

# BIOLOGICALS, BIOSIMILARS, DRUG SUBSTITUTION: A MANDATORY SEQUENCE?

Professor Harald H Sitte



**Biological and biosimilar drugs are produced in specialised expression systems. But differences between systems occur and a biopharmaceutical from two different companies does not mandate bioequivalence. Thus automatic substitution of a given biological drug to a biosimilar has distinct shortcomings.**

## Biologicals

Biological drugs (biologicals) are compounds produced by bioorganisms. As such, this class comprises vaccines, blood products, cytokines, hormones as well as monoclonal antibodies. Some 200 years ago, Jenner inoculated material from cowpox blisters into subjects that resulted in vaccination against smallpox. This starting point finally led to the establishment of the WHO vaccination programme. Decades later, molecular biology fostered the development of a new generation of specific biological products in large amounts paving the way for industrial production.

Biologicals start off from vectorial plasmid DNA transfected into an appropriate bioreactor, i.e. a cell that harbours the plasmid DNA after transfection (mammalian, *Escherichia coli*, yeast and Sf9 insect cells). In mammalian cells, the nascent protein chain exits the ribosome and enters the endoplasmic reticulum (ER). Here, the newly synthesised protein undergoes a first series of post-translational modifications and passes the rigid ER quality control that ensures the best functional protein quality. Then, the protein leaves for the Golgi apparatus where a second series of post-translational modifications follows. These result in a complex tertiary structural rearrangement and an intricate glycosylation pattern. Finally, the fully functional protein is released from the Golgi apparatus. In contrast, biologicals produced in *E. coli* lack such complex glycosylation.

Biologicals can strongly depend on the glycosylation pattern; this may influence their activity, their folding and stability, and also the pharmacokinetic clearance. Enhanced or reduced glycosylation can

**It is safe to conclude that a second-generation biological cannot be a generic drug to the innovator drug.**

be achieved by creating mutants, but also fusion proteins, conjugates with toxins or polymers may be engineered. For instance, the attachment of polyethylene glycol repeat sequences (PEG-ylation) results in altered pharmacokinetic properties: enhanced water solubility and/or a significant increase in size with decreased renal excretion. However, molecular biology can also be negative: overexpression can be detrimental, leading to a massive overload of non-functional protein in the host cells. The pH value of the formulation may also result in instability or increased formation of aggregates.

Taken together, biologicals stem from unique cell lines or bioreactors that release unique products and differences in the end product can occur at a variety of production steps. Hence, it is not surprising that a recent analysis of erythro-

poietin (EPO) from several different production units all over the world revealed grossly differing protein patterns [1].

## Problems arising from differences among biologicals

Subtle to overt differences of unique biologicals create specific disadvantages. As mentioned, EPO from company A does not resemble EPO from company B. It may not even resemble EPO from another cell line within the same company or the EPO from the same cell line after a change in the manufacturing process. Our immune system senses differences in epitopes due to the given structural complexity of proteins which may, in turn, lead to immunogenic problems [2]. Factors that propagate these effects include structural properties like sequence variation, differences in the glycosylation pattern or the downstream processing, also the dose and length of treatment. Furthermore, individual patients' characteristics may have repercussions on efficacy and safety issues.

The evolution of insulin preparations from animal (mostly porcine) to *E. coli* is useful to illustrate problems with small changes in the amino acid sequence. Porcine and human insulin differ by one single amino acid. Administration of the porcine insulin preparation resulted in the development of circulating insulin antibodies [3] which could potentially contribute to insulin resistance [4]. The occurrence of insulin antibodies became rare after the launch of insulin preparations derived from recombinant bacterial expression systems.

Other examples show that differences relevant to clinical treatment exist even between biologicals with identical composition. Interferon beta is approved for the treatment of multiple sclerosis and a comparison of two interferon beta drugs showed significant differences in efficacy and safety (the EVIDENCE study, [5]). Comparisons with two available interferon alpha preparations also showed differences in antigenicity (neutralising antibodies, drug efficacy, [6]).

