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SHORT COMMUNICATION

Classification of Recombinant Biologics in the EU: Divergence Between National Pharmacovigilance Centers

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Abstract

Background and Objective Biological medicinal products (biologics) are subject to specific pharmacovigilance requirements to ensure that biologics are identifiable by brand name and batch number in adverse drug reaction (ADR) reports. Since Member States collect ADR data at the national level before the data is aggregated at the European Union (EU) level, it is important that an unambiguous understanding of which medicinal products belong to the biological product category exists. This study aimed to identify the level of consistency between Member States regarding the classification of biologics by national authorities responsible for ADR reporting.

Methods A sample list of recombinant biologics from the European Medicines Agency database of European Public Assessment Reports was created to analyze five Member States (Belgium, the Netherlands, Spain, Sweden, and the UK) according to which products were classified as biologics by each Member State. We calculated the Fleiss kappa value to analyze interrater reliability.

Results A considerable divergence was identified regarding the classification of the 146 recombinant biologics from the sample list: one Member State classified 100 % of the recombinant biologics from the sample list as biologics, whereas the classification rates in the remaining four Member States ranged between 70 and 88 % for products available on the national market. The interrater reliability for 87 products available on the market in all five Member States was considered poor.

Conclusion Discrepancies exist between Member States in the classification of biologics; less divergence exists for common well-known biologics. These findings highlight the need to think about the best approaches to translate EU legislation into national practices. Additionally, we recommend a publicly available and frequently updated list of centrally authorized biologics.

Key Points

The European pharmacovigilance system for biologics requires a common understanding of which medicinal products are classified as biologics.

Divergence exists between European Union (EU) Member States with regard to which medicinal products are classified as biologics and are subject to the specific pharmacovigilance requirements for biologics.

Provision of more accurate guidelines and support to EU Member States could solve the issue; however, more consideration is needed with regard to EU regulations that depend on aligned actions of Member States.

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1 Introduction

Biological medicinal products (biologics) are complex medicinal products obtained from natural sources, such as humans, animals, or microorganisms. Biologics differ from other medicines by the use of living cells, the complexity of the manufacturing process, and the highly complex structures of the biological products [1, 2]. A subset of biologics is the recombinant biologics, which are produced by genetic engineering techniques [3]. In 1982, the first recombinant biologic, a human insulin produced in *Escherichia coli*, was introduced on the European Union (EU) market under the brand name Humulin® [4]. Since then, more than 100 recombinant biologics have been introduced, with the number of new market authorizations still increasing each year.

Biologics are sensitive to changes in the manufacturing process: small alterations—for example, to improve product properties or product yield—may influence the safety characteristics of the biological product and can result in batch-to-batch variations [5, 6]. For this reason, biologics are subject to specific regulations and guidelines. In the EU, for example:

- To reduce product-to-product variations, the regulatory approval pathway for follow-on biological medicinal products (biosimilars) differs from the approval pathway for small-molecule follow-on products (generics). For biosimilars, clinical data are required to demonstrate their similarity in terms of quality, safety, and efficacy [7].
- To reduce batch-to-batch variations, biologics undergo much stricter manufacturing requirements than small-molecule medicines, thus minimizing the chance of product variations during the life cycle of the biologic [8, 9].

In light of the above, the pharmacovigilance requirements in place for biologics in the EU differ from those for small molecules. The Pharmacovigilance Directive (Directive 2001/83/EC) dictates that all EU Member States shall ensure that a biological medicinal product that is the subject of a suspected adverse drug reaction (ADR) report is identified by the (brand) name of the medicinal product and the batch number [10].

Since Member States collect ADR data at the national level, a consistent and uniform approach to pharmacovigilance activities is needed in order to maintain European alignment. For biologics, this consistent and uniform approach starts with an unambiguous understanding of which medicinal products belong to the biological product category. However, no comprehensive list of approved biologics in the EU is readily available from an authoritative source (e.g. the European Medicines Agency [EMA] website). This could possibly lead to divergence between Member States on what is regarded as a biologic at the national level. The aim of this study was therefore to identify the level of consistency between EU Member States with regard to the classification of biologics by the authorities responsible for ADR reporting at the national level.

