EXPERT OPINION

Traceability of biologicals: present challenges in pharmacovigilance

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Introduction: Traceability is important in the postmarketing surveillance of biologicals, since changes in the manufacturing process may give rise to product- or batch-specific risks. With the expected expansion of the biosimilar market, there have been concerns about the ability to trace individual products within pharmacovigilance databases.

Areas covered: The authors discuss the present challenges in the traceability of biologicals in relation to pharmacovigilance, by exploring the processes involved in ensuring traceability. They explore both the existing systems that are in place for the recording of exposure information in clinical practice, as well as the critical steps involved in the transfer of exposure data to various pharmacovigilance databases.

Expert opinion: The existing systems ensure the traceability of biologicals down to the manufacturer within pharmacy records, but do not support the routine recording of batch information. Expected changes in supply chain standards provide opportunities to systematically record detailed exposure information. Spontaneous reporting systems are the most vulnerable link in ensuring traceability, due to the manual nature of data transfer. Efforts to improve the traceability should, in the short term, be focused toward encouraging health professionals and patients to systematically record and report detailed exposure information. Long-term solutions lie in expanding the accessibility to, and increasing the electronic exchange of exposure data.

Keywords: adverse drug reaction reporting systems, biologicals, biosimilars, electronic healthcare databases, follow-on biologics, pharmacovigilance, product identification, similar biological products, traceability

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1. Introduction

In 2002, a case series reported the unexpected occurrence of a rare form of anemia, pure red-cell aplasia (PRCA), in 13 patients treated with recombinant human erythropoietin (epoetin) [1]. Some of the patients had been receiving epoetin treatment for years, yet had only recently developed PRCA. At the time, the pharmacovigilance community had observed a similar unexpected surge in the reporting of epoetin-associated PRCA, and was up to the challenging task of addressing the emerging risk. In due course, it was found that most cases could be linked to a common manufacturing source of epoetin for which formulation changes had been issued in 1998 (Eprex®, Johnson & Johnson, New Brunswick, USA), upon which the risk could be successfully countered [2].

The sudden and dramatic rise in the risk of epoetin-associated PRCA has become exemplary for the potential for variability in the safety profile of biological medicinal products (see definition in **Table 1**). Due to the complex nature and manufacturing process of biologicals, small deviations in their manufacturing or formulation might impact the safety profile of the end product [3-5]. These differences in safety

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Article highlights.

- Adequate recording of drug exposure information in clinical practice, and ensuring the correct transfer of exposure data to pharmacovigilance data sources is essential to pharmacovigilance.
- For biological medicinal products, batch- and product-specific exposure information (i.e., beyond the biological substance) should be recorded, as differences in the safety profile could emerge within one product (from batch-to-batch) over time or between products containing the same active substance.
- Product-specific exposure data is routinely available within pharmacy dispensing records. Batch numbers are expected to be infrequently captured at present, but updated supply chain standards may enable the recording of variable product data in the near future.
- The extent to which dispensing data are accessible to other health professionals and patients is assumed to be variable. Detailed exposure information should therefore be recorded at the point of administration.
- Spontaneous reporting systems are the most vulnerable link in ensuring traceability, due to the manual nature of data transfer. Therefore, awareness about the need to report detailed information is necessary.
- Long-term efforts may be focused toward expanding the accessibility to and increasing the electronic exchange of exposure data.

This box summarizes key points contained in the article.

profile will most likely relate to immunological events. Also, in the particular case of Eprex, antibody formation was found to underlie the PRCA [6].

Deviations in safety profile may not only emerge within products, but also between related or similar products (**Table 1**) containing the same active biological substance. A recent study, for example, reported unexpected differences in the risk of inhibitor development between second and third generation recombinant factor VIII products [7]. Also, the unexpected increase in cases of thrombotic microangiopathy among patients treated with a particular formulation of interferon beta for which manufacturing changes had been issued (Rebif®, Merck, Darmstadt, Germany) [8], may indicate that the safety profile of this formulation differs from the related product (Avonex®, Biogen Idec, Cambridge, USA).

