

Identifiability of Biologicals in Adverse Drug Reaction Reports Received From European Clinical Practice

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Biologicals are established treatment options that require pharmacovigilance adapted to their specific nature, including the need for products to be identifiable up to the specific manufacturer in reports of adverse drug reactions (ADRs). This study explored the identifiability of 10 classes of similar and related biologicals up to the level of the manufacturer in ADR reports received from European clinical practice between 2011 and June 2016. Adequate identifiers were reported for 96.7% of the suspected biologicals, ranging from 89.5% for filgrastim to 99.8% for interferon beta-1a. The product identifiability remained consistently high over time for classes of biologicals for which biosimilars were introduced during follow-up. The overall batch traceability was, however, only ensured for 20.5% of the suspected biologicals and needs further improvement. This study shows that the European system for identification of ADRs to the level of the manufacturer is robust, allowing for the timely detection of potential product-specific safety signals for biologicals.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Adverse drug reactions (ADRs) to biologicals may be product-specific or batch-specific, resulting from changes in manufacturing. Due to the increased availability and use of biosimilars in Europe, the product identifiability up to the manufacturer in ADR reports has received scrutiny.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ We investigated the product identifiability in ADR reports received from European clinical practice between 2011 and 2016. We focused on classes of biologicals for which similar or related (bearing the same generic name) products are available.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✓ We show that product identifiers are available for 96.7% of the suspected biologicals in ADR reports. The identifiability remained robust over time for biologicals for which biosimilars were introduced. Traceability of individual batches was identified as an area for improvement.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✓ The high level of product identification is reassuring, and confirms that product-specific safety signals can be timely identified in multisource markets with multiple similar and related biologicals. Fears of poor product identification when switching between products are not justified.

Biological medicinal products, also called biologicals or biologics, are important treatment options for a variety of chronic and life-threatening diseases. As compared with traditional chemically synthesized medicines, biologicals have specific characteristics, including, among others, a complex manufacturing process, limited predictability of preclinical to clinical data, and a high potential for immunogenicity.¹ For biologicals, as for all drugs, pharmacovigilance plays an important role in the discovery, detection, and characterization of adverse drug reactions (ADRs) in the postmarketing setting due to the inherent limitations of clinical trials (e.g., a homogenous population, a relatively low sample size and time

window, and limited use of concomitant medication).² Perceived challenges in the pharmacovigilance of biologicals are the identifiability (identification of the product responsible for the ADR) and traceability (identification of the product and the batch number responsible for the ADR), particularly in those cases in which more than one medicine with the same generic name, the so-called international nonproprietary name (INN), exists on the market.³ Other challenges include immunogenicity studies, manufacturing variability, stability, and cold chain, and are laid down in the regulatory guidance document “Good Pharmacovigilance Practices for biological medicinal products.”⁴

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With the expiration of regulatory data protection of several biologics, biosimilars, or follow-on biologics, have been approved by the regulatory agencies. Nearly 50 biosimilars have been approved by the European Medicines Agency (EMA) for 14 different active substances.⁵ A biosimilar is a medicine highly similar to another already marketed biological medicinal product, the so-called “reference medicine” (see definitions in **Box 1**). As the manufacturing process of a biological is owned by a pharmaceutical company, the company developing a biosimilar should establish its own production process and show that its finished product is similar to the reference medicine. Biosimilars are extensively being evaluated and compared with the reference product but some differences between the biosimilar and the reference product might exist with regard to some minor quality attributes, for example, in the glycosylation pattern of the protein. The pharmaceutical company developing the biosimilar should ensure that these differences do not have an impact on clinical efficacy and safety.^{6,7} The ability to identify the product, biosimilar, or reference product responsible for a certain adverse event is important in pharmacovigilance. This need is regularly highlighted by organizations representing healthcare professionals and patients.⁷ A previous study in EudraVigilance, the European database for collection of suspected ADR reports, showed that the identifiability up to the product level was 96.2% over the period 2004–2010 for the groups of biologics for which a biosimilar was approved in the European Union (EU), whereas traceability by batch number was only 21.1% and requires improvement.⁸

Biosimilars are approved based on a scientifically tailored data package, which consists of extensive comparability studies between the biosimilar and the reference product.⁹ On the other hand, pharmaceutical companies have been developing the so-called related biological products for a long time. Related biological products are defined as products that contain the same or closely related active substance as another authorized biological medicine and carry the same INN (see **Box 1**). Examples include different interferon beta-1a-containing products (Rebif, Merck Europe, Amsterdam, the Netherlands, and Avonex, Biogen, Badhoevedorp, the Netherlands) and different factor VIII-containing products. The safety profile among these “related” products may potentially differ, as they have been developed on the basis of independent studies, without the inherent need to show similarity to any reference product. A difference in the safety profile can be illustrated by the above-mentioned products containing interferon beta-1a, Rebif, which is approved for subcutaneous use, whereas Avonex is approved for intramuscular administration. A direct comparison showed that injection-site reactions, asymptomatic abnormalities of liver enzymes, altered leucocyte counts, and development of neutralizing antibodies occurred more frequently in the patients treated with Rebif as compared to Avonex.¹⁰ In addition, a safety signal for Rebif was investigated after an unexpected increase in cases of thrombotic microangiopathy was observed for this product following a change in the formulation process.¹¹ These examples underline the importance of being able to clearly identify related biological

