The Introduction of Biosimilar Medicines

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There are currently more than 150 biotechnology medicines on the market. Over 325 million patients worldwide use biotech medicines and 50% of medicines in clinical development are biotech medicines. The first biotechnology medicines have now reached, or are approaching, the end of their patent life, providing an opportunity for products which are similar to the original product to be produced. In the past 12 months, an additional 5 biosimilar medicines have been introduced onto the UK market.

There are significant differences between the biotechnology and chemical medicines. Biotech medicines are made from living cells, whereas chemical medicines are made from a chemical process meaning that biotech medicines are more complex proteins. Additionally, biotech medicines contain a mixture of related molecules which are more difficult to characterise than chemical medicines, which have a simple and well-defined structure. In addition, biosimilar medicines are made with a different cell-line and a different manufacturing and purification process from the originator product. The different manufacturing processes lead to similar, but not identical, biophysical characteristics.

In the debate surrounding the introduction of 'biosimilars', some manufacturers of biosimilars would rather they were referred to as 'biogenerics', as if to suggest they were a usual generic product. Generally, there is no issue with the substitution of generics; however, as the European regulatory body the European Medicines Agency (EMEA) recognise, due to the complexity of biological or biotechnology-derived products, the generic approach is scientifically not appropriate for these products. The EMEA, and the UK regulatory body, the Medicines and Healthcare products Regulatory Agency (MHRA), both classify follow-on biological medicinal products as 'biosimilars'.

In considering the introduction of biosimilars there are four distinct areas that need to be carefully considered by government and regulators. These are: 1) the molecular properties: as described above, biotech medicines are more complex than chemical medicines; 2) the manufacturing process which is extremely sensitive to changes in manufacturing or production – minor variations could produce vastly different products; 3) safety aspects: the long term safety profile of biosimilars needs to be established, which needs to be brought to the attention of prescribers and patients; and 4) the efficacy of the medicine, which can differ significantly with small changes in protein biophysical characteristics or in formulation of the drug product.

The EMEA has introduced a guideline on Similar Biological Medicinal Products, which seeks to consider these four areas and sets an overarching 'umbrella' guideline on the approach to bringing biosimilar products to market. This guideline indicates that biosimilar manufacturers need to identify a single reference product and conduct tests to demonstrate biophysical similarity and accepts that "it is not expected that the quality attributes … will be identical"[1] to the reference product. There is currently an EMEA requirement to provide non-clinical and clinical data to demonstrate clinical similarity to the reference product, however; surrogate endpoints[2] may be used to show similar clinical characteristics only if the endpoint is appropriately validated. If this cannot be validated, an efficacy study in an appropriate indication is required.

If the reference product has multiple therapeutic indications, the biosimilar manufacturer may extrapolate from other indications if the mechanism of action is the same and if appropriately justified. The guidance requires immunogenicity data to be provided before approval, and product-specific annexes provide details for erythropoietin, granulocyte colony stimulating factor, insulin and growth hormone. It is important that healthcare practitioners are aware this data is extrapolated from other indications when choosing which product to prescribe.

To ensure safety within this framework, pharmacovigilance systems need to be robust enough to cope with the introduction of biosimilars. This means they need to ensure traceability. Therefore, company and regulatory agency (in the UK the MHRA) pharmacovigilance reporting systems should distinguish one manufacturer's product from another. If biosimilars have the same International Non-proprietary Name (INN) as the originator product, it is even more important that pharmacovigilance systems are strictly enforced. To prevent repeated uncontrolled substitution, biosimilars should be prescribed by brand name alone with a strict ban on substitution.

In addition to these precautions, there are many simple ways in which inadvertent substitution of biosimilars can be prevented, including making physicians, pharmacists and patients

aware of the data available to support a medicine; making Patient Information Leaflets (PILs) transparent and clear; providing a defined reference product; describing clinical data for approval including unique safety data and offering substitution advice.

Biotechnology medicines are a welcome part of the future healthcare landscape and will become a familiar phenomenon. A regulatory approval process has been established in Europe and both the MHRA and the Government have committed to a robust pharmacovigilance system whilst we continue to learn more about biosimilar medicines; however, awareness of the differences between original biotech medicines and biosimilars is essential for healthcare professionals and patients to ensure appropriate introduction into clinical practice.