The prior examples testify to the importance of having a pharmacovigilance system in place that can signal any potential variability between products, and within products, especially after a change in the production process or formulation, over time. For the conduct of product-specific pharmacovigilance, unique identifiers like the trade name need to be available in pharmacovigilance systems (**Figure 1**). In addition, batch numbers are required to adequately assess the impact of manufacturing changes over time or signal any batch-specific issues.

With the arrival of the first biosimilars in European clinical practice and the expected expansion of the global biosimilar market [9], traceability has become increasingly important and become subject of a widespread debate [10-13]. Although a previous study from our group found that over 96% of the biological medicinal products for which biosimilars had been available were traceable up to the specific manufacturer in a major European spontaneous reporting system [14], it is unknown to what extent product traceability is ensured in other pharmacovigilance data sources. In addition, the same study found that individual batches were traceable in < 25% of the biologicals products, leaving considerable room for improvement.

The aim of the present article is to discuss the present challenges in the traceability of biologicals in relation to pharmacovigilance, by exploring the individual processes involved in ensuring their traceability. First, the existing systems that are in place for the recording of detailed exposure information in clinical practice are explored, as these form an important prerequisite to ensure traceability in pharmacovigilance databases. Second, the critical steps involved in the transfer of exposure data to various pharmacovigilance databases are explored. The primary focus will be on the clinical practice and pharmacovigilance systems in Europe, yet the principles and systems outlined here will, in certain aspects, be comparable to other countries and regions in the world.

2. Recording of exposure information in clinical practice

In the pharmaceutical supply chain from the manufacturer up to the patient, product- and batch-specific exposure information can be recorded during the pharmacy dispensing and/or during the administration or intake of the drug. This step is essential to maintain a link between the administered biological and the patient, also after discarding of the outer packaging.

2.1 Pharmacy dispensing

Biologicals are dispensed through a diversity of pharmacy distribution channels, including hospital pharmacies, community and outpatient pharmacies, and specialty pharmacies. During the pharmacy dispensing process, information about the biological is documented in the pharmacy system through scanning of the barcode, which is presented on the outer packaging. These barcodes typically comprise linear barcodes that hold information on the National Trade Item Number (NTIN) of the biological, like the '*Pharmazentralnummer*' in Germany, the National Drug Code in the US, or the '*Nordisk Varenummer*' in Norway, Sweden and Finland [15,16]. Since the NTIN is unique to the manufacturer, dosage form and strength of a product, product-specific exposure information will automatically be recorded. Also, in situations where no barcode technology is used to facilitate dispensing, the NTIN is likely to be recorded at the point of dispensing as

Table 1. Definitions of biological medicinal products.

Term	Description	Example, human growth hormone
Biological substance	A 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 [45]. Biological substances include substances derived from recombinant DNA technology or other biotechnological processes, substances derived from human blood or plasma, advanced therapy products (gene or somatic cell therapy), and immunological products (vaccines, toxins, serums or allergen products)	Recombinant human growth hormone, somatropin
Biological medicinal product or biological	A medicinal product for which the active substance is a biological substance [51]	Genotropin® (somatropin, Pfizer)
Similar biological product or biosimilar	A biological product containing the same biological substance as an already licensed biological product (i.e., the reference product), and which has been demonstrated to be similar to the reference product in terms of quality characteristics, biological activity, safety and efficacy [52,53]	Omnitrope® (somatropin, Sandoz), which demonstrated similarity to Genotropin
Related biological product	A biological product containing the same biological substance as an already licensed biological product, and which has been developed on the basis of an independent full application procedure, involving an independent benefit–risk assessment, not necessarily with the intention to show similarity to any reference biological product	Somatropin Biopartners® (somatropin, Biopartners), a prolonged-release formulation of somatropin