Box 1 Definitions of similar and related biologics

Biological medicinal product: A medicinal product that contains an active substance that is produced by or extracted from a biological source and that needs for its characterization and the determination of its quality a combination of physicochemical-biological testing, together with the production process and its control.³⁵

Biosimilar: A biological medicinal product highly similar to another biological medicine already marketed in the European Union (the so-called “reference medicine”), in terms of physical, chemical, and biological properties. There may be minor differences from the reference medicine that are not clinically meaningful in terms of safety or efficacy. Biosimilars are approved on the basis of a scientifically tailored data package, often relying on some clinical data obtained with the reference medicine. Companies can market approved biosimilars once the period of market protection of the reference medicine expires (after 10 years).⁹

Related biological product: A medicinal product that contains the same or a closely related active substance (based on the international nonproprietary name) as (an)other authorized biological medicine. These products are approved on the basis of a full application dossier and not as a biosimilar.⁴

products that carry the same INN and may present potential differences in their safety profiles.

After medicines are placed on the market and during their commercial life, companies are likely to improve or upscale processes and/or make changes to the formulation of the end product. These changes always need to be assessed and approved by the regulatory agencies. In addition, production processes can be complex, often consisting of multiple steps that can potentially influence the characteristics of the end product at every single step of the production cascade. Thus, the pharmaceutical company should ensure that their production process is stable and robust to prevent relevant differences between different batches of the end product.^{12,13} Identification of the batch responsible for an adverse event (traceability) is important in this context for all biologics.

Since the previous EudraVigilance study, which included data up to 2010, a considerable number of biosimilars have been approved in Europe and their use in clinical practice has increased substantially. In addition, related biologics are an important category to take into consideration from a pharmacovigilance perspective. This study, therefore, aims to assess the level of precise identification of biologics down to the product level for biologics for which a biosimilar or a related product has been approved, in reports of suspected ADRs received from European clinical practice.

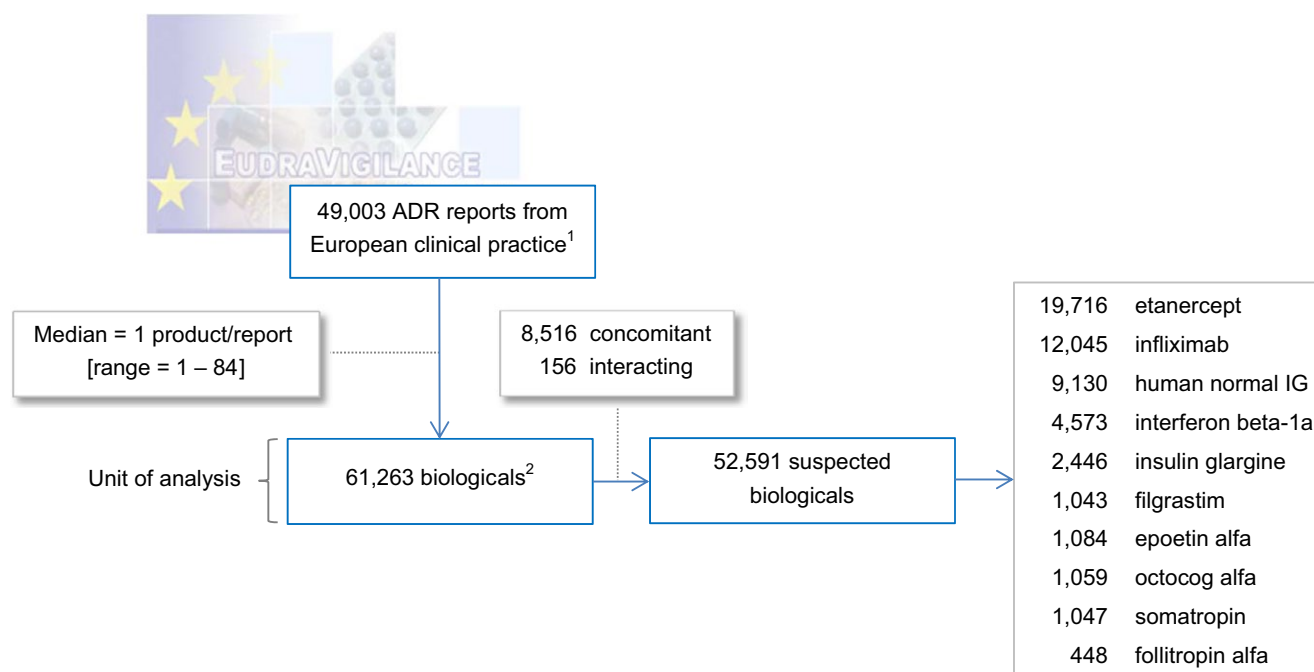


Figure 1 Adverse drug reaction (ADR) reports retrieved from EudraVigilance. IG, immunoglobulin.

