerns, whereas insulin glargine presented the lowest proportion.

In the case of the INNs insulin glargine and infliximab, we were able to compare the RMPs of biosimilars with those of the originators (Figure 1A,B; see Appendix IIa for details on single medicinal products). The regulatory safety information for the insulin glargine biosimilar (Abasaglar) and originator (Lantus) were highly similar on a qualitative and quantitative level: only one out of six general safety concerns differed (Figure 1A). 'Missing information' on the '*use in children younger than 2 years*' (low clinical relevance) was presented in the RMP of the biosimilar insulin glargine but not in the RMP of the originator.

More differences emerged when comparing the infliximab originator with its biosimilars (Figure 1B). On a qualitative level, two of the 14 general safety concerns included in the RMP of the originator (Remicade) (i.e. '*interstitial lung disease*' and '*interaction with drugs*', of high and low clinical relevance, respectively) were not mentioned in the RMP of the biosimilars. However, the RMPs of the biosimilars presented three general safety concerns – i.e. '*bowel obstruction*', '*haematological reactions*' and '*lack of efficacy*' (all of medium clinical relevance) – that were not mentioned in the RMP of the originator. The quantitative comparison for highly clinically relevant safety concerns showed that the RMP of the infliximab originator (Remicade) listed four types of '*autoimmune events*' (i.e. '*Stevens–Johnson syndrome*', '*toxic epidermal necrolysis*', '*erythema multiforme*' and '*dermatomyositis*') and three types of '*infections*' (e.g. '*invasive fungal infections*', '*parasitic infections*' and '*viral infections*') more than the RMP of its biosimilars. The RMPs of the biosimilars listed three types of *neoplasm* (e.g. *paediatric malignancy, leukaemia* and *colon carcinoma*) more than the RMP of the originator.

For other INNs – i.e. erythropoietins, filgrastim, follitropin-alfa and somatropin – the RMP of the biosimilars was compared with the SmPC of the originator (Figure 2A–D; see Appendix IIb for details on single medicinal products). Overall, the safety profiles of the biosimilars and their originators were highly similar (Figure 2A–D). In the case of erythropoietins, there were no differences at all between Eprex and its biosimilars when the comparison was conducted at both a qualitative and quantitative level. The RMP of the biosimilars of filgrastim presented only one (out of 15) general safety concerns more than their originator, defined as being of low clinical relevance (i.e. '*general safety and long-term use*'). Similarly, the RMP of follitropin-alfa biosimilars had only one (out of 10) additional general safety concern compared with the originator – i.e. '*use in women older than 40 years*' (of low clinical relevance). In the somatropin comparison, the RMP of the biosimilar presented one additional highly clinically relevant safety concern ('*intracranial vascular disorders*') compared with the originator.

Considering the quantitative level comparing highly clinically relevant terms, few differences were noted. Filgrastim biosimilar RMPs presented the safety concern '*cytokine release syndrome*', which was not present in the SmPC of the originator; however, the safety concern '*capillary leak syndrome*' (considered strongly related to '*cytokine release syndrome*') was reported for both the originator and biosimilars. At the quantitative level, the comparison of somatropin showed that the RMP of the biosimilar presented three additional highly clinically relevant safety concerns compared with its originator Genotropin (i.e. '*new neoplasm*', '*intracranial aneurysm*' and '*intracranial haemorrhage*')*.*

The originator SmPC–biosimilar SmPC comparison performed as a sensitivity analysis showed one additional MedDRA term not identified in the main analyses concerning filgrastim products (Appendix III). The SmPC of the filgrastim

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Table 1

List of biological medicinal products included in the analysis ($n = 25$) by active substance and regulatory documents available, with corresponding publication dates

Brand name	Approval date	Summary of RMP	Doc post-authorization[a]	SmPC
Genotropin (somatropin)	**1987, May**	**N/A**	**N/A**	**10/11/2014**
Omnitrope (somatropin)	2006, April	25/04/2006[b]	13/5/2015	–
Eprex (erythropoietin)	**1988**	**N/A**	**N/A**	**29/7/2015**
Binocrit (erythropoietin)	2007, August	13/9/2007	21/9/2015	–
Abseamed (erythropoietin)	2007, August	13/9/2007	28/9/2015	–
Epoetin Alfa HEXAL (erythropoietin)	2007, August	13/9/2007	30/9/2015	–
Silapo (erythropoietin)	2007, December	15/1/2008	30/10/2014	–
Retacrit (erythropoietin)	2007, December	15/1/2008	30/9/2015	–
Neupogen (filgrastim)	**1991, March**	**N/A**	**N/A**	**17/9/2015**
Ratiograstim (filgrastim)	2008, September	29/9/2008	3/1/2014	–
TevaGrastim (filgrastim)	2008, September	29/9/2008	3/1/2014	–
Biograstim (filgrastim)	2008, September	29/9/2008	3/1/2014	–
Filgrastim HEXAL (filgrastim)	2009, February	16/2/2009	26/8/2015	–
Zarzio (filgrastim)	2009, February	16/2/2009	19/8/2015	–
Nivestim (filgrastim)	2010, June	23/6/2010	26/8/2015	–
Grastofil (filgrastim)	2013, October	11/11/2013	8/9/2015	–
Accofil (filgrastim)	2014, September	28/10/2014	7/7/2015	–
Gonal-f (follitropin-alfa)	**1995, October**	**N/A**	**N/A**	**29/5/2015**
Ovaleap (follitropin-alfa)	2013, September	23/10/2013	3/10/2014	–
Bemfola (follitropin-alfa)	2014, March	16/05/2014[b]	22/8/2014	–
Remicade (infliximab)	**1999, August**	**10/7/2007**	**27/8/2015**	**–**
Remsima (infliximab)	2013, September	4/10/2013	20/4/2015	–
Inflectra (infliximab)	2013, September	4/10/2013	24/8/2015	–
Lantus (insulin glargine)	**2000, June**	**14/8/2012**	**25/9/2015**	–
Abasaglar (formerly Abasria; insulin glargine)	2014, September	14/10/2014	14/7/2015	–

Text in bold = originator. N/A, not available; RMP, risk management plan; SmPC, Summary of Product Characteristics

[a]Doc Post Authorization = document for procedural steps taken and scientific information after authorization

[b]Update of summary of risk management plan in European public assessment report (Omnitrope 14/01/13; Bemfola 22/07/14)

originator presented '*glomerulonephritis*', whereas the biosimilar SmPCs did not. In the case of erythropoietin products, two biosimilars reported two potentially serious adverse events ('*cerebral haemorrhage*', '*aneurysms*') and three nonserious ones ('*weakness*', '*dizziness*', '*tiredness*') not reported in the originator SmPC. The SmPCs of infliximab biosimilars listed more types of neoplasm than the originator SmPC. Comparisons between other active substances showed no further differences.

Discussion

Summary of main findings

There is a negligible number of differences concerning information on the safety profiles of biosimilars and their corresponding originators, as reported in the publicly available regulatory documents. Most differences were found for infliximab medicinal products. The originator (Remicade) included in the RMP two general safety concerns (i.e. '*interstitial lung disease*' and '*interaction with drugs*') not mentioned in the RMP of the biosimilars, while the biosimilar RMPs presented three general safety concerns (*i.e.* '*bowel obstruction*', '*haematological reactions*' and '*lack of efficacy*') not mentioned in the RMP of the originator.

The qualitative comparisons of general safety concerns for other active substances showed only one difference or none. Overall, none of the differences was related to immunogenicity.

