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# Traceability of biologicals: challenges in pharmacovigilance

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## Introduction

Biological active substances are multifaceted molecules produced by using complex manufacturing processes with many up- or downstream steps that shape the overall safety, quality and efficacy, unlike chemically synthesized medicines. The manufacturing process is a determinant and minor changes in any manufacturing step can affect the product quality, and subsequently its safety and efficacy. Advances in biotechnology and analytical sciences allow greater characterization and control of biologicals, but biologicals fundamental complexity, as well as their immunogenicity, manufacturing variability, stability, cold chain and product traceability creates specific challenges for pharmacovigilance (GVP, 2016).

This article provides an overview regarding the traceability of biological as a high challenge in implementation of good pharmacovigilance practices.

## Materials and methods

Relevant EU legislations have been reviewed, in general, as well as PubMed, Medline and other relevant websites with articles evaluating the impact of EU regulatory requirements and activities related to implementation of good PV practices in order to obtain proper traceability of biologicals.

## Results and discussion

Biologicals constitute a very diverse group of products for a wide range of therapeutic areas and the clinical settings for prescription, dispensing, supply and administration are equally varied. Pharmacovigilance of biologicals is inevitable to ensure continuous product and batch traceability in clinical use, since the manufacturing variability over time in the post-authorization phase within and across products with similar active substances results in greater inherent variability in product characteristics unlike chemically-synthesized medicines.

It is essential to acquire different products with the same INN (reference product, biosimilar or related product) to be readily distinguishable in order that newly emerging and product-specific safety concerns and immunogenicity, are rapidly detected and evaluated throughout a product life-cycle. Than the supply can be traced to locations and even to patients if necessary. Because any product usually retains the same product name following a significant change to manufacturing process, batch traceability is an important aspect to be considered in any associated updates to risk management plan. Product name and batch information are included in the product packaging, so this information is available to be recorded and reported at all levels in the supply chain from manufacturer release to prescription, dispensing and patient administration. (GVP, 2016)

Therefore biological drugs traceability needs to be fully integrated in different healthcare settings and infrastructure. Infrastructure for electronic data recording and record linkage may vary across products and between countries. It is important to acknowledge that most biologicals are supplied in a hospital setting and when record linkage is not established, other methods such as routine bar code scanning at all points in the supply chain have to be used in order to collect exposure information. It is inevitable national health authorities to cooperate towards better integration and automation of prescription information. The product name and batch number of an administered biological should be recorded by the healthcare professional and be provided to the patient especially when different versions of the same active substance are available concomitantly on the market and interchangeably used by the same patient. The routine PV activities assessed in Risk management plans (RMP) always explain the measures that are introduced in clinical

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setting for follow-up on case reports in order to obtain the information of product name and batch number. This information are essential for accomplishment of signal detection activities and identification of batch-specific safety issues and adverse events of special interests (AESIs), recognized as important potential risks for which specific safety surveillance will be necessary. As part of additional PV activities Marketing Amortization Holder (MAH) have to explain any additional measures introduced in collaboration with the national competent authorities to support traceability of the biological product such as provision of "sticky" labels or bar coding; Additional activities are performed with the intention of measurement of background rates for AESIs, preferably by indication, in the age group targeted by the product;

Also continuous monitoring of suspected adverse reaction reporting frequencies or rates for AESIs based on available data on exposure and comparing such rates to relevant defined background rates (using methods such as 'observed vs expected' analyses) are always presented in this part of RMP. Use of existing patient registries, other data sources or establishment of a new registry when existing data sources are inadequate is acceptable approach in additional PV measures. Limited traceability of biologics, in particular with regard to the batch number, is associated with incomplete recording of exposure information in clinical practice. (Vermeer et al., 2015)

Brand name and batch number traceability for biologics ADR reports are generally low. The literature search results confirmed that brand name recording in routine hospital processes ranged from 79 to 91%, whereas batch numbers were less routinely recorded, ranging from 38 to 58%. Additionally, paper-based recording of product details was more commonly used for recording information. A total of 6108 electronic ADR reports were submitted to the Yellow Card Scheme for recombinant biologics, of which 38% had an identifiable brand name and only 15% recognizable batch numbers. I batch number traceability in electronic ADR reports improved slightly after the implementation of the EU pharmacovigilance legislation in 2012, but no improvement of brand name traceability was observed. (Klein et al., 2018, 2019)

The effected guidelines of GVP for Biological medical products, acknowledge that current pharmaceutical barcode standards in the EU do not support the automatic recording of dynamic product information, such as batch numbers and expiry dates, by means of electronic barcode scanning in clinical practice. New barcode requirements, such as the 2D DataMatrix with encoded batch numbers and expiry dates, provided on both the primary and the secondary package, can facilitate routine barcode scanning at all points in the supply chain in different healthcare settings.

## Conclusion

Traceability of biologicals for pharmacovigilance purposes comprises the presence of robust systems to ensure the traceability of individual products and batches throughout the pharmaceutical supply. Establishment of a full track-and-trace system for medicines with electronic imprisonment of relevant exposure information will enable early identification of medication errors, falsified products or other signals and will empower early implementation of risk minimization measures resulting in improved public health. It will also result in improved medication safety and will contribute to enhanced pharmacovigilance system.

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