Ensuring the Safe Use of Biosimilars

The arrival of biosimilars has sparked a debate as to whether the current INN system can guarantee their safe use. Professor Paul Declerck looks at the options and asks whether radical change is needed.

Despite the rigorous process for putting medicines safely on the EU market, the European regulatory system still has some way to go before all outstanding issues on biosimilar medicines are clarified. One of the most important issues relates to safety concerns and has an impact on prescribing practices.

The current International Non-proprietary Name (INN) system was designed to identify chemically derived (small molecule) medicines at a time before biotechnology existed. It has worked well for more than half a century and has been adapted to a limited extent for application to biological and biotechnological substances. But since the recent introduction of the first biosimilars, new questions have arisen regarding naming.

Biosimilars are very similar, but not identical to, the originator. Does this imply that they should 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 that the patient may react differently if a biosimilar is substituted for the originator product?

The INN system was introduced in 1950 and administered by the World Health Organization (WHO). It lays down guidelines for allotting unique international names to pharmaceutical active substances. Such an international nomenclature is crucial to allow doctors, pharmacists and other healthcare professionals to identify precisely each substance and ensure the safe prescription and dispensing of medicines. INNs are selected in principle only for single, well-defined substances that can be unequivocally referred to by a chemical name (or formula). This means that generic chemical substances will have the same INN as the original active substance.

This system makes sense where chemical formulations are concerned, because it is based on the assumption that (1) available analytical tools allow it to be shown unambiguously that two products, from two different manufacturers and/or produced by different processes, with the same INN, are identical; and (2) their effect on the patient will be the same. Therein lies the safety of an INN – it gives the healthcare community the reassurance that all parties involved are speaking the same language on pharmaceutical substances. The arrival of generic versions of chemically derived medicines did not jeopardise the system: generic and originator products are identical, so they can share the same INN.

Biosimilars: a new test

Scientific breakthroughs in healthcare biotechnology have revolutionised treatments in the past 25 years. Cloning of human genetic material and development of in vitro biological production systems have allowed the production of virtually any recombinant DNA-based biological substance for the eventual development of a drug. Monoclonal antibody technology combined with rDNA technology has paved the way for tailor-made and targeted medicines and therapies.

Since the expiry of the patent on the first approved biotech drug, any other company can produce and market these biological substances (called biosimilars) and, as with generics, the products might reduce the cost to patients and social security systems.

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

Indeed, biotech medicines are much more complex in structure and less stable than chemical pharmaceuticals. Small differences in the cell line, the manufacturing process or the surrounding environment can make a major difference in side-effects during treatment – ie two similar biologics can trigger very different immunogenic responses in patients. Therefore, unlike chemical pharmaceuticals, substitution between biologics, including biosimilars, can have clinical consequences and so create health concerns for patients.

This does not mean that biosimilars are unsafe: they are subject to an approval process that requires substantial additional data compared with that required for chemical generics, although...
not as comprehensive as for the original biotech medicine. However, the safe application of biologics also depends on informed and appropriate use by healthcare professionals. Doctors and pharmacists must know if and when changes happen in the system, so they can effectively manage patient safety. The current 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 prescribing doctor knowing.

**Responding to the challenge**

How can the healthcare community respond appropriately to this new challenge? The INN system remains a cornerstone of chemical pharmaceutical identification, and the system provides clarity for the healthcare community so that patient safety is not compromised. Appropriate conventions to provide separate names for biotech medicines would be one possibility to help to avoid inadvertent substitution by pharmacists. This in turn would help to avoid imprudent compromises in patient safety or pharmacovigilance.

The onus of responsibility on healthcare professionals cannot be underestimated. At the very least, doctors must ensure that the specific biotech medicine (the originator or any biosimilar) prescribed in the first instance is taken throughout the patient’s course of treatment. The doctor must ensure that the biotech medicine prescribed is carefully chosen, and the pharmacist must ensure that the prescription is precisely dispensed. There is little, if any, room for substitution, and this must be clearly understood by the medical community.

Without significant education and discipline among medical practitioners, inadvertent substitution could harm human health, while at the same time making it impossible to trace which medicine caused any adverse reaction. As we move into a time of personalised medicine, identification and traceability become increasingly important and require a stronger and more robust classification system.