RESULTS

Overall, a total of 49,003 ADR reports related to 10 classes of biologicals for which similar or related products have been approved in Europe were retrieved from EudraVigilance. The reports had been received from European clinical practice between January 2011 and June 2016. As shown in **Figure 1**, the included reports reported a total of 61,263 biologicals, corresponding to a median of 1 (range: 1–84) biological per ADR report. Among the reported biologicals, 52,591 were categorized by the reporter as “suspected” to have caused or contributed to the reported ADR (hereafter referred to as “suspected biologicals”), and the remaining biologicals were categorized by the reporter as either concomitant (not suspected to have contributed to the ADR) or interacting (subject of a suspected interaction) medications. The most frequently reported suspected biologicals involved etanercept ($n = 19,716$) and infliximab ($n = 12,045$), followed by human normal immunoglobulins ($n = 9,130$), and interferon beta-1a ($n = 4,573$).

As shown in **Table 1**, most of the ADR reports had been received from reporters in France (9,145; 18.7%), the United Kingdom (8,592; 17.5%), and Germany (7,569; 15.5%). Overall, 25% ($n = 12,266$) of all ADR reports included in the present study were received directly from patients, without any medical confirmation by a healthcare professional, and the remaining 75% was received either directly from patients with subsequent confirmation by a healthcare professional or directly received from a healthcare professional.

The identifiability of the reported biologicals was first assessed along the information reported in the designated fields for drug identification in ADR reports. The overall identifiability was 96.7% (50,833 of 52,591) for suspected biologicals, and 86.3% (7,484 of 8,672) for biologicals that had been categorized as concomitant or interacting medications. Interestingly, the

identifiability of suspected biologicals was higher in ADR reports received directly from patients (99.3%; 12,611 of 12,695 suspected biologicals) than in reports received from healthcare professionals (95.8%; 38,073 of 39,746 suspected biologicals). As shown in **Table 2**, the identifiability differed between the classes of biologicals, ranging from 89.5% for suspected filgrastim-containing products up to 99.8% for suspected interferon beta-1a-containing products.

For the 2,946 biologicals reported as suspected, concomitant, or interacting (pertaining to 2,635 ADR reports) that were not identifiable based on the information in the designated fields for drug identification, the narrative and reporter’s comments were retrieved from EudraVigilance (available for 2,059 of the 2,635 ADR reports) and explored for further drug identifying information. Overall, for an additional 393 (of which 281 suspected) reported biologicals adequate drug identifiers were retrieved by this search strategy. The identifiability of suspected biologicals hereby increased to 97.2% (51,114 of 52,591), as further shown in **Table 2**.

Although the main aim of this study was to explore the level of identification of biologicals down to the marketed product name, we also explored the traceability up the batch level for the reports biologicals. The overall batch traceability was ensured for 20.5% of the suspected biologicals, and varied widely from 1.8% (8 of 448) for follitropin alfa-containing products up to 69.3% (6,326 of 9,130) for human normal immunoglobulin-containing products (not shown in table). No clear trend was observed in reporting of batch numbers for traceability purposes over time. The overall batch traceability was ensured for 29.3% of the suspected biologicals in 2011, 11.4% in 2012, 16.3% in 2013, 21.0% in 2014, 21.7% in 2015, and 23.5% in 2016 (up to June 30, 2016).

Table 1 Characteristics of the ADR reports (n = 49,003) included in the present study

	Number of ADR reports, proportion of total	
Year of receipt		
2011	8,191	16.7%
2012	9,214	18.8%
2013	9,126	18.6%
2014	8,101	16.5%
2015	9,509	19.4%
2016 (up to June 30)	4,862	09.9%
Primary receiver		
Pharmaceutical company	28,997	59.2%
Regulatory authority	20,006	40.8%
Reporter type		
Healthcare professional ^a	36,580	74.6%
Patient	12,266	25.0%
Unknown	157	00.3%
Reporter country		
France	9,145	18.7%
United Kingdom	8,592	17.5%
Germany	7,596	15.5%
Italy	5,786	11.8%
The Netherlands	4,714	09.6%
Spain	2,250	04.6%
Sweden	2,026	04.1%
Other countries	8,894	18.1%

ADR, adverse drug reaction.

^aCases for which reports had been received from both a patient as well as a healthcare professional were classified as healthcare professional cases.