Interpretation of results

Similarity between biosimilars and originators should be demonstrated at the time of authorization for both

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Table 2

Clinical relevance classification of general safety concerns

Erythropoietins	**L**	**M**	**H**
Pure red cell aplasia			x
Thrombotic vascular events		x	
Neoplasms			x
General safety and long-term use	x		
Total	1	1	2
Filgrastim	**L**	**M**	**H**
Immunogenicity		x	
Splenic complications		x	
Osteoporosis		x	
Leukaemia			x
Arthritis		x	
Pulmonary infiltrates			x
Interaction with drugs	x		
Graft *vs*. host disease			x
Severe pulmonary disorders			x
Serious skin conditions		x	
General safety and long-term use	x		
Cytokine release syndrome			x
Sickle cell anaemia with crisis			x
Risks in pregnancy and lactation	x		
Interstitial lung disease			x
Total	3	5	7
Somatropin	**L**	**M**	**H**
Neoplasms			x
Immunogenicity		x	
General risks in PWS patients	x		
Pancreatitis			x
Diabetes			x
Intracranial vascular disorders			x
Total	1	1	4
Follitropin-alfa	**L**	**M**	**H**
Immunogenicity		x	
Severe adverse pregnancy outcomes			x
Ovarian hyperstimulation syndrome		x	
Multiple pregnancy		x	
Thrombotic (vascular) events in women		x	
Asthma aggravated/exacerbation		x	
Gynaecomastia in males		x	
Female reproductive neoplasm			x
Potential porphyria with family history		x	
Women older than 40 years	x		
Total	1	7	2
Insulin glargine	**L**	**M**	**H**
Immunogenicity		x	
Hypoglycaemia		x	
Medication errors (incorrect insulin)	x		
Malignancies			x
Use in pregnancy	x		
Use in children younger than 2 years	x		
Total	3	2	1
Infliximab	**L**	**M**	**H**
Infections			x
Immunogenicity		x	
Autoimmune events			x
Neoplasms			x
Long-term use	x		
Pregnancy and lactation exposure	x		
Bowel obstruction		x	
Sarcoidosis			x
Interstitial lung disease			x
Heart failures			x
Lack of efficacy		x	
Hepatobiliary disorders		x	
Haematological reactions		x	
Interaction with drugs	x		
Total	3	5	6

(*continues*)

Table 2

(Continued)

Text in bold = active substance. L, low clinical relevance; M, medium clinical relevance; H, high clinical relevance; PWS, Prader–Willi syndrome

efficacy and safety, and regulatory documents (RMPs, SmPCs) are continuously updated during the life cycle of the products, so we expected to find no major differences in the available safety information reported. Our study confirmed that information about the safety of biosimilars and originators was reported consistently across the regulatory documents.

During drug life cycle management, it is expected that the differences that occur between biosimilars and originators are those linked to the production process (e.g. immunogenicity), and they may lead to less frequent and serious adverse events [29]. However, we found that immunogenicity was reported in the safety profile for each biological medicinal product (despite the various manufacturing processes). This confirms that immunogenicity is not an exclusive risk for biosimilars.

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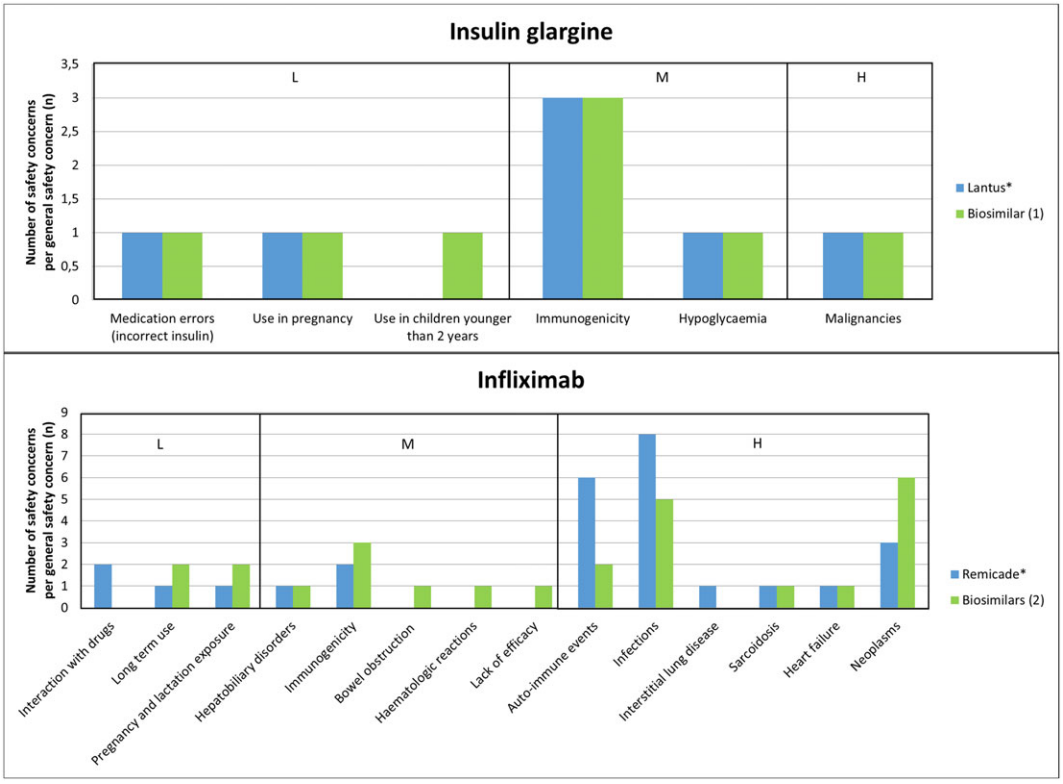

Figure 1

(A) Frequency of safety concerns contained in each single general safety concern in the summaries of risk management plans (RMPs) and documents for procedural steps taken and scientific information after the authorization of insulin glargine products (safety concerns of biosimilars were grouped and biosimilars are presented as a category). (B) Frequency of safety concerns contained in each single general safety concern in the summaries of RMPs and documents for procedural steps taken and scientific information after the authorization of infliximab products (safety concerns of biosimilars were grouped and biosimilars are presented as a category). H, high clinical relevance; L, low clinical relevance; M, medium clinical relevance; * = originator; Biosimilars (n), number of biosimilars that are grouped

We also tried to provide further explanations for the remaining few observed differences. The regulatory safety information for infliximab biosimilars and their originator showed differences, especially on a quantitative level (i.e. counting the various safety concerns contained for each general safety concern). However, the safety concerns of the infliximab originator and of the biosimilars share the same origins but are otherwise specified (e.g. '*Merkel cell carcinoma and melanoma*' for originator *vs*. '*skin cancer*' for biosimilars).

Few differences emerged from the comparison of RMPs of biosimilars with the SmPC of the originator. In the case of somatropin, the biosimilar (Omnitrope) reported '*new neoplasm*', '*intracranial aneurysm and intracranial haemorrhages*' as potential risks reported in the RMP which were not shared by the SmPC of the originator (Genotropin) [30–32]. This discrepancy has an explanation; in fact, this risk was the result of the French Safety and Appropriateness of Growth hormone treatments (SAGhE) study, which triggered an EMA referral procedure, resulting in the decision to present an RMP for the originator also containing the above-mentioned risks (although it is not publicly available, as it has not been approved centrally) [30, 33, 34].

The regulatory documents of Eprex, Silapo and Retacrit specified the risk of pure red cell aplasia only with subcutaneous administration in renal patients. The other erythropoietin biosimilars did not specify this and were not registered for subcutaneous use in these patients [35–37]. As a conclusion, the safety profile also considers different administration routes in addition to the various indications of the biosimilars.

Specific differences also emerged for filgrastim biosimilars. For example, the potential risk of cytokine release syndrome was only established with the use of Accofil (filgrastim) in the RMP. However, this particular safety concern follows a PRAC decision published on 11 April 2013, valid for all the MAHs of filgrastim [38]. This means that in the near future, with periodic RMP updates, differences will be further reduced.

