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# Pharmacovigilance of Biopharmaceuticals
## Challenges Remain

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## Abstract

Biopharmaceuticals are important treatment options for a variety of chronic and sometimes life-threatening diseases. Compared with the traditional small molecule drugs, biopharmaceuticals have specific characteristics, which might also influence their safety profile. They have, for example, a complex production process, limited predictability of preclinical to clinical data, a high potential for immunogenicity, and adverse events can often be related to an exaggerated pharmacology. The limited predictability of preclinical to clinical data and the known limitations of randomized controlled trials results in limited knowledge of the safety profile of biopharmaceuticals at the point of their approval, underlining the need for pharmacovigilance. Due to their specific characteristics, pharmacovigilance activities required for biopharmaceuticals might differ from those required for small molecules. This review discusses characteristics and potential challenges with the pharmacovigilance and risk management of biopharmaceuticals as compared with small molecules, and proposes remedies for some of the emerging problems.

Spontaneous reporting of adverse drug reactions (ADRs) is important in the detection of new, rare and/or serious ADRs. However, causality assessment remains complicated because of concomitant diseases or drugs. This is particularly the case with biopharmaceuticals, as they are often indicated to treat severe and/or life-threatening diseases in patients who often have other diseases and are treated with concomitant medication.

Proactive risk management has been implemented in the EU by the obligatory submission of an EU risk management plan (EU-RMP). In this, the (potential) risks should be described and pharmacovigilance activities proposed. Pharmacovigilance activities can be either routine or additional

(post-authorization safety studies [PASS]) activities. During safety assessment, stakeholders are encouraged to use knowledge obtained with biopharmaceuticals with a comparable pharmacology. PASS of biopharmaceuticals with a comparable pharmacology may therefore be used to complement each other.

Since biopharmaceuticals are often used in a specialized hospital setting, it is expected that large population-based databases will contain limited information on biopharmaceuticals. Registries have therefore been shown to be an important tool to obtain pharmacovigilance data.

Since small changes in the production and purification process might alter the safety profile, activities to improve traceability of the specific biopharmaceutical responsible for the ADR should be taken into account.

Key messages in safety management of biopharmaceuticals remain: be prepared for the unexpected, be aware of confounding by disease (severity) and maintain exposure ascertainment/traceability throughout the logistical chain.

More than 25 years ago, recombinant DNA and hybridoma technologies were introduced, which enabled the large-scale production of biopharmaceuticals. This resulted in new treatments for a variety of chronic diseases such as rheumatoid arthritis and Crohn's disease, and in some cases life-threatening diseases such as cancer. Today's practice of medicine would be unthinkable without the availability of these compounds, which have shaped important innovative therapeutic options.[1,2] However, compared with small molecules, biopharmaceuticals have specific characteristics and therefore may carry specific risks. Some striking examples of risks related to the use of biopharmaceuticals are the occurrence of tuberculosis with the use of tumour necrosis factor (TNF)-α inhibitors, especially infliximab,[3,4] the dramatically increased incidence of pure red cell aplasia in patients treated with one particular formulation of recombinant human epoetin,[5] and the cytokine storm occurring in healthy volunteers treated with the superagonist anti-CD28 monoclonal antibody TGN1412 (TeGenero).[6]

The risks of biopharmaceuticals can be related to their specific characteristics (table I). Adverse events can often be explained by an exaggerated pharmacology.[7] TNFα has a role in the immune response to the mycobacteria responsible for tuberculosis. Inhibition of TNFα will lead to an increase of the activity of the bacilli and cause disease.[3] The increased incidence of pure red cell aplasia was explained by an immunogenic response to endogenous molecules, which occurred following changes in the manufacturing of epoetin alfa.[8,10] The limited predictability of preclinical trials has been illustrated by the cytokine storm occurring in the TeGenero phase 1 trial. The cytokine storm had not been seen in the preclinical phases.[6]