To assess whether the reporting of drug identifying information changed after the introduction of the first biosimilar product, the identifiability was compared for two exemplary product classes: infliximab-containing and insulin glargine-containing products were compared prior to and after the introduction of the first biosimilar (September 2013 and September 2014, respectively). In both classes, there has been considerable marketing experience since the introduction of the first biosimilar, although their vastly different contexts of use—from primarily home-care settings (insulin glargine) to hospital care (infliximab)—may have an impact on the recording and reporting of drug identifying information. As shown in **Figure 2**, the product identifiability remained consistently robust over time for both product classes.

DISCUSSION

This study shows that product identifiers were reported for 96.7% of the biologicals reported as suspected in ADR reports received from European clinical practice between 2011 and June 2016. This is in line with the results from earlier studies in European,⁸ Italian,¹⁴ and US¹⁵ pharmacovigilance databases, which showed robust levels of product identification for classes of biologicals for

Table 2 Product identifiability of suspected similar and related biologicals in spontaneous reports received from European clinical practice between 2011 and June 30, 2016

Product, totals (n)	Identifiable product		Identifiable product, including narrative search		
	n	%	n	%	
Similar biologicals					
Etanercept	19,716	19,012	96.4%	19,167	97.2%
Infliximab	12,045	11,342	94.2%	11,395	94.6%
Insulin glargine	2,446	2,364	96.6%	2,381	97.3%
Filgrastim	1,043	934	89.5%	944	90.5%
Epoetin alfa	1,084	1,045	96.4%	1,056	97.4%
Somatropin	1,047	1,007	96.2%	1,023	97.7%
Follitropin alfa	448	442	98.7%	442	98.7%
Related biologicals					
Human normal IG	9,130	9,070	98.7%	9,086	99.5%
Interferon beta-1a	4,573	4,562	99.8%	4,564	99.8%
Octocog alfa	1,059	1,055	99.6%	1,056	99.7%
Overall	52,591	50,833	96.7%	51,114	97.2%

IG, immunoglobulin.

which similar products are available. The current study also found that the product identifiability remained consistently high over time for those classes of biologicals for which biosimilars were introduced during the study period. Due to the increasing availability and use of biosimilars in European clinical practice over the past few years, with now circa 50 biosimilars having received regulatory approval, adequate product identifiability has become increasingly important. The findings from the current study are reassuring, showing that identification of ADRs to the product level is robust, thereby ensuring that safety signals for biologicals can be detected and related to a specific product in a timely manner.

As already illustrated in the introduction by the case of interferon beta-1a, related biological products are approved based on conventional data package, and differences with regard to safety and efficacy between these products might exist.¹⁰ Early detection of potential safety signals and the ability to relate a potential safety signal to a specific brand name is of high importance for regulators to act in a timely manner to ensure safe and efficacious use of these agents in clinical practice. This study supports that the current system of reporting is robust and reliable to identify the product.

In contrast to related biological products, the regulatory pathway for approval of a biosimilar is a thorough comparability exercise, in which similarity needs to be shown to the reference product at the level of quality, safety, and efficacy.⁶ In the current climate of cost-savings and concerns regarding the price of effective but expensive biological therapies for chronic and life-threatening conditions, there is high interest in the introduction of biosimilar medicines. It is expected that the introduction of biosimilars will lead to cost reduction and that a larger proportion of patients