Strengths and limitations

The present study used official publicly available regulatory documents in which all safety information is collected about the biosimilars and corresponding originators analyzed. Comparisons between biosimilar RMPs and originator SmPCs were affected by heterogeneous terminology (meaning that different words are used to describe the same concept, as

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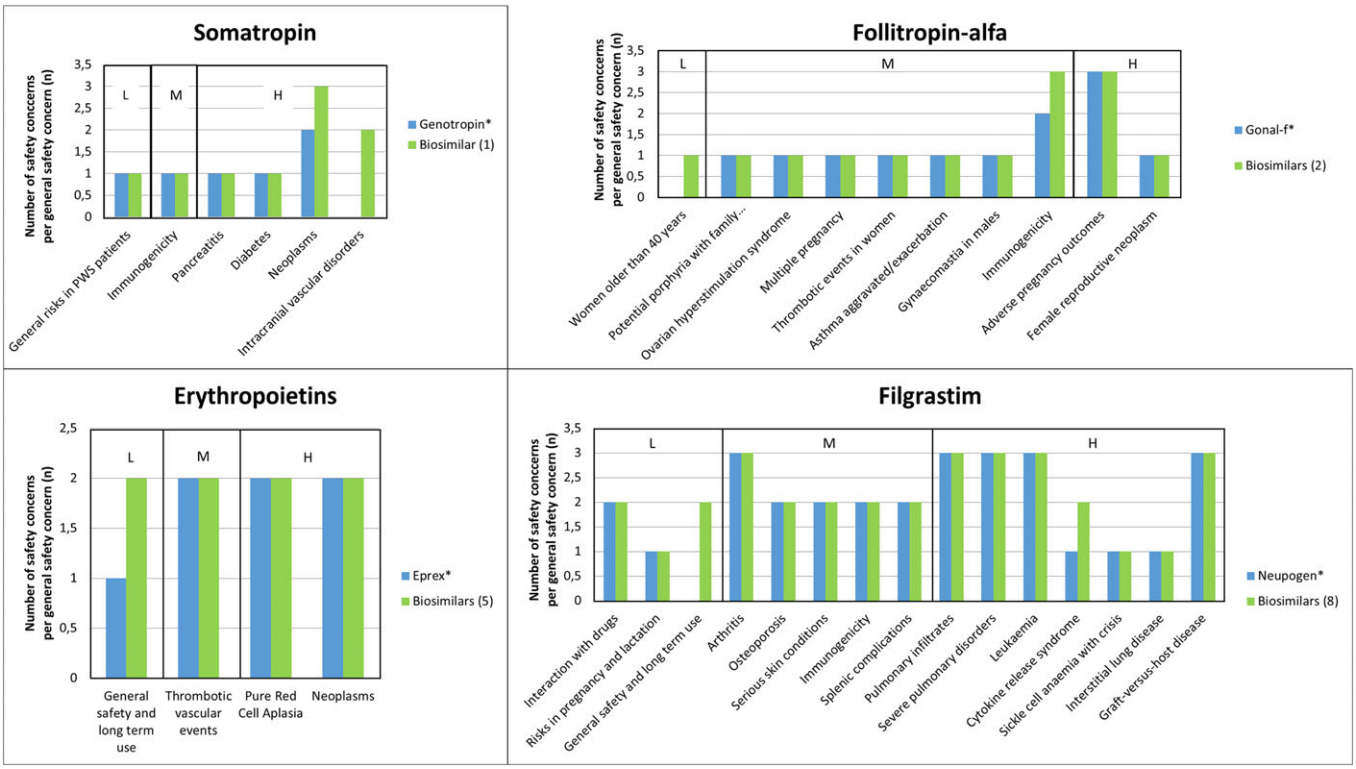

Figure 2

(A) Frequency of safety concerns contained in each single general safety concern in the summaries of risk management plans (RMPs) and documents for procedural steps taken and scientific information after the authorization of erythropoietin biosimilars or the Summary of Product Characteristics (SmPC) of erythropoietin originator (safety concerns of biosimilars were grouped and biosimilars are presented as a category). (B) Frequency of safety concerns contained in each single general safety concern in the summaries of RMPs and the documents for procedural steps taken and scientific information after the authorization of somatropin biosimilar or the SmPC of somatropin originator (safety concerns of biosimilars were grouped and biosimilars are presented as a category). (C) Frequency of safety concerns contained in each single general safety concern in the summaries of RMPs and the documents for procedural steps taken and scientific information after the authorization of filgrastim biosimilars or the SmPC of filgrastim originator (safety concerns of biosimilars were grouped and biosimilars are presented as a category). (D) Frequency of safety concerns contained in each single general safety concern in the summaries of RMPs and the documents for procedural steps taken and scientific information after the authorization of follitropin-alfa biosimilars or the SmPC of follitropin-alfa originator (safety concerns of biosimilars were grouped and biosimilars are presented as a category). H, high clinical relevance; L, low clinical relevance; M, medium clinical relevance; PWS, Prader–Willi syndrome; * = originator; Biosimilars (n), number of biosimilars that are grouped

detailed in Appendix I). However, the results of the originator SmPC–biosimilar SmPC comparison performed as a sensitivity analysis confirmed the overall consistency in safety information reported.

The publication of the 'Procedural steps taken and scientific information after authorization' document was not aimed at updating the RMP, and it also fueled further heterogeneity. Additionally, few updated RMPs were available, which resulted in more data extraction from the 'Procedural steps taken and scientific information after authorization' documents themselves. To reduce heterogeneity, the safety concerns in regulatory documents could be harmonized by using standard terminology (e.g. MedDRA or World Health Organization - Adverse Reactions Terminology). Additionally, the heterogeneity in presenting nonspecific *vs*. specific safety concerns (e.g. '*autoimmune events*' *vs*. '*systemic lupus erythematosus*') can also be avoided. Nonspecific safety concerns valid for particular pharmacodynamics could be 'imposed' in all RMPs. In the example of infliximab, '*opportunistic infections*' could be stated as a potential risk that always needs to be assessed.

In principle, the safety concerns can be resolved over time with continuous life cycle product management which is dynamic in nature. However, an RMP is updated after a request from a national competent authority or when the benefit–risk ratio is changed significantly [39]. Additionally, earlier research on RMP development showed that identified risks are seldom removed from an RMP [40].

In our study, using the regulatory documents publicly available at the time of the analysis, the resolved safety concerns could not be identified systematically. However, we found only two (out of 21) RMPs updated, so the risk of not considering a removed safety concern was minimized.

It is understandable that a thorough RMP update in line with regulatory requirements takes time and is therefore

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done infrequently [40]. Regular RMP updates may be made mandatory, to avoid delays in the publication of new information available.

According to the EMA, the safety profile of a drug can be influenced by different study designs and populations, which justifies the evolution of RMPs independently for each specific product, even though medicinal products contain the same active substance [41]. However, a safety concern occurring more frequently with a specific study design and population could also emerge earlier owing to a higher level of use. With the current policy of adding safety concerns to the RMP, it is likely that rare adverse reactions will stay undetected for products which are used less often. Therefore, it is appropriate to add each established safety concern to the RMP for each biological medicinal product with the same active substance, as a potential risk [39]. This policy for updating an RMP is already applied by the PRAC.

The safety concerns that are not shared between biosimilars and originators, and become a safety signal require additional direct comparisons through postmarketing effectiveness and safety studies, which can be promoted both by MAHs and public research institutions. Future research should investigate whether reported safety concerns have led to differential additional risk minimization measures or post-authorization safety studies between biosimilars and originators.

Although our study showed that safety information reported in the official regulatory documents is reported consistently both for biosimilar and originators, a direct comparison between biosimilars and related originators through formal postmarketing studies (observational or clinical trials) is mandatory for specific safety and effectiveness issues emerging during the products' life cycle.

The present study included the first cohort of biosimilars approved until 1 November 2015. The approval scenario for biosimilars is dynamic, and during the last months new biosimilars were approved in the EU for five INNs (etanercept, enoxaparin sodium, teriparatide, rituximab and adalimumab). These new biosimilars were not part of our analysis of first biosimilars, and the results cannot be extrapolated to these drugs.

Promoting biosimilar use

The risks of low clinical relevance include the unknown effects of use in specific populations and long-term use, and interactions with other drugs. The nature of these safety concerns is precautionary – i.e. it is inappropriate to exclude them *a priori* from the safety profile, and is therefore valid for biosimilars as well as originators. Such differences should have little impact on the prescribing choices between an originator and a biosimilar.

Some differences emerged when comparing infliximab originator with its biosimilars. However, it should be noted that infliximab showed the majority of general safety concerns (14 general safety concerns) of all analyzed substances. On a qualitative level, the originator (Remicade) presented two (out of 14) general safety concerns of high, and one of low clinical relevance that were not mentioned by the RMP of its biosimilars, while the biosimilars presented three general safety concerns of medium clinical relevance which were not mentioned in the originator RMP. This suggests that, in general, further postmarketing research is warranted for infliximab (both originator and biosimilars). Although the analysis suggests variance in safety information, a systematic review showed similar safety outcomes between biosimilars and originator [42].

Conclusion

Based on the currently available official information filed for regulatory purposes at EMA level, no substantial differences were observed in the reporting of safety information on biosimilars and related originators. Some differences were found between infliximab biosimilars and originator, but only one was considered to be a highly clinically relevant safety issue. Immunogenicity was reported in the safety information for each product considered, for biosimilars and originators alike.

Although similarity has been shown in licensed biosimilars, a direct comparison between biosimilars and related originators through formal postmarketing studies (observational or clinical trials) remain important to evaluate specific safety and effectiveness issues emerging during the products' life cycle.