1 EMEA Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived proteins as Active Substance: Quality Issues. 22 February 2006, London . EMEA/CHMP/BWP/49348/2005 http://www.emea.europa.eu/pdfs/human/biosimilar/4934805en.pdf

2 Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important are called surrogate outcomes.

SAFETY ISSUES RELATED TO THE INTRODUCTION OF BIOSIMILAR MEDICINES INTO UK HEALTHCARE

Biosimilars and Patient issues

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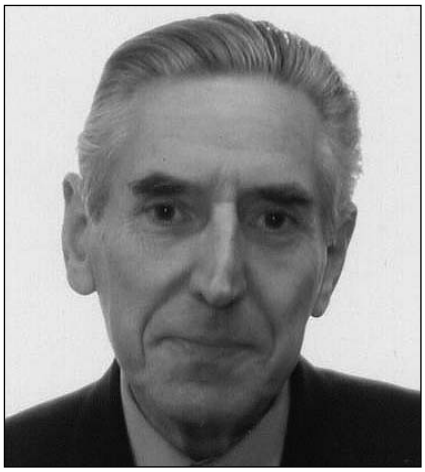

The Patients Association is a national charity providing patients with an opportunity to raise concerns and share experiences of healthcare. We are committed to making a difference to the 'Patient Journey', educating our members, patients, healthcare practitioners and politicians about the key issues affecting patients, including advances in technology and the impact this will have on patients.

As part of this representation, we feel the introduction of biosimilar medicines to patient care in the UK raises important issues for patients and patients' organisations. The significant advance in available treatments necessitates caution during their introduction until all participants are fully familiar with these products.

Whilst safe and effective biosimilars have the potential to play a role in stimulating competition, and broadening treatment options for patients, it remains important for doctors and patients to recognise that biosimilars are not directly substitutable in the same way that traditional generic medicines are substituted for chemical medicines. Biosimilars may bring benefits to patients, including lower cost to the NHS; however, it is not yet known how significant the cost savings will be compared with originator medicines but it seems the differences are unlikely to be as great as those seen with generics of chemical medicines.

Due to current gaps in knowledge, there have been a number of movements by patient organisations to improve patient understanding of treatment with biotechnology, and biosimilar, medicines. The National Patient Safety Association has launched a 'Please Ask' campaign encouraging patients to ask about their treatment and discuss options with healthcare staff. Meanwhile, the International Alliance of Patients' Organisations (IAPO) has launched an educational programme on biosimilar medicines to help patient organisations make informed judgements on their value and the scientific, social, ethical and economic issues.

A patient survey conducted by IAPO in 2006 showed that whilst patients were concerned by the cost of medicines, their main concerns related to efficacy and safety. Whilst there was a positive interest in biosimilars, all patient groups called for biosimilars to be introduced in a safe and appropriate way. This was summed up by Charles Gore, President of the European Liver Patients' Association who said *"Biosimilars offer a tremendous opportunity to reduce medicinal costs but offer equally important challenges – they must offer true comparability with the original products because ultimately safety comes first. We do not want to give ourselves a dangerous legacy"*. In addition, this survey indicated there should be a risk assessment of labelling and packaging of dispensed medicines to minimise harm from 'look-alike' products.[1]

Low levels of awareness of biosimilar medicines hinders the role of patients, and patient groups, in engaging in this debate. In turn, this restricts patient knowledge in discussing health needs with their healthcare providers. Where biosimilars are available, patients must understand the choice they are making and be involved in that choice. Transparent and clear information and involvement of patients in policy debates is essential to build trust in new medicines.

The importance of easy tracing and clear indications of side-effects will be essential to patient safety in the event of adverse drug reactions (ADR). The

patient has an important role, and responsibility, in this. To help patients, medicines must be clearly marked, easily identifiable and well labelled to enable tracing in the event of an ADR. Clear educational material will be essential and healthcare staff have a key role to play in making sure patients are aware of any associated risks. They must understand both the positive and negative side-effects of any treatment, ie patients need to be 'risk-literate', so they understand the actual risks associated with a treatment, in realistic terms. There is a responsibility on all participants in the health agenda to make sure this information is conveyed in the clearest and most effective way.