It is known that knowledge on the full safety profile of a drug is limited at the point of marketing due to the limitations of randomized controlled trials, including, among others, limited sample size and duration and a homogeneous population.[11] For biopharmaceuticals this is further complicated due to the limited data available from animal studies.[2] Postmarketing safety data therefore offer a valuable and necessary complement to the clinical trials.[11] Pharmacovigilance activities can consist of a variety of activities, including spontaneous reporting of adverse drug reactions (ADRs) [routine pharmacovigilance] and additional pharmacovigilance (post-authorization safety studies [PASS]).[12]

Because of the differences between biopharmaceuticals and small molecules, the question arises what implications these may have for pharmacovigilance and risk management of

biopharmaceuticals (vaccines not taken into account) compared with small molecules. This review, therefore, aims to discuss characteristics and potential challenges with the pharmacovigilance and risk management of biopharmaceuticals compared with small molecules, and to propose remedies for some of the emerging problems.

## 1. Pharmacovigilance of Biopharmaceuticals

### 1.1 Nature of Safety Problems Identified Postmarketing

The safety problems associated with small molecules that are identified postmarketing can usually be categorized into the system organ classes (SOCs) 'hepatic disorders', 'cardiac disorders', 'blood and lymphatic system disorders', or 'nervous system disorders'.[13-15] For biopharmaceuticals, these safety problems are usually categorized into the SOCs 'general disorders' and 'administration site conditions' due to the hypersensitivity and infusion reactions related to the intravenous mode of administration of many biopharmaceuticals, and in the SOC 'infections and infestations' due to the immunomodulatory effect of many biopharmaceuticals.[16] Differences in the nature of these safety problems may have implications for risk management.

### 1.2 Spontaneous Reporting of Adverse Drug Reactions

Routine pharmacovigilance, including spontaneous reporting of ADRs, has an important function in the detection of new, rare and/or serious ADRs.[17] However, as widely described and acknowledged, causality assessment to establish a relationship between a drug and an ADR remains difficult[18] and may be confounded by a variety of factors, including concomitant diseases, genetics, severity of disease, and concomitant medication. In addition, a plausible temporal relationship between intake of the drug and occurrence of the event is a factor that is usually taken into account during causality assessment.[19] For biopharmaceuticals, multiple difficulties related to spontaneous reporting of ADRs are identified and expected. Biopharmaceuticals are often indicated to treat severe and/or life-threatening diseases.[2] Patients treated with biopharmaceuticals therefore often have multiple diseases and are treated with multiple drugs, which may hamper adequate causality assessment. The possible relationship between the use of infliximab and the occurrence of lymphoma in

**Table I.** Differences between biopharmaceuticals and small molecules, and examples of safety-related problems related to these differences[1,2,7-9]

| Biopharmaceuticals vs small molecules | Examples of safety-related problems |
|---|---|
| Large complicated molecules and often mixtures of different isoforms | |
| Relatively unstable | Formation of aggregates can influence the immunogenic potential |
| Complex production and purification process/(small) changes in manufacturing process can influence safety | Pure red cell aplasia in patients treated with epoetin alfa following manufacturing changes |
| Manufactured in living cells | The host cell used and contamination with host cell DNA and host cell material can influence the immunogenic potential, e.g. natural interleukin (IL)-2 was reported to be less immunogenic than IL-2 produced by *Escherichia coli* |
| Potential for immunogenicity | Thrombocytopenia after treatment with recombinant thrombopoietin due to neutralizing antibodies blocking endogenous thrombopoietin |
| Limited predictability of preclinical to clinical data due to species-specific action and immunogenicity of human proteins in animals | Cytokine storm in TeGenero phase I trial<br>Human interferon has a different pharmacological effect to mouse interferon in mice |
| Adverse events often related to exaggerated pharmacology | Tuberculosis with the use of the tumour necrosis factor-$\alpha$ inhibitor infliximab |

patients with inflammatory bowel disease has, for example, been confounded by concomitant use of other immunosuppressive agents.[20] In addition, the relationship between intake of the drug and occurrence of the adverse event is often difficult to assess. This can be illustrated by the recently published letter in which an indication of a relationship between the use of TNFα inhibitors and occurrence of leukaemia was described. Exposure time until the diagnosis of leukaemia differed between a few months up to several years.[21] The difficult-to-assess relationship between intake of the drug and occurrence of ADRs should be kept in mind by the healthcare professionals, regulators and industry.