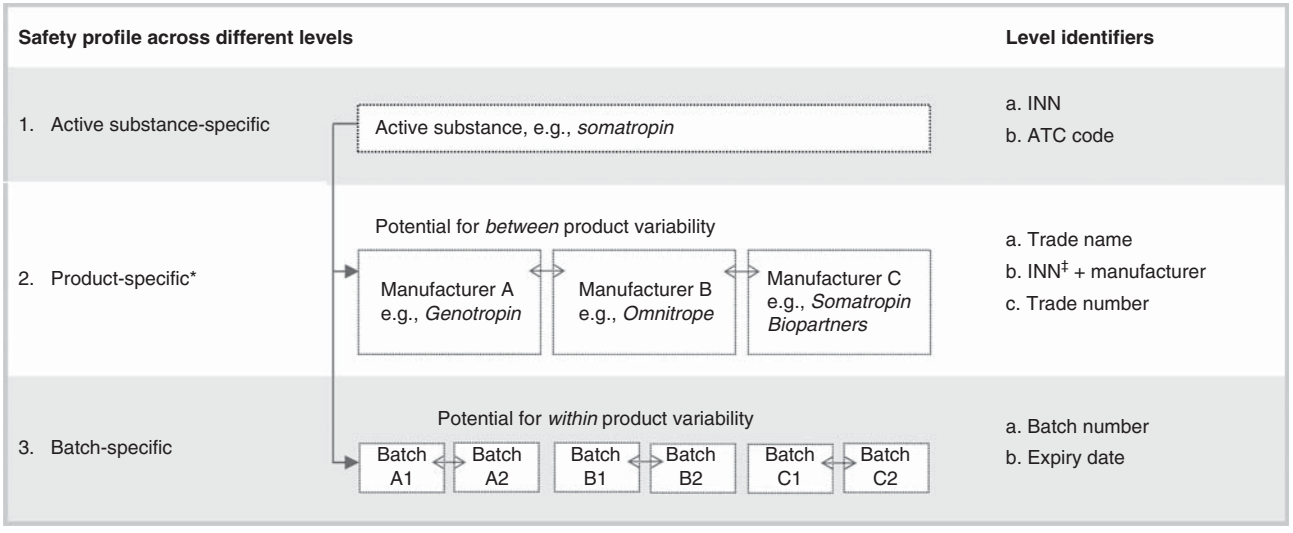

Figure 1. Potential for variability in the safety profile beyond the level of the active substance of biological medicinal products, and required unique identifiers.

*Products containing the same active biological substance comprise either similar biological products (established similarity in terms of quality, efficacy and safety), or related biological products (no implied similarity, see **Table 1**). The provided examples are for illustrative purposes only.

‡The International Nonproprietary Name (INN), or generic name, is a globally recognized name that facilitates the unambiguous identification of active substances. However, since biosimilars and other related biologicals regularly share the same INN, other product identifiers like the trade name are required for the conduct of product-specific pharmacovigilance.

ATC: Anatomical therapeutic chemical.

this is required to support the back office (e.g., for drug procurement and reimbursement). A survey among hospital and outpatient pharmacies in the Netherlands (***see methods in* Box 1**) confirmed that biological products listed in the individual patient's pharmacy records can always be traced back to the manufacturer.

The product batch number should, however, be manually recorded when linear barcodes are used to facilitate dispensing, as these barcodes typically do not include variable

Box 1. Description of research methods.