The Government and health regulatory bodies need to take all necessary actions to protect patient safety during the introduction of biosimilars. This should include:

- A programme that ensures clinicians are aware of the possible risks and that these should be fully discussed with patients.
- Many more biotechnology products are due to come on to the market in the coming years. Patients should be made aware of the difference between traditional medicines and biotechnology medicines.
- Patients should be made aware of their role in ensuring full pharmacovigilance with any new medicines. They should also understand why it is important that they report adverse reactions and how these should be reported.

1 Biosimilar Medicines, The Views and Roles of Patients and Patients' Organisations, Jo Harkness, International Alliance of Patients Organisations, 4th EGA symposium on Biosimilar Medicines, 19 May 2006, London, UK

The following points were raised during discussion:

This is an awareness session following on from the Panel discussion and a recent Adjournment Debate designed to draw attention to the potential danger inherent in the use of powerful, largely protein based drugs, which differ from generic drugs in their inherent variability among several other factors.

Is there possibility of regulatory creep in relation to a defined reference point? The greatest danger arises from confusion. An example was then presented where two cancer patients died very rapidly. They were receiving an antifungal agent (amphotericin B) to treat a fungal infection. This was the standard drug for this treatment 30 years ago. However, amphotericin, which has evolved as a drug over the years, was prescribed currently by a doctor recently transferred from a different hospital where different practices applied. An amphotericin B dose was then delivered at 5 times the strength required for treatment over one hour instead of six hours and the two patients were dead within twelve hours. Similar problems arising from confusion are likely to arise where a product becomes known by a single name irrespective of several significant changes in performance over time and confusion arises over the appropriate dose required for treatment from the version of the drug actually prescribed, which could be very toxic to the patient. The question arises as to where the responsibility for such a situation lies. Is it the pharmacist or the GP?

The actual version of a drug selected for treatment such as erythropoietin, for example, which is used by renal physicians, may be subject to financial drivers on drug purchase operating at a high level, such as the London Purchasing Authority for example, where the consideration is primarily financial rather than considerations of the safety of patients exposed to a range of differing variants of a given drug, who may be subsequently informed that their drug has been switched, without their involvement or any further justification of reasons. Drug firms should take more interest in the way their products are used. Diagnostic laboratories also need to be aware that patients are taking differing versions of the same drug.

The knowledge base of biosimilars among clinicians and physicians and laboratory doctors and nurses is generally very low. It is not a topic considered suitably attractive for international meetings. A high degree of upskilling is required of the medical professionals involved in treatment with biosimilars. What is the method of characterisation of the biosimilar drugs used by the companies that produce them? Companies all go through the same assessment process in order to satisfy the requirements of the European Medicines Agency (EMEA). Most products are hospital-driven products. A patient with kidney failure comes into hospital and is started on erythropoietin and then moves out into primary care. The MHRA is responsible for monitoring drugs approved for use within the EU by the EMEA. Prices of biosimilars will become cheaper by about 20% in future.

Treatment of, for example, Paroxysmal nocturnal haemoglobinuria, which is a rare and devastating disorder will be carried out using Eculizumab, an Ultra Orphan drug produced by Alexion. This is a new anti-complement C5 antibody costing £250,000 per patient, per year, and treatment will be prescribed, following the Darzi reforms, at Leeds and Kings but will also be available more widely through clinics based at local hospitals managed and run by major hospitals. It has been reported that this year the NHS have treated more patients for less for the first time. However new biotech drugs could prove very expensive in future.

It was recommended at the Panel established to consider biosimilars that they should carry a black triangle. If an innovative product is approved by NICE then it is unlikely that they will be involved with the assessment of biosimilars. There may be a health technology assessment. However, a single group of hospitals may decide jointly to select a single product for their use to reduce the complexity of managing the supply of five different variants, for example. This reduces patient choice although some patients may respond differently to each of the variants. In addition, the NHS are treating 25 different nationalities with differing responses due to the varying background of different individuals.

Communication needs to be continually improved together with upskilling of all those involved in the management of biosimilars. Biosimilar copy companies are primarily concerned with the financial benefits of their products following registration with the EMEA, but they rarely engage with the medical community once that approval for use has been obtained.