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Lessons learned from biosimilar epoetins and insulins

MARTIN KUHLMANN[1], MICHEL MARRE[2]

Abstract

Patients with diabetes and renal failure may already be receiving biosimilar epoetin and may receive biosimilar insulin in the near future. Because these biosimilar pharmaceuticals (or follow-on biologics) are complex protein molecules manufactured in lengthy and inherently variable processes involving living organisms, they have the potential to induce an immunogenic, rather than a therapeutic, response. This response is dependent as much on the method of manufacture and formulation, as on the protein itself. Apparently small and innocuous differences in manufacture and formulation can lead to unforeseen clinical consequences. This article discusses two case studies illustrating this principle, that of three insulin formulations which were physicochemically similar to comparator insulins, but with pharmacokinetic and pharmacodynamic profiles sufficiently different to have potentially serious clinical consequences and that of Eprex, for which an apparently minor change in one formulation caused an upsurge of cases of pure red cell aplasia which resulted in fatalities or complete transfusion dependence. Comprehensive and rigorous testing and long-term pharmacovigilance programmes are essential to detect and forestall such consequences.

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Key words: biosimilars, EMEA, epoetin, Eprex, insulin, Marvel, pure red cell aplasia.

Biosimilar (follow-on biologic): A therapeutic protein whose active substance is shown by appropriate testing to have similar physicochemical, preclinical and clinical properties to an originator therapeutic protein. Because it is manufactured in living systems with inherent variability, biosimilar proteins cannot be identical to the corresponding originator protein.

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Abbreviations and acronyms

AUC	area under the curve
CHMP	Committee for Medicinal Products for Human Use
EMEA	European Medicines Agency
GMP	Good Manufacturing Practice
HbA_{1C}	glycated haemoglobin A_{1C}
IGF	insulin-like growth factor
PD	pharmacodynamic
PK	pharmacokinetic
PRCA	pure red cell aplasia

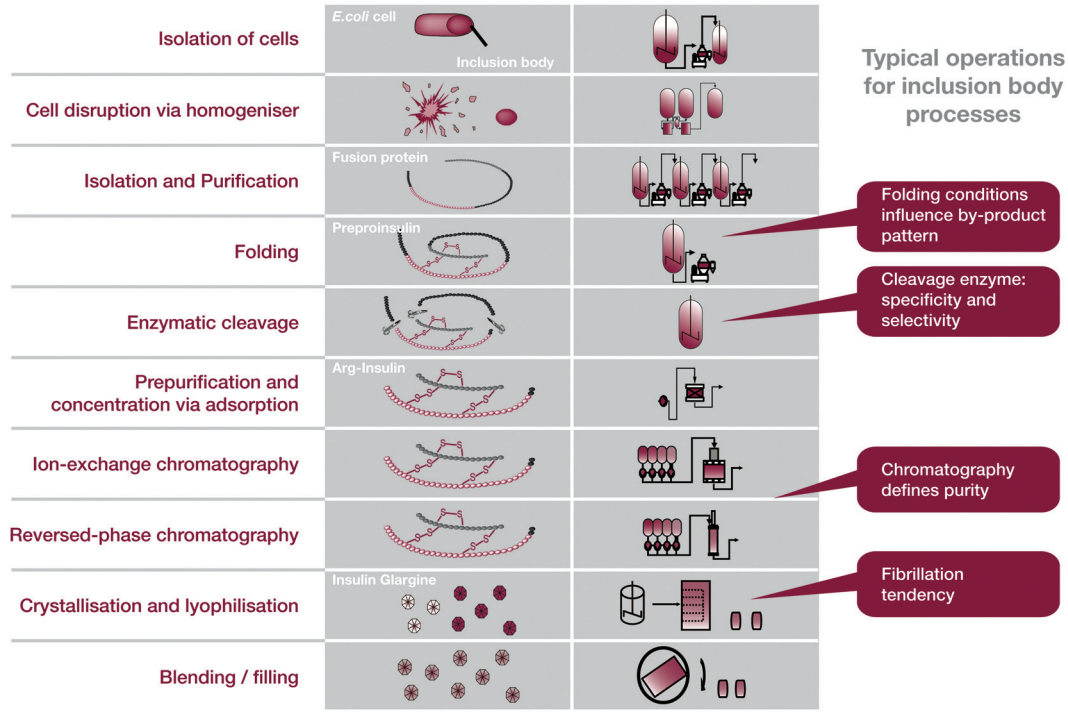
Generic: A small-molecule drug whose active substance is shown by appropriate testing to have identical physicochemical, preclinical and clinical properties to an originator small-molecule drug.

