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Biotherapeutics in the Era of Biosimilars

What Really Matters is Patient Safety

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Unlike generics of chemical drugs, biosimilars are similar but not identical to the original product. Therefore questions are being raised, in relation to their safe use and pharmacovigilance, about the adequate naming of biotherapeutics in general and biosimilars in particular. 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? Should prescribing practices be adapted? How does the arrival of biosimilars affect adequate pharmacovigilance within the context of unintentional substitution?

1. The International Nonproprietary Name (INN) System: Developed with Chemically Derived Molecules in Mind

The international nonproprietary name (INN) system,[1] introduced in 1950 and administered by the WHO, lays down guidelines for the universal, unique naming of pharmaceutically active substances. Such an international nomenclature is crucial for clinicians, pharmacists and other healthcare professionals to enable them to precisely identify each substance and to ensure the safe prescription and dispensation of medicines. INNs are selected in principle, "only for single, well-defined substances that can be unequivocally characterized by a chemical name (or formula)";[2] thus, 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 assumptions that (i) available analytical tools can prove unambiguously that two products, from two different manufacturers and/or produced by different processes, having the same INN, are identical; and (ii) subsequently, that the effect of these products on the patient will be the same. Therein lies the security of an INN: it gives the healthcare community confidence in the knowledge that all parties concerned are speaking the same language on pharmaceutical substances. The arrival of generic versions of chemically derived medicines has not jeopardised the system; generic and originator products are identical, which allows them to share the same INN.

2. Biosimilars: Challenging the INN System

Scientific breakthroughs in healthcare biotechnology have revolutionised treatments in the past 25 years. The cloning of human genetic material and the development of *in vitro* biological production systems have allowed the production of virtually any recombinant (r)DNA-based biological substance for eventual development into 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 of the first approved biotechnology drug, the 'copying' and marketing of these biological substances (thus called

'biosimilars') can be undertaken by any other biotechnology company and might possibly, as with generics, reduce the cost to patients and social security systems.

Biological medicines are made in living cells. Because no two independently developed cell lines can be considered identical, biological 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, whilst biosimilar products are similar to the original product, they are not exactly the same.[3] Whereas European legislation now includes specific guidelines for the approval of biosimilars, adaptation of US legislation is still being debated.

Biological medicines are much more complex in structure and less stable than chemical pharmaceuticals. Small distinctions in the cell line, the manufacturing process or in any step from the cell line stage through to administration to the patient can make a major difference in adverse effects observed during treatment (i.e. 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 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 to that required for chemical generics, although not as comprehensive as for the originator biological medicine. However, the safe application of biologics is also dependent on informed and appropriate use by healthcare professionals. Doctors and pharmacists must be made aware of any changes in the naming system, so they can effectively manage patient safety. It should be realised that the current INN system, whereby drugs with the same active ingredient (irrespective of their production processes) are given the same name, could easily lead to inadvertent substitution without the prescribing clinician being aware.

3. Currently Approved Biosimilars

Currently, two preparations of human growth hormone (somatropin), Omnitrope® [1] and Valtropin®, biosimilars of Genotropin® and Humatrope,® respectively have been approved by the European Medicines Agency (EMEA).[4,5] On the other hand, the marketing authorisation for the interferon-α-2a Alpheon® (claimed biosimilar of Roferon®-A) has been rejected by the EMEA.[6] This negative 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 observed, insufficient data on stability was provided, and the manufacturing procedure was not fully validated. Clinical differences included an increase in hepatitis C relapse and the observation of more adverse effects when using Alpheon®.[6] The EMEA decision demonstrates the 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 biological drug. Very recently, the Committee for Medicinal Products for Human Use (CHMP) of the EMEA adopted a positive opinion for three biosimilars of erythropoietin α; Binocrit®, Epoetin alfa Hexal® and Abseamed®.[7] It is not clear, however, what precautions have been taken to prevent possible serious adverse effects, such as pure red-cell aplasia. This adverse effect has been observed in the past with fully evaluated epoetins and was shown to be dependent on subtle differences in both the manufacturing process and the route of administration. Strikingly, one of these new epoetins bears a brand name (i.e. Epoetin alfa Hexal®) that is very similar to the name of the active substance. In the absence of universal legislation with respect to unambiguous naming and prescribing practices (see section 5) for biologics, this situation may compromise their safe use and an adequate level of pharmacovigilance.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

4. To Substitute or Not to Substitute

To date, limited clinical experience with comparability exercises and biosimilars necessitates the inclusion of sufficient precautions to ensure patient safety during the use of biosimilars. Therefore, three important aspects, namely problems of substitution, pharmacovigilance and traceability, should be taken into account.

As a consequence of the complexity of both the biotechnology product and the production process (e.g. more than 240 analytical tests are required during the production of interferon-α-2b; Intron A®[8]), and the limitation of sensitivity of analytical tools (i.e. the process determines the product), no solid scientific grounds exist to guarantee safe interchangeability between any biologics bearing the same INN but obtained through different manufacturers.

Even relatively simple biotechnology drugs, for example somatropin (191 amino acids, non-glycosylated), can exhibit a wide range of metabolisation rates,[8] therefore excluding bioequivalency. Thus, for the sake of patient safety, automatic substitution must be ruled out. Comparability exercises for biologics are extremely difficult and depend on (i) the ease of molecular characterisation; and (ii) 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 may be able to predict that two biologics might be the same. However, only clinical data and postmarketing surveillance will ultimately provide evidence for their efficacy and safety.

Strikingly, growing awareness with respect to these concerns is also observed at the level of national legislation in Europe. In February 2007, the French parliament adopted a new law on medicines,[9] including the recognition of the unique nature of biological medicines and the prohibition of their automatic substitution.