Competing Interests

All authors declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. Only public employees of the national competent authorities were involved in conceiving, planning and conducting the study; no additional funding was received. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of, or reflecting the position of, any national competent authority, the EMA, or one of its committees or working parties.

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Appendix 1

Overview of grouping process of the terms retrieved in the regulatory documents into a general safety concern

The grouping was conducted combining single safety concerns (with similar origin with regard to the type of event) into a unique general safety concern. The number reported in the 'General safety concern' column, listed after the term, indicates the number of autonomous safety concerns contained by the general safety concern.

	Safety concerns as reported in summary of the RMP	**General safety concern**
Erythropoietins	Pure red cell aplasia (PRCA)	PRCA, 2
	Increased risk of PRCA with subcutaneous administration in renal failure patients	
	Tumour growth potential	Neoplasm, 2
	Increased mortality (cancer patients)	
	Relatively high target haemoglobin concentrations	Thrombotic vascular events, 2
	Thrombotic vascular events	
	General safety and long-term use	General safety and long-term use, 2
	Potential off-label use regarding s.c. application in renal anaemia patients in respect of missing comparative data on safety and immunogenicity between HX575 and Erypo in these patients	
Filgrastim	Hypersensitivity	Immunogenicity, 2
	Immunogenicity	
	Immunogenicity in individual patients treated;	
	Immunogenicity (Incidence and clinical implications of anti-G-CSF antibodies);	
	Immunogenicity which may manifest as lack of effect;	
	Splenic rupture	Splenic complications, 2
	Splenomegaly	
	Osteoporosis (PT)	Osteoporosis, 2
	Bone pain	
	Osteoporosis in patients with severe chronic neutropenia;	
	Transformation to leukaemia (PT) or myelodysplastic syndrome (PT); Transformation to leukaemia or myelodysplastic syndrome with severe chronic neutropenia;	Leukaemia, 3
	Haematological malignancy	
	Myelodysplastic syndrome	
	Transformation to leukaemia or myelodysplastic syndrome in chronic severe leukaemia patients (PT – chronic myeloid leukaemia transformation, myelodysplastic syndrome)	
	Malignant cell growth haematological malignancy and myelodysplastic syndrome) associated with G-CSF use in normal donors (PT – haematological malignancy, myelodysplastic syndrome);	
	Risk of haematological malignancies with G-CSF use in normal donors (PT: haematological malignancy)	
	Exacerbation of rheumatoid arthritis	Arthritis, 3
	Myalgia	
	Pseudogout (10/08/2011)	
	Haemoptysis	Pulmonary infiltrates, 3
	Pulmonary haemorrhage	
	Lung infiltrates	
	Interaction with lithium	Interaction with drugs, 2
	Interaction with myelosuppressive cytotoxic chemotherapy (decreased effectiveness of filgrastim)	
	Chronic graft *vs*. host disease	Graft *vs*. host disease, 3
	Acute graft *vs*. host disease	
	Graft *vs*. host disease	

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	Safety concerns as reported in summary of the RMP	General safety concern
	Graft *vs*. host disease in cancer patients	
	GvHD in recipients of allogeneic PBPC mobilized with filgrastim;	
	Graft *vs*. host disease (10/08/2011)	
	Acute respiratory distress syndrome	Severe pulmonary disorders, 3
	Respiratory failure	
	Pulmonary oedema	
	Cutaneous vasculitis	Serious skin conditions, 2
	Acute febrile neutrophilic dermatosis	
	Off-label use	General safety and long-term use, 2
	Long-term use	
	Capillary leak syndrome;	Cytokine release syndrome, 2
	Cytokine release syndrome	
	Capillary leak syndrome (30/10/2013)	
	Sickle cell anaemia with crisis (UNCHANGED)	Sickle cell anaemia with crisis, 1
	Use during pregnancy and lactation (potential risk)	Risks in pregnancy and lactation, 2
	Risks in pregnancy and lactation	
	Interstitial lung disease (UNCHANGED)	Interstitial lung disease, 1
	Safety concerns as reported in summary of RMP	**General safety concern**
Somatropin	Occurrence of malignancies in rhGH-treated patients	Neoplasms, 3
	New neoplasm	
	Second neoplasm in childhood cancer survivors	
	Occurrence and clinical implications of anti-rhGH antibodies	Immunogenicity, 1
	Risks of rhGH treatment in PWS patients	General risks in PWS patients, 1
	Pancreatitis (UNCHANGED)	Pancreatitis, 1
	Diabetogenic potential of rhGH therapy in short children born SGA	Diabetes, 1
	Intracranial aneurysm	Intracranial vascular disorders, 2
	Intracranial haemorrhage	
Follitropin-alfa	Immunogenicity which may manifest as lack of effect	Immunogenicity, 3
	Hypersensitivity	
	Anaphylactic reactions (22/7/14)	
	Ectopic pregnancy	Severe adverse pregnancy outcomes, 3
	Pregnancy loss	
	Neonatal congenital malformations;	
	Congenital abnormalities	
	Ovarian hyperstimulation syndrome (UNCHANGED)	Ovarian hyperstimulation syndrome, 1
	Multiple pregnancy (UNCHANGED)	Multiple pregnancy, 1
	Thrombotic events in women (UNCHANGED)	Thrombotic events in women, 1
	Asthma aggravated/exacerbation (UNCHANGED)	Asthma aggravated/exacerbation, 1
	Gynaecomastia in males (UNCHANGED)	Gynaecomastia in males, 1
	Reproductive system neoplasms in women;	Female reproductive neoplasm, 1
	Breast cancer;	
	Other reproductive system cancers (e.g. ovarian cancer, cervical cancer)	
	Potential porphyria with family history (UNCHANGED)	Potential porphyria with family history, 1
	Women older than 40 years (UNCHANGED)	Women older than 40 years, 1
Insulin glargine	Hypersensitivity reactions	Immunogenicity, 4
	Immunogenicity	
	Antigenicity	
	Injection site reactions	

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	Safety concerns as reported in summary of RMP	General safety concern
	More frequent injection site reactions less than 19 years old;	
	Hypoglycaemia (UNCHANGED)	Hypoglycaemia, 1
	Medication errors (incorrect insulin) (UNCHANGED)	Medication errors (incorrect insulin), 1
	Malignancies (UNCHANGED)	Malignancies, 1
	Use in pregnancy (UNCHANGED)	Use in pregnancy, 1
	Use in children younger than 2 years (UNCHANGED)	Use in children younger than 2 years, 1
Infliximab	Opportunistic infections	Infections, 9
	Serious infections including sepsis (excluding opportunistic infections and tuberculosis)	
	Tuberculosis	
	Intestinal or perianal abscess [in Crohn's disease (CD)]	
	Invasive fungal infections (06/03/09)	
	Parasitic infections (15/03/10)	
	Viral infections (27/04/10)	
	Risk of serious infections in elderly patients (29/11/10)	
	HBV reactivation;	
	HBV reactivation (24/7/07)	
	Serum sickness (delayed hypersensitivity reactions);	Immunogenicity, 3
	Hypersensitivity	
	Delayed hypersensitivity reactions	
	Infusion reactions; Serious infusion reactions during a reinduction regimen following disease flare;	
	Infusion reaction associated with shortened infusion duration (in RA)	
	Systemic lupus erythematosus	Autoimmune events, 7
	Autoimmune events	
	Stevens–Johnson Syndrome (18/10/07)	
	Toxic epidermal necrolysis (18/10/07)	
	Erythema multiforme (30/11/07)	
	Worsening of symptoms of dermatomyositis (25/7/13)	
	Demyelinating disorders;	
	Peripheral demyelinating diseases (18/6/08)	
	Paediatric malignancy	Neoplasms, 9
	Leukaemia	
	Malignancy (excluding lymphoma)	
	Colon carcinoma	
	Dysplasia (in UC)	
	Skin cancer	
	Melanoma (22/11/12)	
	Merkel cell carcinoma (22/11/12)	
	Lymphoma	
	Hepatosplenic T cell lymphoma (HSTCL)	
	Occurrence of lymphomas including HSTCL	
	HSTCL (04/07/06)	
	Long-term safety in adult patients with UC, psoriatic arthritis or psoriasis	Long-term use, 2
	Long-term safety in children with CD and UC;	
	Long-term safety in paediatric CD and UC patients (EPAR: 21/3/12)	
	Use of infliximab during lactation	Pregnancy and lactation exposure, 2
	Pregnancy exposure;	