Survey among Dutch pharmacists
All 75 hospital pharmacies and 20 outpatient pharmacies pertaining to the Utrecht Pharmacy Practice Network for Education and Research (UPPER) [49] were approached to evaluate the measures taken in clinical practice to ensure the traceability of biological medicinal products. Two separate, standardized online questionnaires were developed. The questionnaires were in Dutch and consisted of five parts: general information about the pharmacy, prescription policies, registration of detailed product information, reporting of adverse drug reactions and final suggestions/remarks.
Pharmacies were first approached on 20 December 2013, and a reminder was sent on 7 January 2014. Overall, 20 (27%) hospital pharmacies and 7 (35%) outpatient pharmacists completed the online questionnaire.
Survey among national competent authorities in Europe
A non-urgent information (NUI) request was circulated among the national competent authorities of all 31 countries in the European Economic Area to evaluate the measures taken to ensure the traceability of biological medicinal products in adverse drug reaction (ADR) reports. A NUI is an established method for the exchange of non-urgent pharmacovigilance information between national competent authorities and the European Medicines Agency (EMA) [50]. The NUI request consisted of six questions relating to the procedures, systems and requirements in place to ensure traceability of biological products, and on the national implementation of the new pharmacovigilance directive.
The NUI request was circulated on 16 December 2013, and a reminder was sent on 16 January 2014. Six weeks after the first mailing, the last responses were received. Overall, 19 (61%) countries responded to the NUI request.

product data due to limited capacity. Therefore, batch numbers of biologicals are expected to be infrequently captured in dispensing records. This was confirmed within the pharmacist survey: only 2 out of the 27 pharmacies (7%) stated batch numbers are routinely recorded for biological products. The most frequently cited reasons for not recording this information comprise the lack of specific tools to facilitate the registration (n = 17; 63%), but also the perceived absence of any need (n = 12; 44%). Interestingly, the survey showed that batch numbers are, on the other hand, routinely recorded for products that are prepared for administration in the hospital pharmacy, which probably relates to good preparation practice. Likewise, batch numbers are also expected to be routinely recorded for blood- and plasma-derived products, due to legal requirements [17].

Several initiatives are currently ongoing, or have recently been implemented, to improve the supply chain traceability. As of 2011, France has been the first EU country to require a data matrix on all pharmaceutical packaging that not only encodes the NTIN, but also the batch number and expiry date [18]. Through barcode-scanning this variable product information will be automatically recorded in the patient's pharmacy records. Also, three other EU countries (Belgium, Italy and Greece) have recently adopted a serialization requirement, allowing tracing of individual units of a medicinal product (i.e., each different package of the same presentation within the same batch) along a unique serial number [15]. The recently introduced EU legislation on falsified medicines will also ensure supply chain traceability down to the individual package level in other EU countries [19]. As of 2016, barcodes will be required on individual packages that will be checked into a database by the manufacturer, and checked out during the pharmacy dispensing process. However, it is still undecided whether these new barcodes (or radio-frequency tags) will also encode the product batch number and/or expiry date [20]. Similar initiatives to secure the pharmaceutical supply chain are ongoing in other countries and regions in the world, including in the US and China [21,22].

2.2 Administration of biologicals

Use of biologicals is often hospital-based, due to the multiple and complex procedures involved in the preparation and administration of these medicines, and in the clinical monitoring of the patients receiving them. The recording of exposure information will hereby depend on, among others, the type of medical records (electronic vs paper-based), the existence of a linkage between pharmacy and medical records or full integration of both, the local procedures with regard to the recording of exposure information and the type of biological. With respect to the latter, requirements may apply for specific products. For example, EU guidelines require that the product name and batch number for blood- and plasma-derived products are recorded at the point of administration [17]. Also, since the approval of the first infliximab biosimilar, the EU product information of infliximab-containing products recommends the recording of the product name and batch number in the patient file [23]. The patient alert card for infliximab has accordingly been updated with the recommendation for patients to also record the trade name and batch number. New developments that may result in the systematic recording of drug exposure information at the point of administration include the increasing use of barcode medication-verification technology at the site of administration [24,25].

A substantial proportion of biological therapies is nowadays self-administered by the patient, or at least administered in the home care setting. To facilitate the recording of detailed exposure information in home administration (i.e., product- and/or batch-specific information), specific aids have been developed such as mobile phone applications [26,27].

3. Transferring exposure information to pharmacovigilance databases

Several data sources and methods are used to assess the benefit–risk balance of biologicals after initial licensure [28,29].

