Identifiability of Biologicals: An Analysis Using EudraVigilance, the European Union's Database of Reports of Suspected Adverse Drug Reactions

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The relevance of biological therapies for an increasing number of conditions is on the rise. Following the expiry of the initial period of market exclusivity, many of these successful therapies have seen the arrival of biosimilars on the market. The clear identification of the precise medicine responsible for an adverse drug reaction (ADR) report is an important element for pharmacovigilance, allowing timely detection of potential product-specific safety signals. We looked at the identifiability of biologicals up to the level of commercial product name in ADR reports received from European clinical practice between 2011 and December 2019. A good level of identification (91.5%) was observed overall, but at the same time a downward trend was observed in the last 5 years. This reduction in the level of identifiability of biological products (originators and biosimilars) at the commercial name level in general was driven by five widely used substances, whereas the identification of all other biologics stayed consistent over time (at over 90%). We observed that those five substances were used mostly within oncology. The introduction of the first biosimilar in the market did not appear to affect their identifiability. These results show that although the general level of identification at the commercial product name level in ADRs in Europe is robust and generally stable over time, decreasing trends can be down to a few commonly used substances, which need to be monitored to reverse the trend.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ A high level of commercial name identifiability on all reports of adverse drug reactions (ADRs) is important to ensure timely and effective discrimination of products. The increased availability of biosimilars in Europe and potential changes in reporting practices over time might influence identifiability. It is, therefore, important to regularly monitor the level of identifiability.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We investigated the product identifiability in ADR reports received from European clinical practices between 2011 and 2019 for biological products for which biosimilars are approved.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ We show identifiability to be, on average, 91.5%. Identifiability decreased over time. This decrease was mainly driven by five products mostly used in oncology. Availability of biosimilars does not seem to negatively impact identifiability.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The high level of identifiability is reassuring, supporting the timely identification of product specific safety signal. The downward trend on identifiability over time needs attention and improvement for all biologicals.

Biological medicinal products, also called biologicals, are key therapies for several acute and chronic diseases.[1] However, as spending on biologicals is high, these agents play an increasing role in cost-control and sustainability of healthcare systems (e.g., of the top 10 drugs in 2019), by revenue, eight were biologicals.[2] The introduction of biosimilars has shown to lower the prices of high-cost biologicals due to competition,[3,4] and can potentially facilitate wider access to patients to effective therapies.

Biosimilars in the European Union are defined as highly similar to another biological medicinal product already licensed in the

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European Union, also called the reference product.[5] The approval of biosimilars is based on an extensive comparability exercise between the intended biosimilar and the reference product. The physicochemical and functional characterization and comparison is the cornerstone for approval as a biosimilar supplemented by pharmacokinetic/pharmacodynamic studies and, generally one, comparative phase III clinical trial.[6] Up-to-date information on approved biosimilars[7] as well as guidance for health care professionals[5] can be found on the European Medicines Agency (EMA) website.

Since the approval of the first biosimilar in the European Union in 2006, many biologicals and their biosimilars have co-existed on the European market.[6] As of January 2021, there have been 62 approved biosimilars on the EU market, and several are under consideration. Pharmacovigilance activities, which monitor the safety of all medicines, have not detected any serious safety concerns related to the use of biosimilars in the European Union. Moreover, no safety or efficacy differences have been identified between reference products and their corresponding biosimilars.[1,5,6,8,9] Although there could be changes in the product characteristics over time, these need to be approved by competent authorities, and essentially occur with all biologicals, including biosimilars.[10,11]