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	Safety concerns as reported in summary of RMP	General safety concern
	In infants exposed to infliximab *in utero* (infection, preterm birth, low birth weight, very low birth weight, detection of infliximab up to 6 months postpartum in the serum of infants) (21/2/11)	
	Bowel stenosis, stricture, obstruction (in CD)	Bowel obstruction, 1
	Fibrotic stricture (5/12/2014)	
	Sarcoidosis/sarcoid-like reactions;	Sarcoidosis, 1
	Sarcoid-like reaction (29/11/10)	
	Interstitial lung disease (UNCHANGED)	Interstitial lung disease, 1
	Congestive heart failure;	Heart failures, 1
	Heart failure (10/01/05)	
	Lack of efficacy (UNCHANGED)	Lack of efficacy, 1
	Hepatobiliary events;	Hepatobiliary disorders, 1
	Hepatobiliary events (24/7/07)	
	Haematological reactions (UNCHANGED)	Haematological reactions, 1
	Neutropenia with concurrent use of Anakinra (27/04/10)	Interaction with other drugs, 2
	Administration of live vaccines and therapeutic infectious agents concurrently with Remicade (25/7/13)	

G-CSF, granulocyte colony-stimulating factor; HBV, hepatitis B virus; PT, preferred term; PWS, Prader–Willi syndrome; RA, rheumatoid arthritis; rhGH, recombinant human growth hormone; RMP, risk management plan; s.c., subcutaneous; SGA, small for gestational age; UC, ulcerative colitis

Appendix IIa

Comparison of general safety concerns extracted from summaries of risk management plans (RMPs) and documents for procedural steps taken and scientific information after the authorization of medicinal products

Boxes containing an 'x' indicate that the general safety concern is found in the summary of the RMP or document for procedural steps taken and scientific information after the authorization. Safety concerns (green background) that had similar descriptions were combined to a general safety concern (white background) as indicated in Appendix I. The originator is indicated with an asterisk. A date after the safety concern indicates that the safety issue is established in the document for procedural steps taken and scientific information after the authorization, and signifies when the risk was established.

Insulin glargine	Lantus*	Abasaglar
Malignancies	x	x
Malignancies	1	1
Hypoglycaemia	x	x
Hypoglycaemia	1	1
Hypersensitivity reactions	x	x
Injection site reactions	x	x
Antigenicity	x	
Immunogenicity		x
Immunogenicity	3	3

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Insulin glargine	Lantus*		Abasaglar
Medication errors (incorrect insulin)	x		x
Medication errors	1		1
Use in pregnancy	x		x
Use in pregnancy	1		1
Use in children younger than 2 years of age			x
Use in children younger than 2 years	0		1
Infliximab	**Remicade***	**Remsima**	**Inflectra**
Demyelinating disorders	x	x	x
Systemic lupus erythematosus		x	x
Autoimmune events	x		
Stevens–Johnson Syndrome (18/10/07)	x		
Toxic epidermal necrolysis (18/10/07)	x		
Erythema multiforme (30/11/07)	x		
Worsening of symptoms of dermatomyositis (25/7/13)	x		
Autoimmune events	6	2	2
Hepatitis B reactivation	x	x	x
Opportunistic infections	x	x	x
Serious infections including sepsis (excluding opportunistic infections and tuberculosis)	x	x	x
Tuberculosis	x	x	x
Invasive fungal infections (06/03/09)	x		
Parasitic infections (15/03/10)	x		
Viral infections (27/04/10)	x		
Intestinal or perianal abscess (in Crohn's disease)		x	x
Risk of serious infections in elderly patients (29/11/10)	x		
Infections	8	5	5
Interstitial lung disease (21/12/07)	x		
Interstitial lung disease	1	0	0
Sarcoidosis	x	x	x
Sarcoidosis	1	1	1
Heart failure	x	x	x
Heart failure	1	1	1
Lymphoma	x	x	x
Paediatric malignancy		x	x
Leukaemia		x	x
Malignancy (excluding lymphoma)		x	x
Colon carcinoma		x	x
Dysplasia		x	x
Melanoma (22/11/12)	x		
Merkel cell carcinoma (22/11/12)	x		
Skin cancer		x	x

(*continues*)

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(Continued)

Infliximab	Remicade*	Remsima	Inflectra
Neoplasms	3	7	7
Hepatobiliary disorders	x	x	x
Hepatobiliary disorders	1	1	1
Serum sickness	x	x	x
Infusion site reactions	x	x	x
Hypersensitivity		x	x
Immunogenicity	2	3	3
Bowel stenosis, stricture, obstruction (in Crohn's disease)		x	x
Bowel obstruction	0	1	1
Haematological reactions		x	x
Haematological reactions	0	1	1
Lack of efficacy		x	x
Lack of efficacy	0	1	1
Neutropenia with concurrent use of Anakinra (27/04/10)	x		
Administration of live vaccines and therapeutic infectious agents concurrently with Remicade (25/7/13)	x		
Interaction with drugs	2	0	0
Long-term safety in children	x	x	x
Long-term safety in adult patients with ulcerative colitis, psoriatic arthritis or psoriasis		x	x
Long-term use	1	2	2
Use of infliximab during lactation		x	x
Exposure during pregnancy	x	x	x
Pregnancy and lactation exposure	1	2	2

Appendix IIb

Comparison of general safety concerns extracted from summaries of risk management plans (RMPs) and documents for procedural steps taken and scientific information after the authorization of biosimilars compared with the Summary of Product Characteristics (SmPCs) of their originators

Boxes containing an 'x' indicate that the general safety concern is found in the summary of the RMP, document, procedural steps taken and scientific information after the authorization or SmPCs. Safety concerns (green background) that had similar descriptions were combined to a general safety concern (white background) as indicated in Appendix I. The originator is indicated with an asterisk. A date after the safety concern indicates that the safety issue is established in the document for procedural steps taken and scientific information after the authorization, and signifies when the risk was established.

Erythropoietins	Eprex* (EPO-alfa)	Binocrit (EPO-alfa)	Epoetin Alfa HEXAL (EPO-alfa)	Abseamed (EPO-alfa)	Silapo (EPO-zeta)	Retacrit (EPO-zeta)
PRCA	x	x	x	x	x	x
Increased risk of PRCA with subcutaneous administration in renal failure patients	x				x	x
PRCA	2	1	1	1	2	2
Tumour growth potential	x	x	x	x	x	x
Increased mortality (cancer patients)	x	x	x	x	x	x

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Erythropoietins	Eprex* (EPO-alfa)	Binocrit (EPO-alfa)	Epoetin Alfa HEXAL (EPO-alfa)	Abseamed (EPO-alfa)	Silapo (EPO-zeta)	Retacrit (EPO-zeta)
Neoplasms	2	2	2	2	2	2
Thrombotic vascular events	x	x	x	x	x	x
Relatively high target haemoglobin concentrations	x	x	x	x	x	x
Thrombotic vascular events	2	2	2	2	2	2
Potential off-label use regarding s.c. application in renal anaemia patients in respect of missing comparative data on safety and immunogenicity between HX575 and Erypo in these patients	x	x	x	x		
General safety and long-term use					x	x
General safety and long-term use	1	1	1	1	1	1

Somatropin	Genotropin*	Omnitrope
Pancreatitis (19/9/2013)	x	x
Pancreatitis	1	1
Diabetogenic potential of rhGH therapy in short children born SGA	x	x
Diabetes	1	1
Occurrence of malignancies in rhGH-treated patients	x	x
New neoplasm		x
Second neoplasm in childhood cancer survivors	x	x
Neoplasms	2	3
Intracranial aneurysm		x
Intracranial haemorrhage		x
Intracranial vascular disorders	0	2
Occurrence and clinical implications of anti-rhGH antibodies	x	x
Immunogenicity	1	1
Risks of rhGH treatment in PWS patients	x	x
General risks in PWS patients	1	1