Spontaneous reporting systems, which rely on adverse drug reaction (ADR) reporting from routine practice, have traditionally formed the mainstay of pharmacovigilance. Electronic healthcare databases, including databases of medical records, claims databases and disease or drug registries, play, however, an increasingly important role in pharmacovigilance [29]. Due to the difference in data collection between spontaneous reporting systems and healthcare databases (*ad hoc* vs systematic), differences may exist in the availability of detailed exposure information.

3.1 Spontaneous reporting systems

Nowadays, virtually every country in the world has some sort of scheme in place to allow health professionals and/or patients to submit ADR reports to national or regional pharmacovigilance centers [30]. Although international standards have been developed on the data elements within these ADR reports [31], the actual amount of data provided is up to the discretion of the reporter. Namely, the individual data elements need to be manually filled into the electronic or paper-based ADR reporting form. The traceability in ADR reports will consequently depend both on the availability of exposure information to the reporter as well as their willingness to report the information.

Several factors come into play with respect to the availability of the exposure information to the reporter. For ADRs with a relative short time-to-onset, exposure information might be obtained from the still available packaging. However, in case the package has already been discarded, it will either depend on the reporter's ability to recall exposure, or on the available information in the pharmacy and/or medical records, including the extent to which these records are accessible to the reporter. For example, the doctor confronted with the ADR might not have been the doctor prescribing the biological and could consequently not have access to the required exposure information. Similarly, in case of patient reporting, it will be particularly challenging to retrieve the exposure information for hospital-administered biologicals, such as monoclonal antibodies used in cancer treatments.

The recently updated EU pharmacovigilance legislation has provided an important opportunity to improve the traceability of biologicals in ADR reports. Article 102(e) of the new directive states that Member States should ensure that '*all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, and the batch number*' [32]. As a first deliverable, the guideline on good pharmacovigilance practices now requires follow-up on ADR reports pertaining to biologicals in which information about the batches and products involved is lacking [33]. The further implementation of this legislation is, however, up to the individual Member States, for which specific legal obligations may be imposed on health professionals.

A survey among EU member states (***see methods in*** **Box 1**) showed that 1 out of the 19 responding countries had used the opportunity to impose specific obligations related to traceability on health professionals. Specifically, the competent authority had developed an ADR reporting guideline that, after adoption into the national law, made it obligatory for health professionals to report brand names and batch numbers for biologicals. In addition, 9 out of the 19 (47%) responding countries had introduced or were intending to introduce new measures to improve biological traceability. As shown in **Table 2**, these measures include, among others, informing patients and health professionals about the need to provide detailed information of biological medicinal products when reporting ADRs (n = 8), and the introduction of new functionalities to spontaneous reporting systems (n = 4). One country was exploring the possibility of establishing a connection with hospital and pharmacy IT systems, allowing exposure information to be automatically transferred in ADR reports.

3.2 Electronic healthcare databases

Databases of electronic healthcare information have the advantage of ensuring the routine and systematic recording of clinical data. The availability of detailed exposure information consequently directly relates to the extent to which these data are systematically recorded in medical or pharmacy records, provided that this information is correctly and completely transferred. Claims databases are, for example, an important data source for studying the safety profile of biologicals in routine clinical care in the US [34,35]. Drug exposure in these databases is typically recorded along the NTIN (or reimbursement number) of the drug, which ensures that products are traceable up to the manufacturer, dosage form and strength. Therefore, these claims database can be a readily available tool for the conduct of product-specific pharmacovigilance, whereas batch-specific pharmacovigilance will not be possible.