In Europe, reports of adverse drug reactions (ADRs) are collected in EudraVigilance (EV),[12] the EU database of spontaneous ADRs. If a safety signal is detected, identification at the proprietary name (commercial product name) level is required to recognize the precise medicine that may have caused it. Clinical experience over the past 12 years has shown that identification of the commercial product name of a medicine is adequate to perform pharmacovigilance activities and guarantee the safety of medicines in the EU market.[5] Maintaining a high level of commercial name identifiability on all reports of ADRs is important to ensure timely and effective discrimination of products even if they have the same active substance, and thus effective pharmacovigilance of products in the market.[5] There are concerns raised occasionally in the literature and in medical conferences questioning the level of identifiability of biosimilars in relation to their reference products, which, in turn, may cause problems if a safety signal cannot be firmly attributed to a specific medicine (biosimilar, original biological, or related biological with the same substance but approved with full marketing authorization).[13–16] The number of compounds in the market continues to increase every year, and as reporting practices can change with the increased use, it is important to regularly monitor the level of commercial name level identifiability of this large pool of products, and to analyze potential trends.

To this end, we have performed an analysis, in line but not identical to previous studies,[17] with the aim of investigating the current level of identifiability of biologicals in ADR reports received in the EV database. We have looked at biologicals with at least one biosimilar on the EU market and studied reporting changes over the last 12 years and identified the main drivers of observed changes.

METHODS

Database

Data were sourced from the European Union's central database of reports of suspected ADRs, EV.[18] The reporting requirements of EV are detailed in the legislation and accompanying guideline on good pharmacovigilance practices (GVP) Module VI.[19]

Duplicate reports are routinely detected and handled according to a predefined algorithm, as described in the Addendum I of the GVP Module VI. No additional deduplication steps were undertaken for the current study.

All individual case safety reports classified as spontaneous reports and sent from a reporter within the European Economic Area between January 1, 2011, and December 31, 2019 were sourced. Cases stemming from the medical literature or those reported by lawyers were excluded as the probability of the product name being reported in these cases is affected by factors extrinsic to pharmacovigilance systems (e.g., journals may specifically require product names not to be mentioned and legal strategies may require product names to always be stated).

Products

The biologicals considered in this study were all biologicals for which at least one biosimilar has been authorized in the European Economic Area up to 2019. The date at which biosimilars were considered to be available in the market was defined as the date of the marketing authorization of a product with the same active substance (i.e., the European Commission's decision date).

Identifiability

An identifiable medicine was defined as a medicine reported by its commercial product name. For biosimilar brand names, multilingual depiction of the substance name was permitted (e.g., enoxaparin Rovi or enoxaparina Rovi were both identifiable products).

Determinants

The following factors were explored as potential factors related to identifiability: primary receiver (regulatory authorities vs. marketing authorization holder), reporter type (healthcare professional vs. non-healthcare professional, including patients, legal representatives, and caregivers), seriousness (serious vs. nonserious), outcome (fatal, not recovered/not resolved, recovered/ resolved, recovered/ resolved with sequelae and recovering/ resolving) and period (January 2011–June 2016 and July 2016–December 2019).

Data analysis

The number and percentage of precise product identification was calculated for the reported biologicals and stratified by the different determinants.

RESULTS

From 2011 to 2019, 130,248 reports with 134,005 product or substance names of the selected biologicals were received in EV. The percentage of these biologicals with reported ADRs hovered around 9–10% up to 2017 but increased to over 16% in 2018 and 2019. Regulatory authorities and healthcare professionals are the main source of case reports, with 65% and 76%, respectively (**Table 1**).

During the study period, overall identifiability by product name was 91.5%. The five most frequently identifiable products were reported for the following substances: follitropin alfa (99.1%), etanercept (97.0%), somatropin (96.6%), epoetin alfa (95.9%), and adalimumab (95.0%). Higher identifiability was found for reports received from non-healthcare professionals as compared with healthcare professionals (96.9 vs. 89.8%). Introduction of the biosimilar did not seem to result in lower identifiability (92.9 vs. 90.2%; **Table 2**).