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

5. Adequate Naming and Prescription Practices: A Prerequisite to Prevent Inadvertent Substitution and to Allow Pharmacovigilance

How can the healthcare community, including the responsible legal bodies, respond appropriately to the introduction of biosimilars? 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 similar biological medicines would be one possibility to help avoid inadvertent substitution by pharmacists. This in turn would help to avoid compromises in patient safety or pharmacovigilance.

The onus of responsibility on healthcare professionals cannot be underestimated. At the very least, clinicians must ensure that the specific biotechnology medicine (originator or biosimilar) prescribed in the first instance is taken throughout the entire course of each patient's treatment. The clinician must ensure that the biological medicine prescribed is carefully chosen, and the pharmacist must ensure that the prescription is dispensed precisely. 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 the health of patients, while at the same time making it impossible to trace which medicine caused the 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 biotechnology substances? This is certainly an issue for debate within the international medical and pharmaceutical communities, through the appropriate authorities such as

the WHO, EMEA, European Commission and the US FDA. Recently, the FDA presented a position paper[10] stating that there is no need for modification of the INN system for the appropriate naming of biosimilars. Their view is mainly based on the fact that, in the US, alternative mechanisms exist 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.[10]

Previously, the European Generic Medicines Association (EGA) also urged that the INN-based naming system not be changed.[11] They argued that demonstration of comparability between two biologics is sufficient to give the same INN.[11] On the other hand, in a joint position paper, the European Biopharmaceutical Enterprises (EBE) and the European Federation of Pharmaceutical Industries and Associations (EFPIA)[12] stated 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. To date, the WHO, founder of the current INN system, has not presented a position on the current problem regarding the application of the INN system to the naming of biosimilars.

At first glance, the most sensible course of action would appear to be the assignment of distinct INNs to biosimilars. However, it should be realised that (i) the INN system was originally developed to be applied to well defined, chemical substances; and (ii) 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 (e.g. 'som-' for growth hormones) or suffixes (e.g. '-relin' for hormone release stimulating factors, or '-cog' for blood coagulation factors). However, none of the current INN rules is able to solve the problem of naming biosimilars. Moreover, a number of elements may point towards the 'inappropriateness' of adopting different INN names. These are as follows:

- The introduction of the first biotechnology-produced active substances as substitutes 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 originator products and biosimilars, and between different biosimilars. It should be noted, however, that the introduction of the first biotechnology drug required a much more extensive comparability exercise prior to marketing approval than is currently required for biosimilars.
- Different naming within the current INN system is based on a well defined, easily characterisable molecular difference. Straightforward application to biosimilars is therefore impossible, since it is generally well recognised that subtle, but clinically important, molecular and structural differences do exist, of which the detailed nature cannot be fully determined, because of the lack of sensitivity of currently available methods of analysis.
- The introduction of (slight) changes in the production process, drug formulation or manufacturing process has never led to the adoption of new names, even though it is known that such changes might, beyond the detection limits of current analytical methods, affect the clinical efficacy and adverse-effect profile of the drug.

Therefore, the development of a new naming system, independent of the INN rules, is preferred for providing an unambiguous link between a unique name and a unique, process-dependent, biological product.

Considering the problems associated with issues such as unambiguous naming, substitution or replacement, prescription based on active substance name, and subsequent traceability of the actual compound administered to the patient, there is a strong need for extremely reliable pharmacovigilance and postmarketing surveillance upon introduction of biosimilars. In this respect, it is important to realise that procedures to ensure reliable and unambiguous traceability should be put in place. Indeed, procedures for the correct linking of an adverse event to the causative biologic, naming of the medicine, pre-

scription practices and dispensation and administration of the medicine should be critically evaluated.

Therefore, to avoid inadvertent substitution and to ensure adequate pharmacovigilance, the following actions should be taken:

- Establishment of an obligation to assign different brand names explicitly, using names that are not suggestive towards the originator nor towards other biosimilars containing the same active substance.
- Addition of an explicit warning to the summary of product characteristics (SPC) and patient information leaflet stating 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.
- Prohibition of the prescription of biologics based on active substance name, unlike the situation with chemically derived substances.
- Institution of a routine application of, for example, barcode-type systems of traceability (drug vs patient).

For the benefit of patients, the medical community and the biosimilars market, it is strongly encouraged that companies manufacturing biosimilars as well as originator companies recognise the potential differences between similar biologics and subsequent related hazards. Both should recognise the need for either a different naming or prescription system and join forces to ensure that, at all times (i.e. during prescription, dispensation and administration), distinction is made between differently produced but apparently similar biological medicines. Regarding the development of a different naming system, it should be stressed that a simple adaptation of the INN naming system, merely suggesting the incorporation of an indicator of the manufacturer, would be easy but would not be appropriate. This would be too similar to the current situation with chemical generics and would give a false feeling of safety by neglecting the possibility of clinically relevant differences.

6. Conclusion

Overall, in order to maintain current rigorous standards concerning patient safety and the use of biologics (whether originator agents or biosimilars), a distinct brandname, together with an adapted SPC, should be prerequisites for granting marketing authorisation for each biosimilar. Obviously, automatic substitution and active substance-based prescription of biologics should be prohibited. However, it is realised that these suggested requirements may interfere with current legislation. In particular, the differences observed between the different member states in Europe and between Europe and the US may complicate the proposed approach. Therefore, the legal authorities concerned should liaise with national medicines agencies to prevent legal hurdles from compromising patient safety. Importantly, the search for a long-term, adequate solution regarding the design of a new, possibly INN-independent, naming system for biosimilars should be started as soon as possible.

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