There have been cases of pure red cell aplasia (PRCA) reported after subcutaneous, but not intravenous, administration of a specific EPO formulation (Eprex) that resulted in the production of anti-erythropoietin antibodies [7, 8]. Eprex was manufactured as a second-generation biological and differed from other EPO's only in the number of sial-glycosylated residues. The underlying cause for PRCA is still a matter for intense debate [9]. Hence, this incidence underscores the importance of strict and detailed control over manufacturing and formulation processes for the activity and safety of biologicals. In a long-term follow-up of the 200 patients with erythropoietin-associated PRCA, some 60% received immunosuppressive treatment and some 10% underwent renal transplantation [10].

Taken together, biological drugs all bear the potential to result in unpredictable reactions that can ultimately lead to unexpected adverse events; even small changes in the molecules may give rise to immunogenicity and loss in efficacy of the administered drug [11].

### Biosimilars: what are they?

In Europe biosimilars, in the US follow-on biologics, are the second generation biologicals that closely resemble the innovator product. The interest of generics companies in biosimilars stems from the fact that patents on several biologicals are about to expire and also the economic market situation for biologicals is growing while the traditional small chemical drugs market stagnates [12].

Biologicals differ in size, molecular het-

erogeneity and complexity from classical small drug molecules. While biologicals are made by living cells, chemicals are synthesised according to standard chemical procedures. Therefore, it is conceivable that generic companies can synthesise chemicals wherever, their equality can be tested in standardised



procedures (e.g. by simply demonstrating bioequivalence). Differences between biological drugs render predictions on their physicochemical and biological, thus, clinical effects difficult to impossible; all these properties depend on the uniqueness of the cell lines used and the chosen production procedure.

The EMEA (*European Medicines Evaluation Agency*) issued several stringent guidelines to make sure that the novel biosimilars are manufactured with the

greatest care possible to ensure the highest standards in patient safety. Thus, the procedure to approve a biosimilar drug on the European market is much more difficult in comparison to a generic chemical drug.

### Biosimilars: to substitute or not to substitute...

In the case of generic chemical drugs, exchangeability is given between originator drugs and generics; thus, authorities in several countries mandate automatic substitution whenever economically needed. It is more complicated in the case of biosimilars: is the similarity adequate to claim equivalence of the innovator drug and the follow-on drug? For the reasons outlined, it is safe to conclude that a second-generation biological cannot be a generic drug to the innovator drug; for obvious reasons, bioequivalence may simply not be given. Due to the complex nature of biological drugs, both the biological as well as the biosimilar drug have gone through the same preclinical development process. Therefore, changes from one batch to another even within one brand of biological or biosimilar drug, for instance, can create difficulties, especially when the manufacturing procedure has been changed. Hence, automatic substitution from a biological drug to a biosimilar drug seems even less favourable. Consequently, this could also create problems in pharmacovigilance; the traceability of an administered drug might be lost.

However, the first biosimilars entered the European market half a year ago: somatotropins [13]. They are among the best characterised biopharmaceuticals with the least complexity; hence, it is conceivable that they will serve as the test case. The EMEA has put patient safety as the prime issue in its regulations on biosimilar drugs; thus, it will be of vital importance to also extend this to drug substitution. Therefore, due diligence is mandatory until we gather sufficient data to build up databases as well as true experience on how to deal with biologicals and biosimilars in an appropriate manner.

## Author

Professor Harald H Sitte  
Institute of Pharmacology  
Center for Molecular Medicine and  
Pharmacology  
Medical University Vienna  
13a Währinger Str  
A-1090 Vienna, Austria  
harald.sitte@meduniwien.ac.at