Table 1 Characteristics of the biologicals reported

Characteristics	Frequency	
	n	%
N individual case safety reports	130,248	
N biologicals reported	134,005	
Year		
2011	11,919	8.9
2012	12,046	9.0
2013	13,179	9.8
2014	12,156	9.1
2015	12,872	9.6
2016	12,404	9.3
2017	14,558	10.9
2018	22,211	16.6
2019	22,660	16.9
Primary receiver		
Regulatory authorities	87,394	65.2
Marketing authorization holders	46,611	34.8
Reporter type		
Healthcare professional	102,201	76.3
Patients	31,802	23.7
Not specified	2	0
EEA reporter country		
France	28,318	21.1
United Kingdom[a]	24,443	18.2
Italy	21,361	15.9
Germany	18,973	14.2
Spain	7,509	5.6
Netherlands	5,732	4.3
Others	27,669	20.4

Abbreviation: EEA, European Economic Area.
[a]During the period covered, 2011–2019, the United Kingdom was an EEA country.

Over a span of 9 years, the identifiability of the biologicals included in this analysis has decreased on average 6%. The decrease seems to have been driven by 5 of the 15 substances analyzed: bevacizumab, filgrastim, infliximab, rituximab, and trastuzumab (**Figure 1**).

The identifiability of bevacizumab, rituximab, and trastuzumab in 2019 is over 10% lower as compared with the highest recorded identifiability of each substance for the entire period (**Table 3**).

The trend of identifiability for the 5 substances with lowest identifiability in 2019 is shown in **Figure 2**.

For rituximab, the average year-on-year decrease of identifiability the 2014–2019 period was 5.28%, with the largest drop in identifiability occurring from 2014 to 2015 (9.7%), prior to the introduction of biosimilars. For the other products, the introduction of the biosimilar did not seem to result in a further decrease in identifiability as compared with the period before the introduction of the biosimilar.

Table 2 Product identifiability of selected biologicals in spontaneous reports received from European clinical practice between 2011 and 2019

Characteristics	Identifiable products	
	n	%
N identifiable product name	122,608	91.5
N non-identifiable product / only substance name	11,397	8.5
Active substance		
Adalimumab	23,454	95.0
Bevacizumab	8,568	85.5
Enoxaparin	9,635	92.7
Epoetin alfa	1,065	95.9
Epoetin zeta	292	86.6
Etanercept	28,802	97.0
Filgrastim	1,635	87.4
Follitropin alfa	1,191	99.1
Infliximab	13,074	90.3
Insulin glargine	6,277	92.7
Insulin lispro	3,536	92.2
Rituximab	9,311	75.1
Somatropin	2,351	96.6
Teriparatide	6,988	94.2
Trastuzumab	6,429	87.4
Primary receiver		
Regulatory agencies	80,229	90.5
Marketing authorization holders	44,705	92.9
Reporter type		
Healthcare professional	91,791	89.8
Non-healthcare professional	30,815	96.9
Not specified	2	100
Seriousness		
Seriousness: serious	80,684	91.1
Seriousness: nonserious	41,924	92.3
Outcome		
Fatal	3,483	87.6
Not recovered/not resolved	16,272	93.2
Recovered/resolved	29,614	90.4
Recovered/resolved with sequelae	1,596	89.4
Recovering/resolving	12,424	90.5
Products in the market		
Originator only	60,882	92.9
Originator and biosimilars	61,726	90.2
Period		
January 2011 to June 2016	64,023	93.5
July 2016 to December 2019	58,585	89.4

DISCUSSION

The average identifiability of biological products for which biosimilars have been approved within the 9-year period between