Filgrastim	Neupogen*	Ratiograstim	Tevagrastim	Biograstim	Filgrastim HEXAL	Zarzio	Nivestim	Grastofil	Accofil
Haemoptysis	x						x	x	x
Lung infiltrates	x	x	x	x			x	x	x
Pulmonary haemorrhage	x							x	x
Pulmonary infiltrates	3	1	1	1	0	0	2	3	3
Respiratory failure	x	x	x	x					
Pulmonary oedema	x	x	x	x					
Acute respiratory distress syndrome	x	x	x	x	x	x	x	x	x
Severe pulmonary disorders	3	3	3	3	1	1	1	1	1
Transformation to leukaemia or myelodysplastic syndrome	x	x	x	x	x	x	x	x	x
Myelodysplastic syndrome	x						x	x	x
Haematological malignancy	x	x	x	x	x	x	x	x	x
Leukaemia	3	2	2	2	2	2	3	3	3
Capillary leak syndrome	x	x	x	x					x
Cytokine release syndrome									x

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Filgrastim	Neupogen*	Ratiograstim	Tevagrastim	Biograstim	Filgrastim HEXAL	Zarzio	Nivestim	Grastofil	Accofil
Cytokine release syndrome	1	1	1	1	0	0	0	0	2
Sickle cell anaemia with crisis	x	x	x	x			x	x	x
Sickle cell anaemia with crisis	1	1	1	1	0	0	1	1	1
Interstitial lung disease	x	x	x	x	x	x		x	x
Interstitial lung disease	1	1	1	1	1	1	0	1	1
Increased risk of chronic GvhD	x	x	x	x	x	x	x	x	x
Acute GvhD	x	x	x	x	x	x	x	x	x
GvhD	x	x	x	x	x	x	x	x	x
GvhD	3	3	3	3	3	3	3	3	3
Pseudogout (10/08/2011)	x				x	x			
Myalgia	x	x	x	x			x		
Exacerbation of rheumatoid arthritis	x	x	x	x	x	x	x	x	x
Arthritis	3	2	2	2	2	2	2	1	1
Osteoporosis	x	x	x	x	x	x	x	x	x
Bone pain	x						x		
Osteoporosis	2	1	1	1	1	1	2	1	1
Acute febrile neutrophilic dermatosis	x	x	x	x			x	x	x
Cutaneous vasculitis	x	x	x	x	x	x	x	x	x
Serious skin conditions	2	2	2	2	1	1	2	2	2
Hypersensitivity	x	x	x	x	x	x	x	x	x
Immunogenicity	x	x	x	x	x	x	x	x	x
Immunogenicity	2	2	2	2	2	2	2	2	2
Splenic rupture	x	x	x	x	x	x	x	x	x
Splenomegaly	x	x	x	x	x	x	x	x	x
Splenic complications	2	2	2	2	2	2	2	2	2
Interaction with lithium	x						x	x	x
Interaction with myelosuppressive cytotoxic chemotherapy (decreased effectiveness)	x						x		
Interaction with drugs	2	0	0	0	0	0	2	1	1
Risks in pregnancy and lactation	x				x	x		x	x
Risks in pregnancy and lactation	1	0	0	0	1	1	0	1	1
Off-label use		x	x	x			x	x	x
Long-term use							x	x	x
General safety and long-term use	0	1	1	1	0	0	2	2	2

Follitropin-alfa	Gonal-f*	Ovaleap	Bemfola
Pregnancy loss	x	x	
Ectopic pregnancy	x	x	x
Congenital anomaly in offspring	x	x	x
Adverse pregnancy outcomes	3	3	2

(*continues*)

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Follitropin-alfa	Gonal-f*	Ovaleap	Bemfola
Female reproductive neoplasm	x	x	x
Female reproductive neoplasm	1	1	1
Porphyria	x	x	
Potential porphyria with family history	1	1	0
Ovarian hyperstimulation syndrome	x	x	x
Ovarian hyperstimulation syndrome	1	1	1
Multiple pregnancy	x	x	x
Multiple pregnancy	1	1	1
Thrombotic events in women	x	x	x
Thrombotic events in women	1	1	1
Asthma aggravated/exacerbation	x	x	x
Asthma aggravated/exacerbation	1	1	1
Hypersensitivity	x	x	x
Immunogenicity which may manifest as lack of effect		x	x
Anaphylactic reactions	x		x
Immunogenicity	2	2	3
Gynaecomastia in males	x	x	x
Gynaecomastia in males	1	1	1
Women older than 40 years		x	x
Women older than 40 years	0	1	1

EPO, erythropoietin; GvhD, graft *vs*. host disease; PRCA, pure red cell aplasia; PWS, Prader–Willi syndrome; rhGH, recombinant human growth hormone; s.c., subcutaneous; SGA, small for gestational age

Appendix III

Safety information comparison between biosimilars and the corresponding originator Summary of Product Characteristics (SmPCs)

Boxes containing an 'x' indicate that a Medical Dictionary for Regulatory Activities (MedDRA) term is found in the SmPC. The originator is indicated with an asterisk.

Erythropoietins	Eprex* (EPO-alfa)	Binocrit (EPO-alfa)	Epoetin Alfa HEXAL (EPO-alfa)	Abseamed (EPO-alfa)	Silapo (EPO-zeta)	Retacrit (EPO-zeta)
Pure red cell aplasia	x	x	x	x	x	x
Thrombocythaemia	x	x	x	x	x	x
Hyperkalaemia	x	x	x	x	x	x
Headache	x	x	x	x	x	x
Convulsions	x	x	x	x	x	x
Dizziness					x	x
Cerebral haemorrhage					x	x
Hypersensitivity	x	x	x	x	x	x
Anaphylactic reaction	x	x	x	x	x	x
Venous and arterial thromboses	x	x	x	x	x	x
Aneurysms					x	x
Hypertension	x	x	x	x	x	x

(continues)

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(Continued)

Erythropoietins	Eprex* (EPO-alfa)	Binocrit (EPO-alfa)	Epoetin Alfa HEXAL (EPO-alfa)	Abseamed (EPO-alfa)	Silapo (EPO-zeta)	Retacrit (EPO-zeta)
Cough	x	x	x	x	x	x
Respiratory tract congestion	x	x	x	x	x	x
Diarrhoea	x	x	x	x	x	x
Nausea	x	x	x	x	x	x
Vomiting	x	x	x	x	x	x
Rash	x	x	x	x	x	x
Angioneurotic oedema	x	x	x	x	x	x
Urticaria	x	x	x	x	x	x
Arthralgia	x	x	x	x	x	x
Bone pain	x	x	x	x	x	x
Myalgia	x	x	x	x	x	x
Pain in extremity	x	x	x	x	x	x
Porphyria	x	x	x	x	x	x
Pyrexia	x	x	x	x	x	x
Chills	x	x	x	x	x	x
Influenza-like illness	x	x	x	x	x	x
Injection site reaction	x	x	x	x	x	x
Peripheral oedema	x	x	x	x	x	x
Drug ineffective	x	x	x	x	x	x
Weakness					x	x
Tiredness					x	x
General safety and long-term use	x	x	x	x	x	x
Total	29	29	29	29	34	34

Filgrastim	Neupogen*	Ratiograstim	Tevagrastim	Biograstim	Filgrastim HEXAL	Zarzio	Nivestim	Grastofil	Accofil
Splenic rupture	x	x	x	x	x	x	x	x	x
Splenomegaly	x	x	x	x	x	x	x	x	x
Sickle cell crisis	x				x	x		x	x
Graft *vs.* host disease	x				x	x		x	x
Drug hypersensitivity	x	x	x	x	x	x	x	x	x
Blood uric acid increase	x	x	x	x	x	x	x	x	x
Blood lactate dehydrogenase increase	x	x	x	x	x	x	x	x	x
Decreased appetite	x	x	x	x	x	x	x	x	x
Pseudogout	x	x	x	x	x	x	x	x	x
Headache	x	x	x	x	x	x	x	x	x
Hypotension	x	x	x	x	x	x	x	x	x
Veno-occlusive disease	x	x	x	x	x	x	x	x	x
Fluid volume disturbances	x	x	x	x	x	x	x	x	x
Capillary leak syndrome	x	x	x	x	x	x	x	x	x
Angiopathy							x		
Oropharyngeal pain	x	x	x	x	x	x	x	x	x

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(Continued)