### 1.3 Proactive Risk Management

Many reports have asked for a more proactive approach towards the identification and quantification of safety problems as an important step for improvement.[22,23] This has been anticipated by the implementation of guidelines for risk management programmes.[24] In the EU, marketing applicants are obliged to submit an EU risk management plan (EU-RMP) for all marketing applications of new chemical entities, including biosimilars, since November 2005. An EU-RMP summarizes the results of the performed preclinical and clinical trials, laid down in safety specifications, and proposes pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products; the assessment of the effectiveness of these interventions should also be evaluated.[12,25] Safety specifications can be classified as identified risks (adequate evidence of an association with the medicinal product), potential risks (there is a basis for suspicion of an association with the medicinal product but the association has not been confirmed) or missing information, including populations not studied in the pre-authorization phase. As described in the introduction, adverse events related to the use of biopharmaceuticals can often be related to an exaggerated pharmacology and, as shown by the occurrence of tuberculosis with the use of the TNFα inhibitors, in some cases this can be regarded as a class effect. Another example includes the occurrence of progressive multifocal leukoencephalopathy (PML) with the use of certain monoclonal antibodies. The occurrence of PML has already been linked to certain diseases in which the patients were immunocompromised, e.g. HIV infection, and might also be related to certain biopharmaceuticals with a strong immunosuppressive mode of action.[26] We therefore call marketing applicants and regulators to clearly evaluate the knowledge on the safety profile of biopharmaceuticals with a comparable pharmacology and include these adverse events as an identified or a potential risk (based on the available information) in the EU-RMP of the biopharmaceutical under assessment. The pharmacovigilance activities proposed in the EU-RMP comprise both routine and additional activities (PASS).[12] Routine pharmacovigilance by way of spontaneous reports can lead to a new safety signal, which should result in an update of the EU-RMP. PASS is defined as a pharmacoepidemiological study (non-interventional) or a clinical trial (interventional) carried out in accordance with the terms of the marketing authorization, conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product.[27] The requirements for an EU-RMP are similar for biopharmaceuticals and small molecules.

Although the first recombinant insulin was approved in 1982,[28] biopharmaceuticals can be considered as a relatively new class of drugs, and the predictive value of preclinical studies is limited due to species-specific actions and immunogenicity.[29] As a result, more uncertainties may exist regarding the safety profile of biopharmaceuticals at the moment of approval compared with small molecules. This underlines the need for an active approach towards pharmacovigilance of biopharmaceuticals in the EU-RMP. PASS will therefore be an important tool for the identification and quantification of safety hazards related to the use of biopharmaceuticals. However, a difficulty remaining with PASS of biopharmaceuticals is the sometimes difficult-to-establish temporal relationship between occurrence of the adverse event and exposure to the biopharma-

ceutical. The duration of PASS is therefore difficult to determine, which should be taken into consideration during the developmental phase of the study, and, in our opinion, should be discussed in the EU-RMP. In addition, the number of patients to be included in PASS should be taken into consideration, especially with rare adverse events.

The data sources that will provide adequate information for PASS are anticipated to be different between biopharmaceuticals and small molecules. Compared with small molecules, biopharmaceuticals are often used in a specialized (hospital) setting. Large population-based databases, often including general practitioner and community pharmacy data, are therefore expected to include limited data on biopharmaceuticals, and pharmacovigilance data will have to be obtained from different sources. Disease and exposure registries are expected to be a valuable data source for the study of exposure and safety of biopharmaceuticals. The value of these registries has already been established, for example, for the postmarketing safety evaluation of biopharmaceuticals for patients with rheumatoid arthritis. A Danish registry covered approximately 90% of all patients treated with biopharmaceuticals and registered a 20-fold increase of non-serious adverse events and a doubling of serious adverse events compared with the mandatory reports to the Danish Medicines Agency.[30]