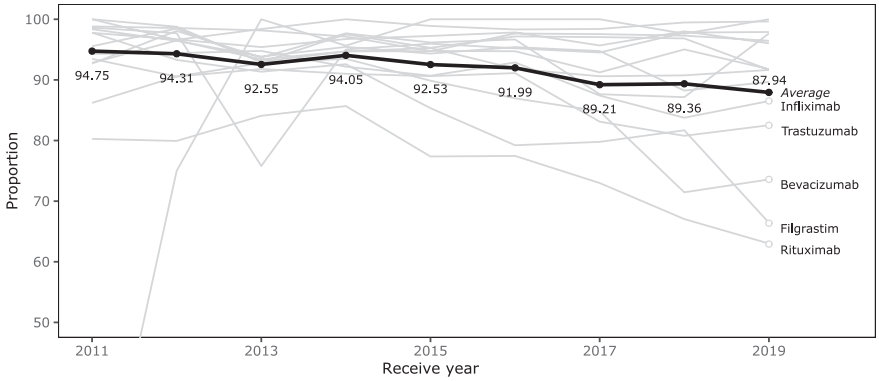

Figure 1 Time series of identifiability of biologicals, 2011 to 2019.

Table 3 Difference between highest recorded identifiability and identifiability in 2019, by substance

Active substance	Highest recorded identifiability	Identifiability in 2019	Difference
Rituximab	85.68	63.01	22.67
Bevacizumab	93.48	73.58	19.9
Trastuzumab	93.47	82.52	10.95
Filgrastim	96.32	86.67	9.65
Insulin lispro	98.36	89.66	8.7
Epoetin alfa	100	91.67	8.33
Infliximab	94.78	86.51	8.27
Adalimumab	98.82	91.77	7.05
Enoxaparin	96.5	91.64	4.86
Somatropin	98.47	96.45	2.02
Etanercept	98.01	96.04	1.97
Teriparatide	98.63	97.9	0.73
Insulin glargine	98.08	97.65	0.43
Follitropin alfa	100	99.64	0.36
Epoetin zeta	100	100	0

2011 and 2019 was 91.5%. A decrease in commercial name level identifiability was found over time, which could mainly be attributed to a lower level of identifiability for biologicals used in oncology. Specially, five of these substances showed a downward trend in identifiability that was mostly already present before the introduction of their respective biosimilars, and therefore no clear association with the introduction of biosimilars could be made. The identifiability decreased in both serious and nonserious cases for these 5 substances since 2016. Identifiability seemed to be higher for ADR reports received from non-healthcare professionals as compared with healthcare professionals.

Commercial name identifiability of the specific biological product for which an ADR is reported is an important aspect within the pharmacovigilance of biologicals and has been a topic for debate, especially since the introduction of biosimilars.[15] Although the overall identifiability during the study period was high, a decrease was found over time and the level of identifiability differed between product classes. In 2011, identifiability was found to be 94.8% but decreased to 87.9% in 2019. Our previous EV study showed an average identifiability of 96.7% for biologicals between 2011 and June 2016.[17] Furthermore, the number of authorized products did not seem to relate to a lower identifiability (e.g., rituximab had 4 products on the market by 2018 and a low identifiability in 2019), whereas teriparatide had one of the highest identifiability in 2019, and had 6 products on the market since 2017.

In contrast to the present study, the previous study also included biologicals without approved biosimilars for which identifiability was generally higher as compared with the biologicals for which biosimilars had been approved.[17] Another study using the database of the Netherlands Pharmacovigilance Centre Lareb also found a decrease in the level of identifiability over time for all biologicals, with a level of identifiability of around 82% in 2009 and 67% in 2014.[20] However, this study only covered one country, the Netherlands, for which the ADR reports are only a limited fraction of the current study. An analysis by Amgen showed product identifiability for filgrastim to be close to 80% between April 2012 and December 2014,[16] which is lower than the identifiability of around 87.4% for filgrastim found in the present and the 90.5% found in the previous study.[17]