Filgrastim	Neupogen*	Ratiograstim	Tevagrastim	Biograstim	Filgrastim HEXAL	Zarzio	Nivestim	Grastofil	Accofil
Cough	x	x	x	x	x	x	x	x	x
Dyspnoea	x				x	x		x	x
Haemoptysis	x				x	x		x	x
Lung infiltration	x	x	x	x	x	x	x	x	x
Pulmonary haemorrhage	x				x	x		x	x
Respiratory failure	x				x	x		x	x
Pulmonary oedema	x				x	x		x	x
Acute respiratory distress syndrome	x				x	x		x	x
Interstitial lung disease	x				x	x		x	x
Diarrhoea	x	x	x	x	x	x	x	x	x
Vomiting	x	x	x	x	x	x	x	x	x
Constipation	x	x	x	x	x	x	x	x	x
Nausea	x	x	x	x	x	x	x	x	x
Gamma-glutamyl transferase increase	x	x	x	x	x	x	x	x	x
Blood alkaline phosphatase increase	x				x	x		x	x
Rash	x	x	x	x	x	x	x	x	x
Alopecia	x	x	x	x	x	x	x	x	x
Sweet's syndrome	x	x	x	x	x	x	x	x	x
Cutaneous vasculitis	x	x	x	x	x	x	x	x	x
Musculoskeletal pain	x	x	x	x	x	x	x	x	x
Exacerbation of rheumatoid arthritis	x	x	x	x	x	x	x	x	x
Dysuria	x				x	x		x	x
Urine abnormality	x	x	x	x	x	x	x	x	x
Glomerulonephritis	x								
Asthenia	x	x	x	x	x	x	x	x	x
Fatigue	x	x	x	x	x	x	x	x	x
Mucosal inflammation	x	x	x	x	x	x	x	x	x
Pain	x	x	x	x	x	x	x	x	x
Total	43	31	31	31	42	42	32	42	42

Somatropin	Genotropin*	Omnitrope
Leukaemia	x	x
Type 2 diabetes mellitus	x	x
Paraesthesia	x	x
Carpal tunnel syndrome	x	x
Benign intracranial hypertension	x	x
Arthralgia	x	x
Myalgia	x	x
Musculoskeletal stiffness	x	x
Injection site reaction	x	x
Peripheral oedema	x	x
Blood cortisol decrease	x	x

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(Continued)

Somatropin	Genotropin*		Omnitrope
Total	11		11
Follitropin-alfa	**Gonal-f***	**Ovaleap**	**Bemfola**
Mild to severe hypersensitivity reactions including anaphylactic reactions and shock	x	x	x
Headache	x	x	x
Thromboembolism associated with severe OHSS	x	x	x
Exacerbation or aggravation of asthma	x	x	x
Abdominal pain	x	x	x
Abdominal distension	x	x	x
Abdominal discomfort	x	x	x
Nausea	x	x	x
Vomiting	x	x	x
Diarrhoea	x	x	x
Ovarian cysts	x	x	x
OHSS	x	x	x
Injection site reactions	x	x	x
Total	13	13	13
Insulin glargine	**Lantus***		**Abasaglar**
Allergic reactions	x		x
Hypoglycaemia	x		x
Dysgeusia	x		x
Visual impairment	x		x
Retinopathy	x		x
Lipohypertrophy	x		x
Lipoatrophy	x		x
Myalgia	x		x
Injection site reactions	x		x
Oedema	x		x
Total	10		10
Infliximab	**Remicade***	**Remsima**	**Inflectra**
Viral infections	x	x	x
Bacterial infections	x	x	x
Tuberculosis	x	x	x
Fungal infections	x	x	x
Meningitis	x	x	x
Opportunistic infections	x	x	x
Viral infections	x	x	x
Hepatitis B reactivation	x	x	x
Parasitic infections	x	x	x
Lymphoma	x	x	x
Non-Hodgkin's lymphoma	x	x	x
Hodgkin's disease	x	x	x

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(Continued)

Infliximab	Remicade*	Remsima	Inflectra
Leukaemia	x	x	x
Melanoma	x	x	x
Cervical cancer	x		
Hepatosplenic T-cell lymphoma	x	x	x
Merkel cell carcinoma	x	x	x
Neutropenia	x	x	x
Leukopenia	x	x	x
Anaemia	x	x	x
Lymphadenopathy	x	x	x
Thrombocytopenia	x	x	x
Lymphopenia	x	x	x
Lymphocytis	x	x	x
Agranulocytosis	x	x	x
Thrombotic thrombocytopenic purpura	x	x	x
Haemolytic anaemia	x	x	x
Idiopathic thrombocytopenic purpura	x	x	x
Anaphylactic reaction	x	x	x
Lupus-like syndrome	x	x	x
Serum sickness	x	x	x
Anaphylactic shock	x	x	x
Vasculitis	x	x	x
Sarcoid osis	x	x	x
Depression	x	x	x
Insomnia	x	x	x
Amnesia	x	x	x
Agitation	x	x	x
Confusion	x	x	x
Somnolence	x	x	x
Nervousness	x	x	x
Apathy	x	x	x
Headache	x	x	x
Vertigo	x	x	x
Dizziness	x	x	x
Hypoaesthesia	x	x	x
Paraesthesia	x	x	x
Seizure	x	x	x
Neuropathy	x	x	x
Transverse myelitis	x	x	x
Demyelinating disorders	x	x	x
Conjunctivitis	x	x	x
Keratitis	x	x	x

(*continues*)

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(Continued)

Infliximab	Remicade*	Remsima	Inflectra
Endophthalmitis	x	x	x
Tachycardia	x	x	x
Palpitations	x	x	x
Cardiac failure	x	x	x
Arrhythmia	x	x	x
Syncope	x	x	x
Bradycardia	x	x	x
Cyanosis	x	x	x
Pericardial effusion	x	x	x
Hypotension	x	x	x
Hypertension	x	x	x
Ecchymosis	x	x	x
Flushes	x	x	x
Peripheral ischaemia	x	x	x
Thrombophlebitis	x	x	x
Haematoma	x	x	x
Circulatory failure	x	x	x
Petechia	x	x	x
Vasospasm	x	x	x
Sinusitis	x	x	x
Dyspnoea	x	x	x
Epistaxis	x	x	x
Pulmonary oedema	x	x	x
Bronchospasm	x	x	x
Pleurisy	x	x	x
Pleural effusion	x	x	x
Interstitial lung disease	x	x	x
Abdominal pain	x	x	x
Nausea	x	x	x
Gastrointestinal haemorrhage	x	x	x
Diarrhoea	x	x	x
Dyspepsia	x	x	x
Gastroesophageal reflux	x	x	x
Constipation	x	x	x
Intestinal perforation	x	x	x
Intestinal stenosis	x	x	x
Diverticulitis	x	x	x
Pancreatitis	x	x	x
Cheilitis	x	x	x
Hepatic function abnormal	x	x	x
Transaminase increase	x	x	x

(*continues*)

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(Continued)

Infliximab	Remicade*	Remsima	Inflectra
Hepatitis	x	x	x
Hepatocellular damage	x	x	x
Cholecystitis	x	x	x
Autoimmune hepatitis	x	x	x
Jaundice	x	x	x
Psoriasis	x	x	x
Urticaria	x	x	x
Rash	x	x	x
Pruritis	x	x	x
Hyperhidrosis	x	x	x
Dry skin	x	x	x
Fungal dermatitis	x	x	x
Eczema	x	x	x
Alopecia	x	x	x
Bullous eruption	x	x	x
Onychomycosis	x	x	x
Seborrhoea	x	x	x
Rosacea	x	x	x
Skin papilloma	x	x	x
Hyperkeratosis	x	x	x
Abnormal skin pigmentation	x	x	x
Toxic epidermal necrolysis	x	x	x
Stevens–Johnson syndrome	x	x	x
Erythema multiforme	x	x	x
Furunculosis	x	x	x
Arthralgia	x	x	x
Myalgia	x	x	x
Back pain	x	x	x
Urinary tract infection	x	x	x
Pyelonephritis	x	x	x
Vaginitis	x	x	x
Infusion-related reaction	x	x	x
Fatigue	x	x	x
Fever	x	x	x
Chills	x	x	x
Oedema	x	x	x
Impaired healing	x	x	x
Granulomatous lesion	x	x	x
Autoantibody positive	x	x	x
Complement factor abnormal	x	x	x
Total	134	133	133

EPO, erythropoietin; OHSS, ovarian hyperstimulation syndrome

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References

1 Barake M, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. J Clin Endocrinol Metab 2014; 99: 852–60.

2 O'Sullivan CC, Bradbury I, Campbell C, Spielmann M, Perez EA, Joensuu H, *et al*. Efficacy of adjuvant trastuzumab for patients with human epidermal growth factor receptor 2 – positive early breast cancer and tumors ≤ 2 cm: a meta-analysis of the randomized trastuzumab trials. J Clin Oncol 2015; 33: 2600–8.