In Europe, on the other hand, academia-initiated registers play an important role in the pharmacovigilance of biologicals. A wide variety of registers are currently in place, ranging from small, single-center drug registers to large, multinational disease registers that include multiple treatment arms and collect information on a range of clinical outcomes. Also, the procedures for the exchange of exposure data may vary according to the register. The majority of existing registers comprise specifically implemented long-term cohorts that collect information on treatment details and patient outcomes at predefined intervals, for example, the British rheumatology register [36,37] or the European PedNet Haemophilia register [38]. The availability of detailed exposure information will thus be determined by the agreed procedures for the reporting of exposure data. On the other hand, for the registers that are based upon the electronic exchange of routinely collected clinical data, for example, the Swedish rheumatology register [36,37] or the Danish Multiple Sclerosis Registry [39], the exposure information will typically be equal to the data recorded in clinical practice.

Table 2. Planned or adopted measures by EU member states (n = 19) to improve traceability of biological products in spontaneous reporting systems.

Category of measures	Member states, n (%)	Specification of measures
Provide extra information to healthcare professionals and patients	8 (42%)	Set up educational programs and/or start dialog with stakeholders to raise awareness and knowledge about the traceability of biologicals. Provide information and guidelines on the website of the competent authority to inform patients, healthcare professional and marketing authorization holders about the need to provide detailed information of biological medicinal products when reporting ADRs
Functionalities to the spontaneous reporting system	4 (21%)	Develop or update electronic reporting systems, including mobile phone applications, to include a specific field for the registration of batch numbers Introduce new features to the electronic reporting system to facilitate brand traceability, for example, by providing a list of brand names when a reporter only selects the INN for a biological product Incorporate extra questions in the electronic reporting systems, to facilitate registration of extra information about previous used biological products and specification of these products
Follow-up on ADR reports of biological products	2 (11%)	Follow-up on all ADR reports of biological products with missing brand name or batch number. Perform quality checks on the ADR reports for biological products by introducing a functionality that is able to identify ADR reports for biological products
Other	2 (11%)	Develop legal tools and technical solutions that make tracing of biological products through the whole supply chain possible. Establish a connection with hospital and pharmacy IT systems

ADR: Adverse drug reaction; INN: International nonproprietary name.

Though beyond of the scope of this review, it should be noted that good pharmacovigilance not only requires careful collection of exposure but also of outcome data. While, for example, some registers only capture routinely available clinical data, for other registers, great efforts are made to collect information on the nature, seriousness and severity of adverse events in much more detail than would be possible based upon routine data.

4. Conclusion

On basis of the review of the existing systems, it is concluded that product-traceability of biologicals is routinely ensured within the individual patient's pharmacy records. Variable product information like the product batch number is, contrarily, expected to be infrequently captured in dispensing records at present, though this may differ according to national traceability regulations and local procedures, as well as the specific type of biological. Similarly, the extent to which product- and batch-specific exposure information is available to other health professionals and patients is assumed to be variable and dependent on, among others, the existence of a linkage between pharmacy and medical records or full integration of both, and local procedures with regard to recording of exposure data. Once adequately available in clinical practice, it is essential that exposure data is correctly and completely transferred in spontaneous ADR reports, and databases of electronic healthcare information.

5. Expert opinion

Traceability of biologicals for pharmacovigilance purposes comprises a multifaceted challenge, involving both the presence of robust systems to ensure the traceability of individual products and batches throughout the pharmaceutical supply chain as well as the correct and complete transfer of exposure information to pharmacovigilance data sources. Overcoming this challenge will, therefore, require a multifaceted approach, tackling both aspects of traceability. At the same time, traceability is not unique to pharmacovigilance, but actually at the interface of multiple needs. Repeated incidents of counterfeit biologicals entering the mainstream drug supply in Europe and the US have, for example, highlighted the need to further improve the supply chain integrity [40,41].

5.1 Ongoing challenges and potential solutions: pharmaceutical supply chain

Various countries around the world are currently implementing, or have recently implemented, enhanced pharmaceutical supply chain standards that will ensure the traceability of each individual unit of a medicinal product from the point of manufacturing up to the patient's pharmacy record. Although these measures arose from the need to prevent falsified medicines from entering the legal pharmaceutical supply chain, they provide an important opportunity to systematically record detailed exposure information in the patient's pharmacy records for pharmacovigilance purposes. This will mostly

benefit the traceability of individual batches, as it has been identified that existing systems already ensure the traceability of biologicals down to the manufacturer.