Overall, there seems to be a decreasing level of identifiability over time for all biological products, but especially driven by very few products, mostly used in oncology. Introduction of biosimilars does not seem to lead to a change of identification trajectory in place—a potential association is difficult to establish. The lower identifiability for products used in oncology might be attributed to the handling of these agents in clinical practice. Most of the monoclonal antibodies used in oncology are prepared in the hospital pharmacy (hospital setting) and are administered by a nurse. Because of Good Manufacturing Practice Guidelines information, product name and batch number are collected in the hospital pharmacy.[15,21] As a consequence, patients and healthcare professionals would need to access information on a specific product and batch number through the hospital pharmacy, which may explain why such information is more frequently lacking for biologicals administered in the hospital setting. Our results show that the identifiability of the products mostly used in the hospital setting have an almost 10% lower identifiability than those mostly used in the home setting. This can be further illustrated by the TNF-alpha inhibitors, where the identifiability for infliximab, which is mostly administered in the hospital setting, is over 5% lower as compared with adalimumab and etanercept, which are administered subcutaneously by the patient in the

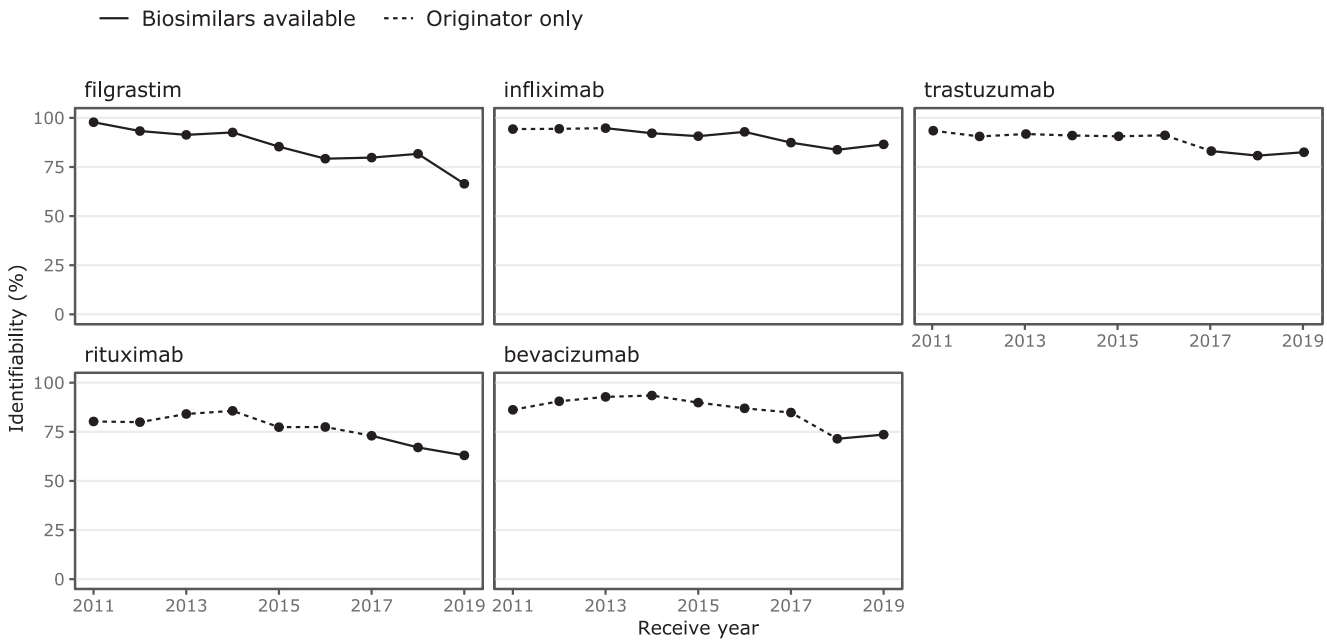

Figure 2 Trend of identifiability for 5 substances with lowest identifiability in 2019.

home setting. Direct access to relevant product information (e.g., in the electronic patient chart), may help to improve identifiability of biologicals used in hospitals in the future.