3 Crommelin DJA, Storm G, Verrijk R, de Leede L, Jiskoot W, Hennink WE. Shifting paradigms: biopharmaceuticals versus low molecular weight drugs. Int J Pharm 2003; 266: 3–16.

4 Pharmaceutical Research and Manufacturers of America. Biopharmaceutical research industry profile 2015 [online]. Available at http://www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf (last accessed 1 April 2016).

5 European Parliament. Directive 2001/83/EC. Off J Eur communities. 2000; L 269: 1–15.

6 Halim LA, Brinks V, Jiskoot W, Romeijn S, Haselberg R, Burns C, *et al*. Quality and batch-to-batch consistency of original and biosimilar epoetin products. J Pharm Sci 2016; 105: 542–50.

7 Ben-Horin S, Heap GA, Ahmad T, Kim HO, Kwon T, Chowers Y. The immunogenicity of biosimilar infliximab: can we extrapolate the data across indications? Expert Rev Gastroenterol Hepatol 2015; 9 (Suppl. 1): 27–34.

8 Mellstedt H. Clinical considerations for biosimilar antibodies. EJC Suppl 2013; 11: 1–11.

9 Committee for Medicinal Products for Human Use (EMA). Guideline on similar biological medicinal products. 2014. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf (last accessed 1 December 2015).

10 World Health Organization (WHO). International nonproprietary names (INN) for biological and biotechnological substances (a review). INN Working Document 05.179, Update 2013. Available at http://www.who.int/medicines/services/inn/BioRev2013.pdf (last accessed 1 December 2015).

11 World Health Organization Collaborating Centre for Drug Statistics Methodology. Structure and principles [online]. Available at http://www.whocc.no/atc/structure_and_principles/ (last accessed 1 April 2016).

12 Committee for Medicinal Products for Human Use (CHMP). Guideline. Guideline on similar biological medicinal products containing monoclonal antibodies – non clinical and clinical issues. EMA/CHMP/BMWP/403543/2010. 2012. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf (last accessed 1 December 2015).

13 Committee for Medicinal Products for Human Use (CHMP). uideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005. London. 2006. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003953.pdf (last accessed 1 December 2015).

14 Emmanouilides CE, Karampola MI, Beredima M. Biosimilars: hope and concern. J Oncol Pharm Pract 2015; 22: 618–24.

15 Reinisch W, Louis E, Danese S. The scientific and regulatory rationale for indication extrapolation: a case study based on the infliximab biosimilar CT-P13. Expert Rev Gastroenterol Hepatol 2015; 9 (Suppl. 1): 17–26.

16 Patel PK, King CR, Feldman SR. Biologics and biosimilars. J Dermatolog Treat 2015; 26: 299–302.

17 QuintilesIMS. The impact of biosimilar competition in Europe. 2017 [online]. Available at http%3A%2F%2Fec.europa.eu%2Fgrowth%2Ftools-databases%2Fnewsroom%2Fcf%2Fitemdetail.cfm%3Fitem_id%3D9146%26amp%3Blang%3Den Available at http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V9.pdf (last accessed 5 August 2017).

18 Ingrasciotta Y, Giorgianni F, Marcianò I, Bolcato J, Pirolo R, Chinellato A, *et al*. Comparative effectiveness of biosimilar, reference product and other erythropoiesis-stimulating agents (ESAs) still covered by patent in chronic kidney disease and cancer patients: an Italian population-based study. PLoS One 2016; 11: e0155805.

19 Generics and Biosimilars Initiative. Biosimilars use in Europe varies widely [online]. July 30, 2015. Available at www.gabionline.net (last accessed 5 August 2017).

20 Trotta F, Mayer F, Mecozzi A, Amato l, Addis A. Impact of guidance on the prescription patterns of G-CSFs for the prevention of febrile neutropenia following anticancer chemotherapy: a population-based utilization study in the Lazio region. BioDrugs 2017; 31: 117–24.

21 Yoo DH. The rise of biosimilars: potential benefits and drawbacks in rheumatoid arthritis. Expert Rev Clin Immunol 2014; 10: 981–3.

22 Cortés J, Curigliano G, Diéras V. Expert perspectives on biosimilar monoclonal antibodies in breast cancer. Breast Cancer Res Treat 2014; 144: 233–9.

23 Aapro MS. What do prescribers think of biosimilars? Target Oncol 2012; 7: Suppl 1: S51–5.

24 Kozlowski S, Woodcock J, Midthun K, Sherman RB. Developing the nation's biosimilars program. N Engl J Med 2011; 363: 1–3.

25 European Medicines Agency. Biosimilars in the EU, information guide for healthcare professionals. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf (last accessed 1 December 2015).

26 Weise M, Kurki P, Wolff-Holz E, Bielsky MC, Schneider CK. Biosimilars: the science of extrapolation. Blood 2014; 124: 3191–6.

27 European Medicines Agency. Guidance on format of the risk management plan (RMP) in the EU part II: module SVII – identified and potential risks. EMA/714754/2012. 2012. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/11/WC500134659.pdf (last accessed 1 December 2015).

28 Electronic Medicines Compendium [online]. Available at https://www.medicines.org.uk/emc/ (last accessed 15 December 2015).

29 Ebbers HC, Mantel-Teeuwisse AK, Moors EHM, Schellekens H, Leufkens HG. Today's challenges in pharmacovigilance: what can we learn from epoetins? Drug Saf 2011; 34: 273–87.

30 Carel JC, Ecosse E, Landier F, Meguellati-Hakkas D, Kaguelidou F, Rey G, *et al*. Long-term mortality after recombinant growth hormone treatment for isolated growth

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hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. J Clin Endocrinol Metab 2012; 97: 416–25.

31 European Medicines Agency. Steps taken and scientific information after the authorisation. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000607/WC500043694.pdf (last accessed 1 November 2015).

32 European Medicines Agency. Assessment report for Omnitrope. EMA/164541/2012. 2012. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000607/WC500137237.pdf (last accessed 1 February 2016).

33 European Medicines Agency. Questions and answers on the review of somatropin-containing medicines. EMA/966325/2011. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Modafinil/human_referral_000236.jsp (last accessed 1 February 2016).

34 Committee for Medicinal Products for Human Use. Somatropin – article 107 referral. Reference Assessment Report 2012; annex IV: 67–8.. Ref Assess Rep [online]. 2012; annex IV: 67–8 [online]. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/somatropin_107/WC500125919.pdf (last accessed 1 February 2016).

35 Medice Arzneimittel Pütter GmbH & Co KG. Summary of product characteristics; Abseamed [online]. Available at https://ec.europa.eu/health/documents/community-register/2016/20160330134537/anx_134537_en.pdf (last accessed 1 November 2016): 10–16.

36 Sandoz GmbH. Summary of product characteristics; Binocrit [online]. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000725/WC500053680.pdf (last accessed 1 November 2016): 10–16.

37 Hexal AG. Summary of product characteristics; Epoetin alfa Hexal [online]. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000726/WC500028282 (last accessed 1 November 2016): 10–16.

38 Pharmacovigilance Risk Assessment Committee. PRAC signal recommendations requesting an update of the product information. EMA/PRAC/720475/2013/Rev. 1. 2014. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/11/WC500156098.pdf (last accessed 1 February 2016).

39 European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). EMA/838713/2011 Rev 1* (superseded version). 2014. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/03/WC500224570.pdf (last accessed 1 February 2016).

40 Vermeer NS, Duijnhoven RG, Straus SMJM, Mantel-Teeuwisse AK, Arlett PR, Egberts ACG, *et al*. Risk management plans as a tool for proactive pharmacovigilance: a cohort study of newly approved drugs in Europe. Clin Pharmacol Ther 2014; 96: 723–31.

41 European Medicines Agency. Questions and answers on the risk management plan (RMP) summary. EMA/156738/2014. 2014. Available at http://www.drugsafety.pl/PRAWO/GPV/GPV_RMP_summary.pdf (last accessed 1 February 2016).

42 Chingcuanco F, Segal JB, Kim SC, Alexander GC. Bioequivalence of biosimilar tumor necrosis factor-α inhibitors compared with their reference biologics: a systematic review. Ann Intern Med 2016; 165: 565–74.

13652125, 2018, 4, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.13454 by Utrecht University Library, Wiley Online Library on [18/10/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License