2 Methods

2.1 Products Included in the Analysis

Since no predefined list of approved biologics in the EU is readily available, we had to define the scope of our analyses first. For the purpose of this study, we decided to focus on recombinant biologics because clear definitions are available for this subset of biologics [11]. A sample list of recombinant biologics was created in two steps, based on the EMA database of European Public Assessment Reports (EPARs) of centrally approved medicinal products. As a first step, we screened the title of Annex II-A of the product information in the EPAR to select a group of candidate biologics. If the title contained the text "Manufacturers of the biological active substance…" we assumed the product was a biologic. As a second step, to select recombinant biologics, we screened Section 2 of the Summary of Product Characteristics (SmPC) "Qualitative and quantitative composition" chapter to assess whether it mentioned recombinant manufacturing techniques. The criteria for inclusion on our sample list were the mentioning of recombinant DNA (rDNA) manufacturing methods and/or the naming of the cell line used in the manufacturing process. Seven recombinant biologics (four somatropins, one epoetin alfa, one insulin human, and one filgrastim) were added to the list because they were approved prior to 1995 (before the EMA started its activities) and are still commonly used in clinical practice. Recombinant vaccines were excluded because vaccines are subject to specific pharmacovigilance practices. The sample list of recombinant biologics was categorized into 11 product classes based on the international nonproprietary names (INNs) and/or anatomical therapeutic chemical (ATC) classifications. We used an extraction of medicinal products from the EMA database on 30 November 2014. The full list can be found in Table S1 in the Electronic Supplementary Material.

2.2 Member States Included in the Analysis

We selected five different national pharmacovigilance centers from EU Member States that take specific measures

to allow the reporter of an ADR (e.g. a physician, patient, or pharmacist) to ascertain that the suspected medicinal product is a biologic: Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG), Belgium; Netherlands Pharmacovigilance Centre Lareb, the Netherlands; Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Spain; Medical Products Agency (MPA), Sweden; and Medicines and Healthcare Products Regulatory Agency (MHRA) Yellow Card Scheme, UK. This ascertainment can be done actively, by notifying the reporter in the online ADR reporting form that the submitted medicinal product is a biologic (through a pop-up feature asking the reporter to provide the batch number), or passively by maintaining a list of biologics on the website, which can be consulted by the reporter. Of the selected Member States, the Netherlands and the UK have implemented an active notification feature; the national pharmacovigilance centers in Belgium, Spain, and Sweden maintain a list of biologics on their website [12–14]. For the purpose of this study, we did not distinguish between active and passive notification features, since both notification features serve the same purpose and were equally suitable for our analysis.

2.3 Analysis of Biologic Classifications in Member States

We assessed which of the products on our sample list of recombinant biologics were classified as biologics in the five selected Member States according to the active or passive methods described above. We limited our analysis to recombinant biologics that were marketed in the respective Member States. To determine which biologics were available on the market in the Netherlands, the UK, and Spain, we assumed that the ability to report a biologic in their respective online ADR reporting forms is an indicator of their availability.[1] For Belgium and Sweden, a list of medicinal products available on the national market was consulted [15, 16]. All analyses were conducted on the basis of the situation on 19 February 2015.

Results were reported as the proportions of biologics from our sample list of recombinant products that were classified as biologics in each Member State. Subanalyses for specific individual biologics and product classes were conducted. We calculated the Fleiss kappa value to assess interrater reliability regarding the classification of the recombinant biologics from our sample list that were available on the market in all five Member States [17]. We anonymized the Member States in this analysis, since the objective of this study was to highlight the diversity in the classification of biologics in different Member States, rather than to judge individual Member States.

[1] The online reporting forms in the Netherlands, the UK, and Spain consist of an autocomplete function, which allows identification of the medicinal products available in the national reporting form.

3 Results

Table 1 shows that one Member State (State E) has classified 100 % of the recombinant biologics that are on our sample list and are available on their national market as biologics, whereas the remaining Member States (States A–D) have classified between 70 and 88 % on this metric. In addition, State E is the only Member State that has all recombinant biologics from the sample list available on its national market.

During the comparison of different product classes, it was observed that the somatropins are the only product class classified as biologics by all Member States. In contrast to the somatropins, the percentages of the follitropins classified as biologics vary from 0 to 100 %. For the recombinant biologics that do not belong to a distinct product class (other), the percentages of the recombinant biologics from our sample list that are classified as biologics vary between 31 and 81 % for the Member States, with the exception of State E (classification rate 100 %).

An assessment of individual product classes reveals that class-specific differences between Member States exist. For example, State A has classified 92 % of the 13 nationally available insulins as biologics, whereas State B has classified 30 % of the 10 insulins available on its market as biologics. However, of the 33 monoclonal antibodies available in State A, 45 % have been classified as biologics, whereas State B has classified 92 % of the 26 monoclonal antibodies available on its national market as biologics.