The extent to which these dispensing data are consequently available to other health professionals and patients will depend on the existence of a linkage between pharmacy and medical records or full integration of both, and the possibility for patients to access their medical and/or pharmacy records. Long-term solutions therefore lie in integrating pharmacy and medical data, and expanding patient access to medical records. It is, however, recognized that most countries are only in the beginning stages of implementing health information technologies and data exchange across providers and with patients is not yet common practice [42,43]. In the short term, it will therefore remain important to adequately record detailed exposure information at the point of administration. A specific paragraph on the importance of traceability could, for example, be included in the healthcare label and/or patient information leaflet. Also, patients may contribute to the traceability of hospital-administered products by recording the batch number and trade name, as, for example, recommended within the patient alert card for infliximab. As administration practices, however, remain a matter of clinical governance and good clinical practice, the actual implementation of these recommendations is uncertain.

5.2 Ongoing challenges and potential solutions: pharmacovigilance data sources

It is recognized that the data transfer to spontaneous reporting systems comprises a particularly vulnerable link in ensuring traceability. Spontaneous reporting systems rely on the voluntary reporting of ADRs by health professionals and patients, and due to the *ad hoc* and manual nature of data transfer, exposure information might be incompletely or incorrectly attributed. Therefore, besides ensuring the recording of detailed exposure information in clinical practice, it is important to encourage reporters to provide product trade names, or other unique product identifiers, and batch numbers. As shown in the survey, several EU member states have plans to further raise awareness of the importance for traceability of biological products. Educational programs for ADR reporting that involve periodic mailings have previously, however, been shown to only have a temporal effect on the reporting behavior [44]. On the other hand, (time-consuming) educational outreach visits and directly accessible reminders did show prolonged effects on the reporting behavior [44,45]. Reminders regarding product traceability might, for example, be provided within the label information of the biological product or in the (electronic) reporting form.

An even more robust solution would be the establishment of direct links to the patient's pharmacy or medical records, as proposed by one of the surveyed member states. Tools for integrating ADR reporting schemes into hospital information systems have previously been developed, and shown to facilitate and increase the rate of ADR reporting [46]. In particular, such integrated ADR reporting systems will eliminate the potential for errors associated with the manual transfer of data, as detailed exposure information can be automatically transferred to the reporting form. Though some regulatory authorities are already exploring the possibilities of integrating ADR reporting schemes into pharmacy/medical software [47], it is recognized that the actual implementation hereof could face many challenges, including legal barriers, concerns related to data protection and privacy and technical difficulties related to the diversity of healthcare systems. Therefore, even though it does appear promising, this may constitute a rather long-term solution.

As compared to the *ad hoc* data collection through spontaneous reports, electronic healthcare databases have the advantage of ensuring the routine and systematic recording of clinical data. With respect to traceability, it is therefore important to ensure that procedures are in place for the transfer or reporting of exposure information.

In the ongoing debate about the International Nonproprietary Names (INN) policy for similar biological products, it has also been suggested that distinguishable INNs are needed to ensure adequate product traceability of biological products [10-13]. According to a draft proposal, a four letter code, distinct from the INN, may be assigned to all biological substances [48]. This 'Biological Qualifier code' uniquely identifies the manufacturer and manufacturing site of the biological. Reporters might erroneously attribute an ADR to the reference product instead of the biosimilar (or vice versa); however, there is currently no data that additional identifiers (on top of distinct brand names) will reduce the potential for misattribution. Regardless of the method used to facilitate the identification of individual products, adequate procedures need to be in place to ensure that either of these unique identifiers are recorded in clinical practice and (where required) transferred to pharmacovigilance databases.

Declaration of interest

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