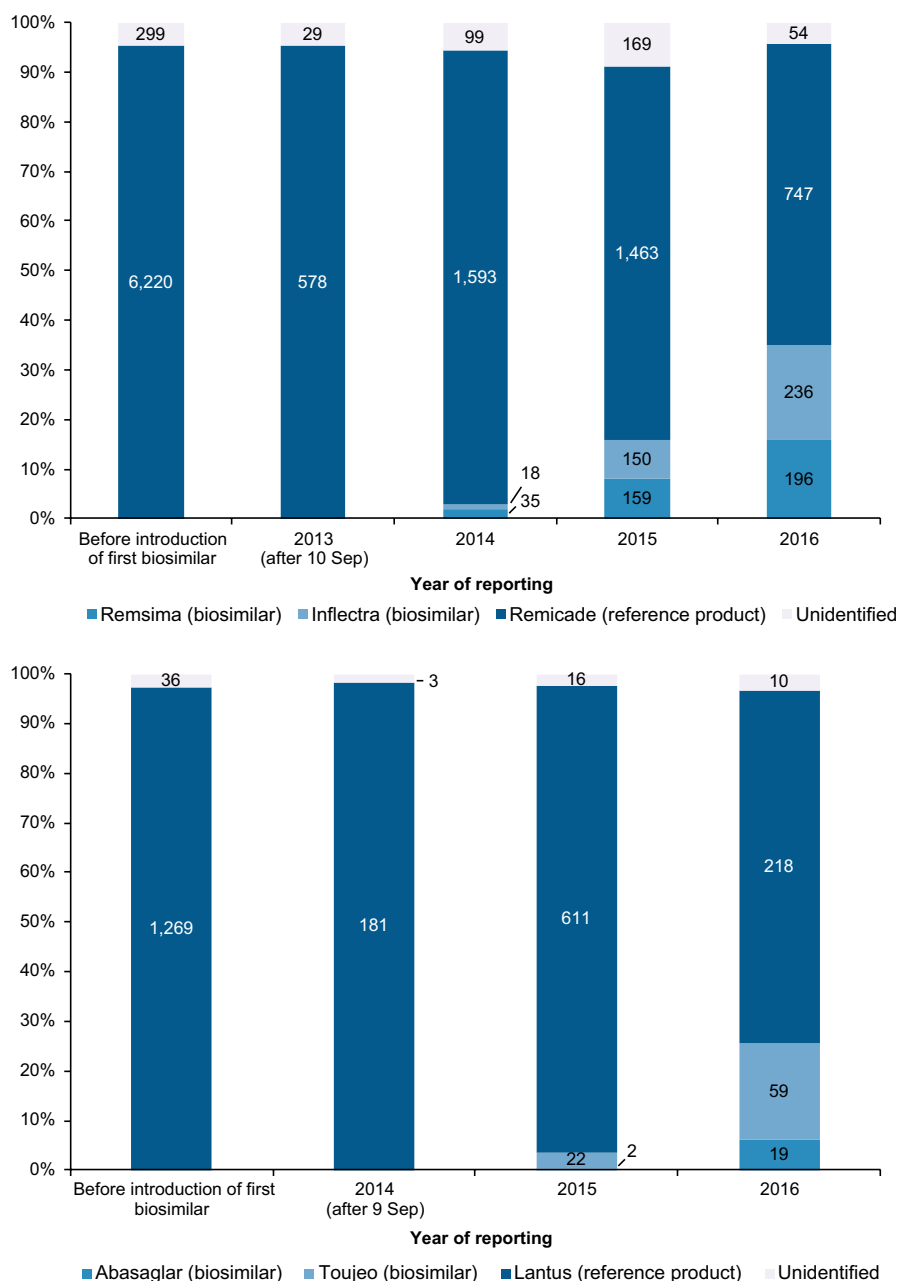


Figure 2 Trends in identifiability for infliximab (top) and insulin glargine (bottom) before and after introduction of its first biosimilar.

could benefit from these treatments.¹⁶ Lack of understanding around how biosimilars are developed and approved have led some patients and practitioners groups to voice some distrust regarding biosimilars, although positions are evolving as knowledge of biosimilars increases. An often-heard argument regarding use of biosimilars is the potential lack of clear identification of suspected drugs, increased when multiple switches occur.^{17–19} This study has, however, shown that identifiability up to the product level for classes of biologicals for which similar products are marketed is high in EudraVigilance.

Identification of the batch number (traceability), however, showed low levels of overall compliance in this study: for 20.5% of the suspected biologicals a batch number was reported. The

requirement for batch traceability applies to all biologicals, including originator biological medicines, related biologics, and biosimilars due to the inherent batch-to-batch variability and manufacturing changes products undergo during their lifecycle.^{12,13} The results from the current study on batch traceability are in line with a previous study in EudraVigilance, in which batch numbers were available for 21.1% of all suspected biologicals reported between 2004 and 2010.⁸ Due to the low availability of batch numbers in ADR reports, a safety issue from a change in an individual product might be difficult to link to a specific manufacturing process. The reason for the low batch reporting has previously been shown to be multifaceted and relates, among others, to inadequate recording of batch

information in pharmacy dispensing and/or medical records, unavailability of the recorded information to the reporter at time of reporting, and unawareness regarding the need to report batch information in ADR reports.^{3,20,21} Efforts to improve traceability, therefore, requires a multifaceted approach, focusing both on ensuring the routine recording of exposure information in clinical practice, as well as enabling and encouraging health-care professionals and patients to report the required exposure information.^{3,22}

The newly developed guideline on good pharmacovigilance practices (GVPs) for biological medicinal products contains detailed guidance on measures that can be taken to ensure batch traceability when implementing pharmacovigilance for biologicals.⁴ The GVP module entered into force in August 2016 and is a deliverable from the 2012 EU pharmacovigilance legislation, which contains a specific provision on traceability of biologicals in ADR reports.²³ In the current study, no effect was yet observed from the 2012 pharmacovigilance legislation, as demonstrated by the findings that the overall batch traceability was in line with the results from the previous EudraVigilance study and that no clear trend over time could be observed in the current study. Future regulatory science studies may, therefore, be helpful to explore the impact of the GVP on batch traceability and help to identify best practice to improve traceability.