## References

1. Schellekens H. Biosimilar epoetins: How similar are they? *Eur J Hosp Pharm* 2004; 10(3):243-7.
2. Frokjaer S, Otzen DE. Protein drug stability: a formulation challenge. *Nat Rev Drug Discov* 2005;4:298-306.
3. Di Mario U, Arduini P, Tiberti C, Lombardi G, Pietravalle P, Andreani D. Immunogenicity of biosynthetic human insulin. Humoral immune response in diabetic patients beginning insulin treatment and in patients previously treated with other insulins. *Diabetes Res Clin Pract* 1986;2:317-24.
4. Fineberg SE, Huang J, Brunelle R, Gulliya KS, Anderson JH, Jr. Effect of long-term exposure to insulin lispro on the induction of antibody response in patients with type 1 or type 2 diabetes. *Diabetes Care* 2003;26:89-96.
5. Panitch H, Goodin DS et al. Randomised, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. *Neurology* 2002; 59(10):1496-506.
6. McKenna RM, Oberg KE. Antibodies to interferon-alpha in treated cancer patients: incidence and significance. *J Interferon Cytokine Res* 1997;17(3):141-3.
7. Casadevall N, Dupuy E, Molho-Sabatier P, Tobelem G, Varet B, Mayeux P. Auto-antibodies against erythropoietin in a patient with pure red-cell aplasia. *N Engl J Med* 1996;334:630-3.
8. Bennett CL, Luminari S, et al. Pure red-cell aplasia and epoetin therapy. *N Engl J Med* 2004;30;351:1403-8.
9. Schellekens H, Jiskoot W. Eprex-associated pure red cell aplasia and leachates. *Nat Biotechnol.* 2006;24:613-4.
10. Bennett CL, Cournoyer D, et al. Long-term outcome of individuals with pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant epoetin: a follow-up report from the Research on Adverse Drug Events and Reports (RADAR) Project. *Blood* 2005;106:3343-7.
11. Killestein J, Polman C. Clinical aspects of protein drugs. *Eur J Hosp Pharm* 2006; 12(6):44-5.
12. Belsey MJ, Harris LM, Das RR, Chertkow J. Biosimilars: initial excitement gives way to reality. *Nat Rev Drug Discov* 2006;5:535-6.
13. Sheridan C. First generic biologics finally approved. *Nat Rev Drug Discov* 2006; 5:445.

## BIOLOGICALS IN THE ERA OF BIOSIMILARS: IMPLICATIONS FOR NAMING AND PRESCRIBING

Professor Paul Declerck, PhD



In this article the debate surrounding the naming system for biosimilars and its impact on future prescribing practice are discussed.

### Introduction

Unlike generics of chemical drugs, biosimilars are similar but not identical to the original product. Therefore, and in relation to their safe use and pharmacovigilance, questions are being raised about the (im)possibility of applying the current INN system for adequate naming of biotherapeutics in general and biosimilars in particular. Should biosimilars have distinct INNs or should a new independent naming system be developed? What measures should be taken to ensure that healthcare professionals realise that biosimilars should not be merely considered as copies, and thus that the patient may react differently upon substitution? Does the approach of naming have an impact on prescribing practices?

### The INN system - developed with chemically-derived molecules in mind

The current International Non-proprietary Name (IN) system [1], introduced in 1950 and administered by the World Health Organization (WHO), lays down guidelines for the universally available, unique naming of pharmaceutically active substances. Such an international nomenclature is essential to precisely identify each substance and ensure the safe prescription and dispensation of medicines. It should be realised that the INN system was designed to identify chemically-derived (small molecule) medicines at a time before biotechnology existed. In this respect, INNs are selected in principle “only for single, well-defined substances that can be unequivocally referred to by a chemical name (or formula)” – thus generic ‘chemical’ substances will have the same INN as the original active substance.

Application of the INN system implies that analytical tools are available to prove unambiguously that two products, from two different manufacturers and/or produced by different processes, having the same INN, are identical and their effect on the patient will be the same. Subsequently the INN provides the healthcare community with a common language on pharmaceutical substances.

Application of the INN system implies that analytical tools are available to prove unambiguously that two products, from two different manufacturers and/or produced by different processes, having the same INN, are identical and their effect on the patient will be the same. Subsequently the INN provides the healthcare community with a common language on pharmaceutical substances.

### Biosimilars: challenging the INN system

Scientific breakthroughs in healthcare biotechnology have revolutionised treat-