Identifiability is generally higher in reports received from non-healthcare professionals as compared with healthcare professionals, which is in line with the results found by a previous study.[20] This difference might be understandable by the fact that healthcare professionals report > 75% of ADRs and might judge sensitivity (i.e., informing authorities) over specificity (i.e., having precise product information and time constrains in clinical practice). In addition, ADR reports from patients are likely to be mostly related to self-administered biologicals making it difficult to draw definite conclusions about the drivers for the higher product identifiability. It is possible that high personal interest in the reporting of a single ADR and the limited amount of time required to report that single reaction are among them.

Potential differences in the safety profile between products with the same active substance (identifiability) and within products produced by the same manufacturer (traceability) has been a topic for debate for several years.[20] During recent years, several cases have been published showing differences in specific quality attributes between different batches of the same product produced by the same manufacturer.[22–24] This supports the need for traceability (e.g., the ability to trace which batch the patient has received despite the observation that, so far, differences in certain quality attributes between batches had limited impact on efficacy and safety). Previous studies have shown that the availability of the specific batch number in spontaneously recorded ADRs is generally low with percentages ranging between 0 and 20%.[20,25] Therefore, traceability needs improvement and several proposals have already been made.[15,26] Questions have, however, been raised about the cost-effectiveness of improvement of traceability as tools for improvement place more pressure on the healthcare budget.[27]

The decrease in identifiability (i.e., the identification of the specific product the patient has received), over time is a point of concern that should be improved. After authorization, manufacturers can introduce changes to the production process and formulation of their products, including biosimilars, without the need to re-establish similarity to the original or reference product, in other words, after approval as a biosimilar, the product is considered a standalone product by regulatory bodies.[28] Several initiatives have been proposed to improve identifiability. Differences in the naming of biologicals and the corresponding biosimilars have been proposed by some regulatory agencies around the world. The US Food and Drug Administration (FDA), for example, has introduced a suffix to the international nonproprietary name (INN) of originator biologicals, related biologicals, and biosimilars and the World Health Organization (WHO) has opted for a biological qualifier but has already dropped this proposal.[29,30] The European network requires a unique product name but has been of the opinion that biosimilars should receive the same INN as the reference product without the addition of a suffix or a biological qualifier. The present system provides adequate identifiability, as supported by the present and the previous studies in EV.[5,17] In addition, there are concerns that differences in INN between biosimilars and the reference product might be confusing and result in decreased trust in biosimilars by healthcare professionals and patients. To improve identifiability and traceability, previous studies have called for a multifaceted approach, involving both the routine recording of batch number and the brand name in clinical practice and the recording of this information during the collection of spontaneously reported ADRs. A future solution to improve identifiability and traceability is a fully integrated information technology infrastructure from production by the pharmaceutical company, delivery to the pharmacy, and preparation in the

pharmacy to administration/delivery to the patient. Information on brand name and batch number should then be available in the electronic patient database and easily accessible.[15,26]

A strength of the present study is the high number of products included and the relatively long period covered. The potential for misclassification, ADRs erroneously attributed to another biological with the same INN, is a potential limitation of the present study. Misclassification is, however, very difficult to quantify. A previous simulation study, which evaluated the risk for misclassification in three 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] In contrast to the previous study by Vermeer *et al*., case narratives were not specifically studied to obtain additional information on product name and batch number.[17] This might partially explain the lower levels of identifiability found by the present study. However, the case narrative search in the study by Vermeer *et al*. resulted in an increase in identifiability of only 0.5%, showing limited added value.

In conclusion, the present study showed identifiability by product name in EV to be over 90% for a relatively high number of biologicals for which biosimilars are approved in the EU market. Commercial name identifiability, however, showed a downward trend over time, which is mainly driven by a lower identifiability of a few products used mostly in oncology. Although the lower level of commercial name identifiability for these biologicals could not be related to the introduction of biosimilars, improvement is needed for all biologicals. Future initiatives to further improve identifiability and traceability based on an integrated information technology infrastructure are warranted.

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