The 10 different classes of similar and related biologicals included in this study differ widely in their clinical context of use including frequency of dosing, duration of use, extent of clinical monitoring, and place of administration (hospital setting vs. home care), which factors have previously been linked to differences in quality of ADR reporting.²⁴ Despite these differences, no major differences were observed in product identifiability among the different classes of biologicals in this study. The batch traceability, however, did differ from 1.8% for follitropin alfa up to 69.3% for human normal immunoglobulins. The high level of batch reporting compliance for the latter group relates to the fact that immunoglobulins have historically been regarded as blood products in several countries, and specific traceability requirements apply.³

Nomenclature of biologicals remains a subject of debate among some authors and has been suggested as a potential solution to improve traceability.¹⁹ However, differences in nomenclature will mainly relate to identifiability. Different regions of the world are considering different options,¹⁷ including the addition of suffixes and addition of a string of letters and numbers attached to the INN to differentiate medicines and improve identifiability. The US Food and Drug Administration has opted to introduce suffixes.²⁵ The World Health Organization has also explored the introduction of a biological qualifier.¹⁹ In Europe, the identification of products using their unique commercial name has the major advantage of simplicity, and reinforces the approach taken by EU regulators that, although related biologicals might not have the same safety profile, biosimilars approved in the EU are equally effective, safe, and of equivalent quality with originators.⁷

Although product identification is essential biological pharmacovigilance, adequate exposure ascertainment is a challenge in pharmacovigilance in general. For small-molecule drugs there have,

for example, been a number of high-profile product-specific incidents in the past, including intestinal perforation with a specific formulation of indomethacin²⁶ and differences in cardiovascular risk between Spiriva Respimat and Spiriva Handihaler.²⁷ Product-specific exposure is equally important for the adequate identification and characterization of such formulation-specific safety signals for small-molecule drugs.

Regarding the geographic origin of reports, we limited our study to those originating in the European Union, as it is the region with more complete presence in the EudraVigilance database.^{28,29} This limits the validity of the analysis to Europe but presents the picture of the area of the world where most biosimilars have been approved and are marketed. The uptake of biosimilars in the European Union is regionally and nationally uneven, but it is clearly on the rise.³⁰ Another potential limitation resides in the period of time chosen for the study. We took our initial time point from the upper limit of the previous study in EudraVigilance.⁸ The cutoff point (June 2016) allowed us to include a large number of reports of nearly 50,000, which makes a representative sample. It is expected that a longer follow-up will not have an impact on our findings. Any potential misclassification of products (ADRs belonging to biosimilars or related biologicals that are erroneously attributed to another biological with the same INN), should also be considered in the context of our results. This is very difficult to quantify, but a previous simulation study in which the effect of exposure misclassification was evaluated in three test cases representing product-specific ADRs showed that low levels of exposure misclassification generally do not result in a delayed detection of product-specific risks.³¹

Considering the good identification levels demonstrated by this study, we can conclude that the system of identification of ADRs to the product level is robust: in the event of a safety signal concerning a biological medicine, the identification of the specific product responsible should be feasible in a very high proportion of ADRs in the EudraVigilance database.

METHODS

The identifiability and traceability of biologicals was explored in spontaneous reports of suspected ADRs received from clinical practice across Europe between January 2011 and June 2016. The reports were identified from EudraVigilance, the European database for collection of ADR reports.

Data setting

EudraVigilance was established in 2001 by the EMA to collect reports of serious suspected ADRs to medicines licensed within the European Economic Area (EEA) and reports of any suspected transmission via a medicinal product of any infectious agents within the EEA. Serious unexpected ADRs occurring outside the EEA are also collected in EudraVigilance. Reporting was extended in 2004 to include suspected unexpected serious adverse reactions to medicines involved in clinical trials in the EEA and further extended in 2012 to include all serious ADRs outside the EEA and reports from nonhealthcare professionals. ADR reports in EudraVigilance are received indirectly through EU national competent authorities and pharmaceutical companies.

Handling of duplicate reports. Duplicate reports are routinely detected and handled according to a predefined algorithm as described in the EMA guideline on duplicate reports.³² No further deduplication steps were undertaken for the current study.

Data extraction

The following ADR reports were retrieved from EudraVigilance: All individual case safety reports received as spontaneous reports from a reporter within the EEA between January 1, 2011, and June 30, 2016, and in which at least one of the reported medicinal products involves a biological for which a biosimilar or related product has been approved in the EEA (see **Table S1**). Literature reports and reports received from lawyers in context of a litigation were not included in the current study, due to their specific characteristics.

Data classification and outcome definition

Product identifiability. The product identifiability—that is, the extent to which a single reported product is identifiable up to the specific manufacturer—was determined for each reported biological. Products were considered identifiable if any of the following information was available: (i) the product trade name, (ii) the name of active substance (INN) plus the name of the marketing authorization holder (MAH), or (iii) when the active substance epoetin zeta was reported, because this INN is specific to a biosimilar of epoetin alfa (from a single manufacturer) and can, therefore, be distinguished from the reference medicinal product. The list of product trade names that was used to assess the identifiability (see **Table S2**) was compiled from Micromedex (international edition, www.micromedexsolutions.com) and the EMA's website (www.ema.europa.eu).