As PASS of biopharmaceuticals may be mostly conducted in registries, we call for marketing applicants to clearly evaluate the validity of proposed registries, taking into account the number of patients included in the registry. In addition, initiation of a registry is time-consuming and costly and healthcare professionals need to be willing to participate and provide patient and treatment data to the registry. In case it is decided that a pharmacovigilance study will be conducted in a registry it is, in our view, important that the independence of the registry and privacy of the patient is guaranteed and that data on patient characteristics should not be used for commercial purposes. In addition to registries, pooling of data from randomized controlled clinical trials has also shown to serve as a valuable tool to assess adverse events of these agents that might be considered in the EU-RMP. This value can be illustrated by the observed 3.3-fold increased risk for malignancies and the 2.0-fold increased risk for serious infections in patients treated with TNF antagonists after pooling of clinical trial data.[31]

In our opinion, safety data obtained with PASS for a particular biopharmaceutical should be used to complement the knowledge on the safety profile of a biopharmaceutical with a comparable pharmacology, which might limit the need for PASS. This can also be related to the recent marketing approval of biosimilars. At the point of marketing of the biosimilar much experience has already been gained with the reference biopharmaceutical, and unless there are specific safety problems expected with the biosimilar, mainly immunogenicity, or PASS is ongoing for the reference biopharmaceutical, there is a limited need to conduct additional PASS for biosimilars. PASS of biosimilars should, therefore, focus mostly on immunogenicity. For example, for biosimilar products containing recombinant erythropoietins, PASS to study the occurrence of pure red cell aplasia should be carried out.[32]

### 1.4 Specific Considerations

Changes in the complex production and purification processes of biopharmaceuticals can lead to serious health problems. To be able to identify this type of problem at an early stage, activities to improve traceability of the biopharmaceutical responsible for the ADR, for example the specific batch, should specifically be taken into account. Recording of batch numbers is therefore important during reports of ADRs. Activities to capture the traceability should, in our view, be discussed in the RMP.

## 2. Conclusions

Biopharmaceuticals have specific characteristics, and challenges are to be encountered during pharmacovigilance and risk management. A summary of the challenges encountered during the pharmacovigilance and risk management of

**Table II.** Summary of the specific challenges expected for pharmacovigilance and risk management of biopharmaceuticals

| Expected challenges | Possible remedies |
|---|---|
| Nature of safety specifications | Because of specific characteristics, the nature of safety specifications are expected to be different for biopharmaceuticals, and the mode of action should be taken into account during preclinical and clinical studies. In addition, adverse drug reactions that might be related to the pharmacology of the biopharmaceutical should be considered for all biopharmaceuticals with a comparable pharmacology |
| Limited predictability of preclinical to clinical data | At point of approval there is limited knowledge on the safety profile of biopharmaceuticals, and more uncertainties for biopharmaceuticals remain. Active pharmacovigilance is therefore important for biopharmaceuticals |
| Often used in patients with multiple diseases using multiple drugs, and difficult-to-establish relationship between intake of the drug and adverse drug reaction | Difficult causality assessment for spontaneous reporting of biopharmaceuticals. These factors should be taken into account by healthcare professionals, regulators and industry |
| Exposure patterns/route to patient | Biopharmaceuticals will be used mainly in the hospital setting. Validity of large population-based databases is therefore limited; patient and drug registries and pooling of randomized clinical trial data have been shown to provide valuable data and will be a valuable data source for post-authorization safety studies (PASS) |
| Traceability | Traceability is important due to the effect of changes in the production process on the safety profile and should be taken into account during spontaneous reporting |

biopharmaceuticals is shown in table II. Although challenges remain regarding spontaneous reporting, this is considered a valuable tool, and recording of batch numbers is important for traceability of the biopharmaceutical responsible for the ADR. Safety problems identified during spontaneous reports should be considered for inclusion in the EU-RMP. Additional pharmacovigilance activities to further explore the potential safety problem need further strengthening. PASS of biopharmaceuticals are hindered by the limited availability of data in the large population-based databases. Registries have been shown to be a valuable data source and should be carefully evaluated in future risk management strategies. Key messages in safety management of biopharmaceuticals remain: be prepared for the unexpected, be aware of confounding by disease (severity) and maintain exposure ascertainment/traceability throughout the logistic chain from industry to patient.

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