Ensuring patient safety in the era of biosimilars

Professor Paul Declerck

Automatic substitution and active substance-based prescribing should be banned for biologicals, argues Professor Paul Declerck. Such requirements might interfere with current legislation – in particular, differences among member states in Europe, and between Europe and the US, may complicate these steps. Therefore, the relevant national authorities need to sit down with medicines agencies and make the necessary changes to prevent legal differences compromising patient safety, he believes.

Because biotech medicines are structurally very complex, small distinctions in the cell line, the manufacturing process or the surrounding environment can make a major difference in the product's side-effects (for example immunogenicity) and efficacy. While chemical-based pharmaceuticals can be substituted by generic versions, substitution among biologics, including biosimilars, raises health concerns where patients are concerned.

Each biotech medicine is made in a living cell, and because no two independently developed cell lines can be considered identical, biotech medicines cannot be truly copied. This fact is recognised by the European regulatory authorities and has resulted in the establishment of the term "biosimilar" in recognition of the fact that, while such products are similar, they are not exactly the same.

European legislation now includes specific guidelines for the approval of biosimilars, and US legislation is being debated. A final decision may be taken in conjunction with the reauthorisation of the US Prescription Drug User Fee Act, which expires on September 30th this year.

The observed differences illustrate the difficulty of making an exact copy of a biotech drug

The current International Non-proprietary Name (INN) system, whereby drugs with the same active ingredient (irrespective of their production process) are given the same name, could easily lead to inadvertent substitution without the doctor or patient being aware of it. The possibility that an independent non-proprietary naming system for biological and biotechnological substances might be needed is being debated within the international medical and pharmaceutical community.

In Europe, two somatropins, Sandoz's Omnitrope and Biopartners' Valtropin, which are biosimilars of Pfizer's Genotropin and Lilly's Humatrope respectively, have been approved by the European Medicines Agency.

However, the EMEA has rejected Biopartners' alpha-interferon product Alpheon, which is claimed to be biosimilar to Roche's Roferon A (interferon alfa-2a). This decision was based on major concerns regarding the comparability of the two products. Differences were observed in quality as well as at the clinical level. Different impurity profiles were seen, insufficient data on stability were provided and the manufacturing procedure was not fully validated. Clinical differences included an increased return of hepatitis C and the occurrence of more side-effects when using Alpheon.

The EMEA's decision showed stringent adherence to appropriate standards of safety and efficacy. The observed differences also illustrate the difficulty (or virtual impossibility) of making an exact copy of a biotech drug.

To date our limited clinical experience with comparability exercises and biosimilars means that sufficient precautions need to be included to guarantee patient safety during their use. Three important aspects – substitution, pharmacovigilance and traceability – should be taken into account.

There are no solid scientific grounds to guarantee safe interchangeability among biologicals

Because of the complexity of the biotech product and the production process (for example, more than 240 analytical tests are required during the production of interferon alfa-2b (Schering-Plough's Intron A)), and the limited sensitivity of analytical tools, there are no solid scientific grounds to guarantee safe interchangeability among any biologicals bearing the same INN but produced by different manufacturers.

Even relatively simple biotech drugs such as human growth hormone (non-glycosylated and with 191 building blocks) can exhibit a wide range of metabolisation rates, thus excluding bioequivalence.

Therefore, for the sake of patient safety, there must be no automatic substitution. Comparability exercises for biologicals are extremely difficult and depend on the ease of molecular characterisation and the extent of detailed knowledge of the molecular mechanism of action in the human body.

At best, based on *in vitro* biochemical characterisation and preclinical data, one might be able to predict that two biologicals might be the same. However, only clinical data and postmarketing surveillance will ultimately provide the evidence for their efficacy and safety.

Interestingly, there is a growing awareness with respect to these concerns

at the level of national legislation in Europe. In February this year, the French parliament adopted a new law on medicines, which included recognition of the unique nature of biosimilars and a prohibition on automatic substitution between biological medicines. The Swedish and the Norwegian medicines agencies issued official statements with a similar message.

It is important to realise that all these measures and requirements need to be considered on a case-by-case basis, and that as more experience is gathered over the years, more insight may be gained into whether or not substitution between particular biologics may be appropriate or should remain forbidden.

...traceability

Postmarketing surveillance necessitates adequate pharmacovigilance plans, and in this respect procedures need to be put in place to ensure reliable and unambiguous traceability. Indeed, to ensure an adverse event can be linked to the correct biological, there is a need for a critical evaluation of the naming of the medicine, prescribing practices and procedures during dispensing and administration of the medicine. Therefore, to avoid inadvertent substitution and to ensure adequate pharmacovigilance, the following principles should be observed:

- The biosimilar must have a different brand name that does not explicitly suggest those of the originator or other biosimilars containing the same active substance.
- There should be explicit warnings in the summary of product characteristics (SPC) and patient information leaflet that, because of different production and formulation processes, the active substance of one brand should not be considered identical to that of another brand.
- Unlike chemically derived substances, prescribing based on active substance name should be prohibited for biologics and should be based exclusively on the unique brand name, implicitly reflecting the production process and manufacturer (including the route of administration).
- There should be routine use of traceability systems, for example using a barcode.

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Both biosimilar and originator companies need to recognise the potential differences between similar biologicals, for the benefit of patients, the medical community and the biosimilars market. And both should acknowledge the need for a different prescription system, and join forces to ensure that at any point – whether at the time of prescription, dispensing or administration – a distinction is made between biotech medicines that are produced differently but are considered similar.

In conclusion, to ensure that current rigorous standards concerning patient safety and the use of biologics, whether originator or biosimilar, are upheld, the following should be prerequisites for granting a biosimilar marketing authorisation: a distinct brand name, an adapted SPC, sufficient clinical data and an adequate pharmacovigilance plan.

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