The identifiability was first determined along the information contained within the designated E2B fields for drug identification in ADR reports: proprietary medicinal product name (E2B field b.4.k.2.1), active substance name (E2B field b.4.k.2.2), and/or name of the MAH (E2B field b.4.k.4.3). E2B has been developed as a guideline to standardize the data elements of ADR reports and provides the basis for the electronic transmission of ADR reports in Europe and several other regions in the world including the United States.³³ Further detailed guidance on the management and reporting of ADR reports in Europe is provided in the respective guidelines on GVPs.³⁴ The GVP requires that, with regard to data, element B.4.k.2.1. should be populated with the proprietary/branded medicinal product name as reported by the primary source. Two researchers (N.V. and A.H.) independently assessed the identifiability along the reported information on an aggregated level. Any inconsistencies in assessment between the researchers were resolved by consensus.

As a second step, for products that were nonidentifiable based on the information in the designated fields for drug identification, the case narrative plus the sender's and reporter's comments were retrieved from EudraVigilance. The case narratives and comments were scrutinized for further drug-identifying information by running text searches for the product trade names. The search strategy was validated by two researchers (N.V. and A.H.) who reviewed all narratives for which the text search indicated a trade name was reported and by manually reviewing a 10% random sample of the case narratives for which the search indicated no trade name was reported.

Assessment of batch traceability. All verbatim data provided in the designated field for batch numbers of at least three characters was considered to be a batch number. To validate whether the verbatim data did not contain any information referring to the unavailability of a batch number (e.g. “don't know” or “discarded package”), data were aggregated and reviewed by two researchers (N.V. and A.H.). Any inconsistencies in assessment between the researchers were resolved by consensus. No additional narrative search was performed to assess the batch traceability.

Primary source information. The primary reporting source was categorized as either healthcare professional (physician, pharmacist, or other health professional) or patient/nonhealthcare professional. Cases for which information was received both from a healthcare

professional and a patient were categorized as healthcare professional cases, as these are regarded as healthcare professional-confirmed cases. Furthermore, the primary receivers were categorized as either competent authorities or marketing authorization holders.

Data analysis

The number and percentage of precise product identification and traceability was calculated for all reported biologicals, and stratified according to the biological category (similar or related biological product), the product class, and the drug role code (suspected/concomitant or interacting).

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Table S1. (A) Product classes for which biosimilars are approved in the EEA (DLP: 1 July 2016). (B) Product classes for which related biologicals are approved in the EEA.

Table S2. Trade names used to assess product identifiability.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

N.V., T.G., S.Z., E.W.-H., and A.H.-S. wrote the manuscript. N.V. and A.H.-S. designed the research. N.V., A.H.-S., and S.Z. performed the research. N.V. and A.H.-S. analyzed the data.

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- Giezen, T.J., Mantel-Teeuwisse, A.K. & Leufkens, H.G.M. Pharmacovigilance of biopharmaceuticals. *Drug Saf.* **32**, 811–817 (2009).
- Stricker, B.H. & Psaty, B.M. Detection, verification, and quantification of adverse drug reactions. *Br. Med. J.* **329**, 44–47 (2004).
- Vermeer, N.S. *et al.* Traceability of biologicals: present challenges in pharmacovigilance. *Expert Opin. Drug Saf.* **14**, 63–72 (2015).
- European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Product- or population-specific considerations II: biological medicinal products. (EMA/168402/2014 Corr.). <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/08/WC500211728.pdf> (2016). Accessed September 28, 2018.
- European Medicines Agency (EMA). Corporate website. <https://www.ema.europa.eu/en/medicines/field_ema_web_categories%