Of the 146 recombinant biologics on our sample list, 87 were available on the national markets of all five Member States. Fifty-one (59 %) of these 87 recombinant biologics were classified as biologics by all five Member States. Of the remaining 36 recombinant biologics, 25 were classified as biologics by four Member States, seven by three Member States, and four by two Member States (Table 2). The Fleiss kappa value for these 87 recombinant biologics is 0.0782. We interpret this as poor agreement among the Member States regarding the classification of these 87 recombinant biologics that are marketed in all five Member States [18].

4 Discussion

The results of this study show that there is considerable divergence between a selected group of EU Member States with regard to which medicinal products are classified as

Table 1 Overview of the percentages and numbers of marketed recombinant biologics classified as biologics in each Member State's national pharmacovigilance system

Product class	N[a]	Classification of marketed biologics as biologics [% (n)][b]				
		Member State A	Member State B	Member State C	Member State D	Member State E
Somatropins	7	100 (6)	100 (6)	100 (5)	100 (5)	100 (7)
Epoetins	11	100 (7)	88 (8)	100 (6)	100 (7)	100 (11)
Filgrastims	11	83 (6)	100 (8)	67 (6)	88 (8)	100 (11)
Follitropins	7	60 (5)	0 (4)	75 (4)	86 (7)	100 (7)
Monoclonal antibodies	35	45 (33)	92 (26)	89 (28)	74 (35)	100 (35)
Insulins	19	92 (13)	30 (10)	100 (10)	100 (13)	100 (19)
Interferons	9	100 (6)	100 (8)	86 (7)	89 (9)	100 (9)
Antihemophilic factors	8	86 (7)	100 (6)	100 (6)	88 (8)	100 (8)
Fusion proteins	5	40 (5)	67 (3)	75 (4)	80 (5)	100 (5)
Enzymes	13	91 (11)	58 (12)	91 (11)	91 (11)	100 (13)
Other	21	53 (17)	31 (16)	75 (12)	81 (21)	100 (21)
Total	146	70 (116)	71 (107)	88 (99)	85 (129)	100 (146)

[a] N is the number of recombinant biologics on our sample list

[b] n is the number of recombinant biologics available on the national market

biologics in their national pharmacovigilance systems. For this topic, it is particularly relevant that national pharmacovigilance practices should be aligned with the EU pharmacovigilance requirements, in order to facilitate timely and accurate ADR signal detection [19]. It seems that less divergence exists for common well-known biologics. For example, of the 51 recombinant biologics from our sample list that are classified as biologics by all five Member States, 31 (61 %) were listed among the top 50 best-selling biologics in the EU and the USA in 2010 [20]. Of the 11 recombinant biologics that were classified as biologics by only two or three Member States, seven (64 %) had been approved by the EMA since 2009. Besides potential limited familiarity with recently introduced recombinant biologics, another reason for this finding could be lack of frequent updates of the national product lists and databases. Three of the four recombinant biologics (75 %) that were classified as biologics by only two Member States are orphan medicines, which may support the hypothesis that biologics rarely used in clinical practice are less likely to be classified as biologics in pharmacovigilance systems.

There are certain limitations that apply to this study. First, we were able to include only a limited number of EU Member States in our analysis, which may have introduced bias and influenced our findings. We also examined national pharmacovigilance centers in other Member States by directly accessing their (online) ADR reporting forms and/or by approaching the national pharmacovigilance centers by e-mail to ask if specific measures have been taken. The majority of the national pharmacovigilance centers did not have an active or passive notification feature, or they were not directly accessible (e.g. because of the requirement for a national ID for access, error messages, or translation issues) and therefore were not included in the analysis. When contacted, several Member States responded that currently there is no comprehensive and centrally obtainable list of all approved biologics available in the EU. The five Member States that were included in this analysis have a long tradition in the field of pharmacovigilance and have been part of the EU regulated space since the launch of the EMA. We therefore expect that the divergence might even increase with more Member States being included in the analysis.

Second, we assumed that the ability to report a recombinant biologic via the online ADR reporting form indicates its availability. However, we do not know exactly how national drug lists are created and how they are linked to online ADR reporting forms. Although we made this assumption, we believe this provided a reasonable estimation of the recombinant biologics available on the market and appropriate to be considered for the analysis in individual Member States.

Third, there may be a time lag between the introduction of a recombinant biologic to the EU market and its classification as a biologic in the national reporting system of each Member State. We did not explore that possibility in this study. However, the discrepancies we identified were not limited to recombinant biologics recently introduced to the EU market.