Is it time for a rethink of the INN system? Or is it more appropriate to develop an independent naming system for biological and biotechnological substances? This is certainly an issue for debate within the international medical and pharmaceutical community, through the appropriate authorities such as the WHO, the European Medicines Agency (EMEA), the European Commission and the US Food and Drug Administration (FDA). Recently the FDA presented a position paper saying there is no need to modify the INN system for the appropriate naming of biosimilars (see also Worldwide Update section of this issue). Its view is mainly based on the fact that the US has alternative mechanisms for preventing inappropriate substitution even if two products have the same INN. The FDA also points out that product interchangeability decisions are beyond the scope of the WHO’s INN experts. The European Generic medicines Association (EGA) also opposes changes to the INN system. It argues that demonstrating comparability between two biologicals is sufficient to give the same INN. By contrast, in a joint position paper the European Biopharmaceutical Enterprises (EBE) and the European Federation of Pharmaceutical Industries and Associations (Efpia) have said that either distinct brand naming or, in view of current prescribing practices in Europe, distinct INN naming is a prerequisite for guaranteeing traceability and adequate pharmacovigilance. The WHO, the founder of the current INN system, is expected to present its position on biosimilar INNs in October 2006.

At first glance the most sensible course of action would appear to be the assignment of distinct INNs to biosimilars. It should be realised, however, that the INN system was originally developed to be applied to well-defined chemical substances and that the INN system has adopted a specific system for particular groups of biological compounds associated with their physiological action. The latter is restricted to the use of common prefixes (eg “som-” for growth hormones ) or suffixes (eg “-relin” for hormone release stimulating factors or “-cog” for blood coagulation factors).

However, none of the current INN rules can be applied to solve the biosimilar naming problem. Moreover, a number of elements suggest that having different INNs is not appropriate:

- the introduction of the first biotech produced active substances as a “replacement” for plasma-derived or tissue-derived human proteins has never raised the question of different INN naming even though the differences, and associated problems, between the recombinant version and the plasma-derived version are comparable to those observed today between the originator and the biosimilar and between biosimilars. It should be noted, however, that the introduction of the first biotech drug required a much more extensive comparability exercise before marketing approval than is currently required for biosimilars;
- different naming within the INN system is based on a well-defined and easily characterised molecular difference. Straightforward application to biosimilars is therefore...
impossible as it is generally well recognised that subtle, but clinically important, molecular and structural differences do exist, whose detailed nature cannot be fully determined because currently available methods of analysis lack sensitivity; and

• the introduction of (slight) changes in the production process, drug formulation or manufacturing process has also never led to new names, even though it is known that such changes might, beyond the detection limits of current analytical methods, affect the clinical (side) effects of the drug.

In view of this combination of problems relating to naming, substitution or replacement, prescribing based on active substance name, traceability and pharmacovigilance, it may be that the following actions should be taken until a scientifically solid, clear and unambiguous differential naming system is produced:

• an obligation to assign different brand names that are not similar to those of the originator or other biosimilars containing the same active substance;

• an explicit warning 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 the active substance of another brand;

• a ban on the prescribing of biologics based on active substance name; and

• routine application of, for example, barcode related systems of traceability (drug vs patient).

For the benefit of the patients, the medical community and the biosimilars market, it is strongly recommended that both biosimilar and originator companies recognise the potential differences between similar biologicals and subsequent related hazards. Both should recognise the need for a different naming or prescribing system and join forces to ensure that at any moment (ie at the time of prescription, dispensing and administration) a distinction is drawn between biotech medicines that are produced differently but are considered similar.

Regarding the development of a different naming system, it should be stressed that simply adapting the INN to indicate the manufacturer would be easy but not appropriate. This would be too close to the current situation of chemical generics and, by neglecting the possibility of clinically relevant differences, would give a false feeling of safety.

**Conclusion**

To maintain the current rigorous standards concerning patient safety and the use of biologics (the originator or a biosimilar), a distinct brand naming system, together with an adapted SPC, should be a prerequisite for granting a biosimilar marketing authorisation. Obviously, automatic substitution and active substance-based prescription should be banned for biologics. It is realised, however, that such requirements may interfere with current legislation. In particular, the differences observed between the different member states in Europe may complicate the proposed approach.

Therefore, the EMEA and the relevant European legal authorities should sit down with the national medicines agencies to prevent the legal hurdles from compromising patient safety. Importantly, in the meantime the search for a long-term solution regarding the design of a new (INN-independent?) naming system for biosimilars should begin as soon as possible.

References
1. www.who.int/medicines/services/inn/en/
2. EMEA guidelines on similar biological medicinal products (EMEA/CHMP/437/04)