- 253Aname_field/Human/ema_group_types/ema_medicine/ema_medicine_types/field_ema_med_biosimilar/field_ema_med_status/authorised-36>. Accessed September 28, 2018.
6. Weise, M. *et al.* Biosimilars: what clinicians should know. *Blood* **120**, 5111–5117 (2012).
 7. Kurki, P., van Aerts, L., Wolff-Holz, E., Giezen, T., Skibeli, V. & Weise, M. Interchangeability of biosimilars: a European perspective. *BioDrugs* **31**, 83–91 (2017).
 8. Vermeer, N.S. *et al.* Traceability of biopharmaceuticals in spontaneous reporting systems: a cross-sectional study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance databases. *Drug Saf.* **36**, 617–625 (2013).
 9. Biosimilars in the European Union. Information guide for healthcare professionals. <http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf>. Accessed September 7, 2018.
 10. Panitch, H. *et al.* Randomized, comparative study of interferon beta-1a treatment regimens in MS: the evidence trial. *Neurology* **59**, 1496–1506 (2002).
 11. Hunt, D. *et al.* Thrombotic microangiopathy associated with interferon beta. *N. Engl. J. Med.* **370**, 1270–1271 (2014).
 12. Ramanan, S. & Grampp, G. Drift, evolution, and divergence in biologics and biosimilars manufacturing. *BioDrugs* **28**, 363–372 (2014).
 13. Vezér, B., Buzás, Z., Sebeszta, M. & Zrubka, Z. Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. *Curr. Med. Res. Opin.* **32**, 829–834 (2016).
 14. Cutroneo, P.M. *et al.* Safety profile of biological medicines as compared with non-biologicals: an analysis of the Italian spontaneous reporting system database. *Drug Saf.* **37**, 961–970 (2014).
 15. Stergiopoulos, S., Brown, C.A., Grampp, G., Felix, T. & Getz, K.A. Identifying and quantifying the accuracy of product name attribution of US-sourced adverse event reports in MedWatch of Somatropins and Insulins. *Ther. Innov. Regul. Sci.* **49**, 706–716 (2015).
 16. Carrascosa, J.M., Jacobs, I., Petersel, D. & Strohal, R. Biosimilar drugs for psoriasis: principles, present, and near future. *Dermatol. Ther. (Heidelb.)* **8**, 173–194 (2018).
 17. McKinnon, R.A. *et al.* Biosimilarity and interchangeability: principles and evidence: a systematic review. *BioDrugs* **32**, 27–52 (2018).
 18. Blandizzi, C., Galeazzi, M. & Valesinic, G. Transitioning from first- to second-generation biosimilars: an appraisal of regulatory and post-marketing challenges. *Pharmacol. Res.* **128**, 306–314 (2018).
 19. Gámez-Belmonte, R. *et al.* Biosimilars: concepts and controversies. *Pharmacol. Res.* **133**, 251–264 (2018).
 20. Klein, K. *et al.* Traceability of biologics in The Netherlands: an analysis of information-recording systems in clinical practice and spontaneous ADR reports. *Drug Saf.* **39**, 185–192 (2016).
 21. O'Callaghan, J., Griffin, B., Morris, J. & Bermingham, M. Knowledge of adverse drug reaction reporting and the pharmacovigilance of biological medicines: a survey of healthcare professionals in Ireland. *BioDrugs* **32**, 267–280 (2018).
 22. Klein, K. & Stolk, P. Challenges and opportunities for the traceability of (biological) medicinal products. *Drug Saf.* **41**, 911–918 (2018).
 23. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. (OJ L 348, 31.12.2010, p. 74–99). <https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf>. Accessed October 29, 2018.
 24. Vermeer, N.S. *et al.* Drug-induced progressive multifocal leukoencephalopathy: lessons learned from contrasting natalizumab and rituximab. *Clin. Pharmacol. Ther.* **98**, 542–550 (2015).
 25. US Food and Drug Administration (FDA). Biosimilar product information. <<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580432.htm>>. Accessed September 28, 2018.
 26. Day, T.K. Intestinal perforation associated with osmotic slow release indomethacin capsules. *BMJ* **287**, 1671–1672 (1983).
 27. Wise, R.A. *et al.* Tiotropium Respimat inhaler and the risk of death in COPD. *N. Engl. J. Med.* **369**, 1491–1501 (2013).
 28. Weise, M., Kurki, P., Wolff-Holz, E., Bielsky, M.C. & Schneider, C.K. Biosimilars: the science of extrapolation. *Blood* **124**, 3191–3196 (2014).
 29. Tabernero, J. *et al.* Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. *ESMO Open* **1**, e000142 (2017).
 30. IQVIA Institute for Human Data Science. Advancing Biosimilar Sustainability in Europe. A Multi-Stakeholder Assessment. Institute Report. <<https://www.iqvia.com/institute/reports/advancing-biosimilar-sustainability-in-europe>>. Accessed September 7, 2018.
 31. Vermeer, N.S., Ebberts, H.C., Straus, S.M., Leufkens, H.G., Egberts, T.C. & De Bruin, M.L. The effect of exposure misclassification in spontaneous ADR reports on the time to detection of product-specific risks for biologicals: a simulation study. *Pharmacoepidemiol. Drug Saf.* **25**, 297–306 (2016).
 32. Committee for Medicinal Products for Human Use (CHMP). Guideline on detection and management of duplicate individual cases and individual case safety reports (ICSRs). June 21, 2012.
 33. ICH Harmonized Tripartite Guideline. Maintenance of the ICH guideline on clinical safety data management: data elements for transmission of individual case safety reports E2B (R2) Current Step 4 version, February 5, 2001.
 34. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VI – management and reporting of adverse reactions to medicinal products (Rev 1). July 28, 2017.
 35. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version: November 16, 2012). <https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf>. Accessed September 7, 2018.