Introduction

Biosimilar proteins are also known as follow-on biologics. These therapeutic proteins are expected to join originator biopharmaceuticals in the marketplace when patent protection for the latter expires. Biosimilars already available in the European Union include epoetin alpha, growth hormone, interferon-β and factor VIII. Insulin analogues continue to have patent protection until 2013 and beyond, but recombinant human insulin biosimilars will be available shortly. Clinicians may therefore expect that many of their patients who have renal failure associated with diabetes will be receiving both insulin and epoetin biosimilars within a few years. This article will use two case studies – the Marvel insulin dossier and PRCA associated with certain formulations of epoetin alpha – to illustrate some essential clinical issues raised by the advent of biosimilars.

Biosimilar products should not be regarded as merely 'biogeneric drugs' analogous to traditional generic drugs, which are relatively small organic molecules. Biopharmaceuticals are generally proteins whose molecular weights are much higher, and whose three-dimensional structures are more complex, than those of traditional generics; hence, they are often correspondingly more fragile physically and chemically, and their formulation and storage requirements are more stringent than those of traditional generics. Moreover, biopharmaceuticals are manufactured using processes that are orders of magnitude more complex than processes used to manufacture traditional generics. Each of the steps in the process has some inherent variability, especially because living organisms are involved and the details of the processes developed by different companies are proprietary.[1-3]

Figure 1. Post-fermentation steps in the manufacture of insulin glargine



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The most important clinical consequence of this variability in manufacture is that an apparently small and innocuous change in any of the steps can have unforeseen consequences. Even if currently available tests show that a biosimilar is physicochemically equivalent to its counterpart originator molecule, the two may not behave in an equivalent manner in a clinical setting.[4] In the case of the Marvel insulin formulations, products with identical amino acid sequences (primary protein structures) had PK and PD properties that deviated significantly from those of the chosen comparator product. Even small changes in the manufacturing process of an originator biomolecule can cause difficulties: for example, a change in one of the formulations of the epoetin alpha Eprex was responsible for the emergence of PRCA up to a year after exposure to the product.[3] Moreover, unpredictable changes in PK or PD properties can arise from process-related impurities (derived from the manufacturing process, e.g. host cell proteins, media components), product-related impurities (e.g. precursors, degradation products) or contaminants (adventitious materials that were not intended to be part of the manufacturing process).[5]

The EMEA and its CHMP lead the world in developing regulatory policies for the marketing of biosimilars.[6] CHMP has produced guideline documents on the general requirements for non-clinical, clinical and quality aspects of biosimilars,[7-9] as well as several guidelines pertaining to specific products, including soluble recombinant human insulin[10] and epoetin alpha products.[11] For example, manufacturing processes for biosimilars, like all human medicinal products, must be in compliance with GMP that addresses areas ranging from buildings and facilities to stability issues; in addition, specific guidance (which addresses areas such as removal of product and process-related impurities and contaminants, and appropriate acceptance criteria for these entities) has been laid out for products that are manufactured by cell culture/fermentation.[12,13]

Biosimilar insulin: EMEA requirements

The manufacture of recombinant human insulin (figure 1) is highly complex.[14] First, the human insulin gene is isolated and attached to a vector, which is then inserted into a host cell (usually *E. coli* or a yeast species). Next the recombinant cells

are screened, a master cell bank is established and the resulting cell lines are cultured and fermented. The recombinant insulin fusion protein thus produced must then be released from the cells, isolated, purified, folded to produce the required secondary structure and enzymatically cleaved to yield the biologically active insulin. This product is further purified and concentrated in several adsorption and chromatographic steps. Eventually, it is crystallised, lyophilised and formulated by adding compounds to prevent protein aggregation and bacterial growth or to change the *in vivo* absorption characteristics of the insulin (e.g. adding protamine results in a longer-acting formulation).[15] Any variation in this long series of steps, ranging from the vector chosen to transfect the host cells to the excipients added during formulation and stabilisation, has the potential to result in an insulin product whose amino acid sequence and structure may be identical to that of native insulin and of originator recombinant insulin, but whose clinical characteristics, e.g. PK or PD behaviour, differ subtly from those of the originator product.[4,15]