Fourth, the sample list of recombinant biologics that we created for this study may not have been complete. Since this was a manual exercise, we might have overlooked some recombinant biologics in the EMA database. This

Table 2 Overview of the 87 recombinant biologics marketed in all Members States and the numbers of Member States classifying each one as a biologic in their national pharmacovigilance systems, sorted by product class

Product class	Number of Member States classifying marketed biologics as biologics			
	5 Member States ($N = 51$)[a]	4 Member States ($N = 25$)[a]	3 Member States ($N = 7$)[a]	2 Member States ($N = 4$)[a]
Somatropins	Somatropin ($n = 5$)[b]			
Epoetins	Darbepoetin alfa	Methoxy polyethylene glycol-epoetin beta		
	Epoetin alfa ($n = 2$)[b]			
	Epoetin beta			
	Epoetin zeta			
Filgrastims	Pegfilgrastim	Filgrastim		
	Filgrastim ($n = 3$)[b]			
Follitropins		Follitropin alfa	Corifollitropin alfa	Follitropin alfa/lutropin alfa
		Follitropin beta		
Monoclonal antibodies	Bevacizumab	Certolizumab pegol	Belimumab	Brentuximab vedotin
	Cetuximab	Canakinumab	Ipilimumab	
	Trastuzumab	Denosumab ($n = 2$)[b]		
	Adalimumab	Tocilizumab		
	Ranibizumab	Golimumab		
	Rituximab	Ustekinumab		
	Infliximab			
	Basiliximab			
	Eculizumab			
	Palivizumab			
	Natalizumab			
	Panitumumab			
	Omalizumab			
	Ibritumomab tiuxetan			
Insulins	Insulin human ($n = 2$)[b]	Insulin glulisine		
		Insulin lispro		
		Insulin glargine		
		Insulin detemir		
		Insulin aspart ($n = 2$)[b]		
Interferons	Interferon alfa-2b			
	Interferon beta-1a ($n = 2$)[b]			
	Interferon beta-1b			
	Peginterferon alfa-2a			
	Peginterferon alfa-2b			
Antihemophilic factors	Eptacog alfa (activated)			
	Octocog alfa ($n = 3$)[b]			
	Moroctocog alfa			
	Nonacog alfa			
Fusion proteins	Etanercept			
	Abatacept			
Enzymes	Idursulfase	Laronidase	Velaglucerase alfa	
	Agalsidase beta	Imiglucerase		
	Alglucosidase alfa	Rasburicase		
	Galsulfase	Tenecteplase		
	Agalsidase alfa	Reteplase		
Other	Palifermin	Thyrotropin alfa	Teriparatide	Mecasermin
	Choriogonadotropin alfa	Dibotermin alfa	Lutropin alfa	Romiplostim
		Pegvisomant	Liraglutide	

[a] N is the total number of marketed biologics classified as biologics by the specified number of Member States

[b] n is the number of recombinant biologics that share the same international nonproprietary name (INN) and are classified by the specified number of Member States

could have skewed the percentages of classification of biologics in the results, although presumably in a limited fashion and most likely nondifferential to the outcome. Furthermore, we included only recombinant biologics in our analysis, although this topic concerns biologics in general.

In the end, the purpose of this study was to assess the level of consistency between EU Member States with regard to which medicinal products are classified as biologics in national pharmacovigilance systems. As stated earlier, our aim was not to take a judgmental view on the appropriateness of the classification of biologics in Member States but to highlight an issue in the area of the pharmacovigilance of biologics that is relevant from an EU perspective. For the topic at hand, a feasible solution would be a publicly available and frequently updated list of centrally authorized biologics. This would help to improve the EU pharmacovigilance system by facilitating alignment of EU Member States in the classification of biologics.

From a broader perspective, these findings also highlight the need to think about the best approaches to translate EU legislation into national practices. As seen in the results, discrepancies between Member States are especially critical for EU-wide regulatory approaches, which call for harmonization of national regulatory requirements and practices.

5 Conclusion

The pharmacovigilance system in the EU requires a harmonized method of classification of biologics in order to make aggregated data sets, such as Eudravigilance, of the highest value [21]. As this study shows, there are considerable discrepancies between Members States in the classification of which medicinal products are biologics, which may influence the quality and quantity of the available aggregated data and hence may hamper tailored pharmacovigilance for biologics. Although this divergence can be (and should be) easily resolved, we would like to encourage policy makers to consider how we can make sure that EU regulation in the area of medicines, which depends on aligned actions by Member States to achieve public health objectives, leads to practices that are able to fulfil all of the requirements of such regulations in an appropriate, pragmatic, and feasible manner.

Compliance with Ethical Standards

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Conflict of interest Kevin Klein, Marie L. De Bruin, Andre W. Broekmans, and Pieter Stolk declare that they have no conflicts of interest.

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