The EMEA has developed specific prerequisites for marketing authorisations for soluble insulin biosimilars. As for all biosimilars, both the drug substance and the drug product must be assessed with appropriate qualitative and quantitative analytical procedures for impurities and their impurity profiles compared with those of an appropriate reference product.[8] Required preclinical studies include *in vitro* PD studies, *in vitro* affinity bioassays, assays for insulin and IGF-1 receptor binding. Required comparative clinical studies include at least one single-dose PK crossover study using subcutaneous administration, preferably in patients with type 1 diabetes, and a PD double-blind, crossover, hyperinsulinaemic, euglycaemic clamp study that demonstrates a time-effect hypoglycaemic response profile. Clinical efficacy trials are not required if the clinical PK and PD studies show that the biosimilar is comparable to the reference product. A further requirement is a clinical trial, of at least 12 months duration, to evaluate the immunogenicity of the product. Such a trial needs to include a comparative phase of at least 6 months. Finally, a pharmacovigilance programme must be proposed that allows the early detection of any clinically significant immunogenicity that may develop over the long term.[10]

Case 1. Marvel Lifesciences Ltd.

The case of the Marvel LifeSciences recombinant insulin dossier illustrates both the potential effects of variations in manufacturing processes and the application of the EMEA requirements to a submission for approval of a biosimilar product. In March 2007, the MJ Group (Mumbai, India) submitted an application for a marketing authorisation for recombinant human insulin in three different formulations: a soluble rapid-acting insulin ('Rapid'); a long-acting isophane insulin product ('Long'); and a 30:70 mixture of these two products ('Mix'). The CHMP raised numerous concerns about the adequacy of the submission.[16-18]

Regarding the quality of all three products, the CHMP noted that the information submitted was sparse in many critical aspects, notably: development, fermentation and purification processes; validation procedures; assays for impurities and stability of the compounds; and in-process controls such as physical separation and cleaning between the different products. Moreover, it was unclear whether the comparators used in studies involving these insulins were actually valid reference products. CHMP also noted that the dose-delivery properties of different presentations (vials and cartridges) had not been adequately tested and validated. Furthermore, in the case of the Long product, the protamine used to form the isophane crystals was not adequately characterised, and neither the manufacturing process nor the crystallisation process was documented in sufficient detail.[17] In the case of the Mix product, there were also no details of formulation studies demonstrating a stabilised 30:70 mixture. The CHMP concluded that none of the three products had sufficiently demonstrated its biosimilarity to a properly chosen reference product.[18]

The CHMP also expressed concerns about the adequacy of the clinical data submitted in this dossier. For each of the formulations, the company carried out a single-dose, randomised, crossover, PD euglycaemic clamp study comparing the Marvel product with a reference originator insulin in 24 healthy male volunteers; however, these studies were not blinded and endogenous insulin secretion was not suppressed. PK data were derived from the euglycaemic clamp PD studies, but no independent PK studies were done. In particular, the single-dose crossover comparative study using subcutaneous injection recommended by CHMP was not carried out.

The total AUC for glucose infusion rate for the Marvel Rapid product could be considered bioequivalent to that for the reference product (Humulin S), because it fell within the classical interval of 80–125%; however, the AUCs up to 2 h after dosing were significantly higher, and the elimination half-life and mean residence time were significantly shorter for the Marvel product. In other words, it had a faster absorption, more potent effect and faster elimination than the reference product (figure 2).[16-18] The CHMP calculated that the Marvel soluble insulin could potentially induce a 45% greater glucose-lowering effect than Humulin S within the first hour after dosing, an unacceptable degree of difference with obvious clinical relevance.[16]

For both the Long and the Mix products, the mean PK and PD curves were largely superimposable on those of Humulin I and Humulin M3, their comparator products, but the study times were not long enough to obtain adequate data on elimination half-lives and clearance. The glucose infusion AUC was 27% lower for the Long product than for Humulin I, but 23% higher for the Mix product (which contains 70% Long) than for Humulin M3. The manufacturer attributed this apparent inconsistency to batch-to-batch variability.[17,18]

In addition, one efficacy and safety clinical trial was conducted in 526 patients with type 1 or type 2 diabetes. This consisted of a 6-month, double-blind, comparative phase testing all three Marvel insulin formulations against their respective reference products, followed by an open-label, 6-month, extension whose results were not part of the dossier. In this trial,

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