Biosimilars: ensuring safety in the search for savings

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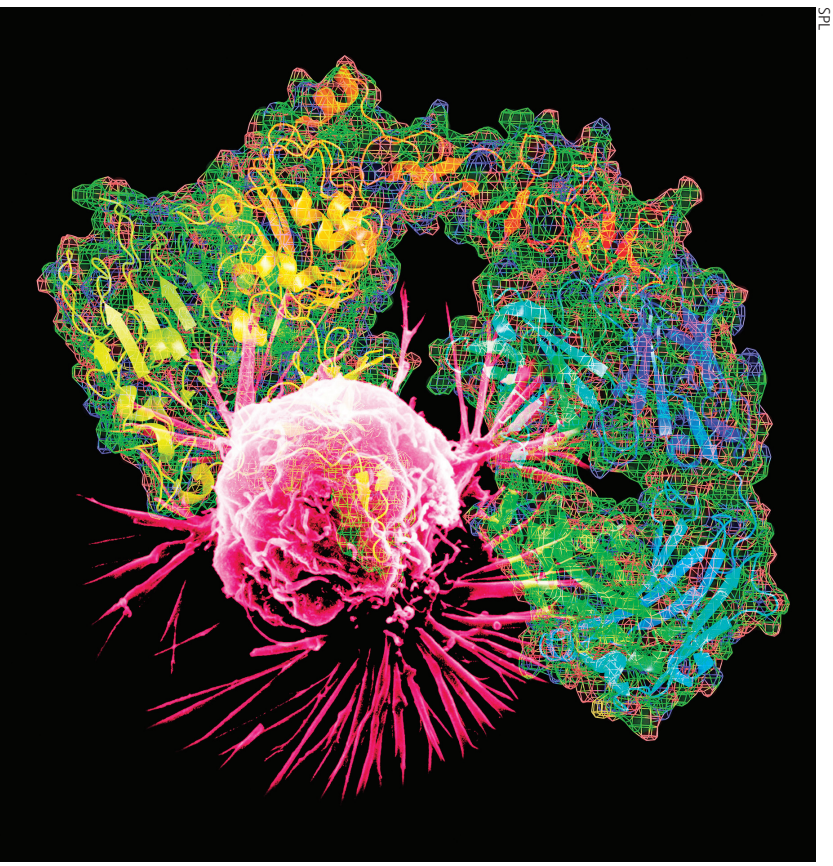

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Biosimilars – cheaper versions of biopharmaceuticals produced by competing companies – have the potential to reduce the NHS drugs bill substantially. However, unlike generic drugs, biosimilars are not interchangeable with the original brand, raising safety concerns. Hence pharmacovigilance and prescribing by brand is essential.

The drugs bill has long offered a tempting target for managers and politicians trying to contain increasing healthcare costs. After all, the NHS spends £32,000 a minute on drugs in England alone. In 2015/16, the drug bill in England reached £16.8 billion, an increase of 29.1% from 2010/11.[1] Eight of the ten most expensive drugs are biopharmaceuticals (see Figure 1), a diverse group of medicines that encompasses monoclonal antibodies, hormones, growth factors, enzymes and receptor proteins.[1] So, the growing number of biosimilars, cheaper versions of biopharmaceuticals, is good news for the cash-strapped NHS, while improving patients' access to previously prohibitively expensive treatments.

Nevertheless, concerns persist over the safety of biosimilars, especially as adverse events arising from the subtle differences between brands are likely to be rare. "Detecting 'safety signals' associated with biosimilars is very challenging," says Yoon Loke, professor of medicine and pharmacology at the University of East Anglia. So, does the search for savings on the biopharmaceutical bill potentially mean sacrificing safety?

Considerable savings

The European Medicines Agency approved the first biosimilars, filgrastim (human granulocyte colony stimulating factor) and epoetin alfa and epoetin zeta (recombinant human erythropoietin), between 2007 and 2008. Table 1 summarises the biosimilars that have so far gained marketing approval in the EU and their therapeutic indications.

While biosimilars help contain the drug bill, they are not generics. Developing a conventional generic of a small, simple chemically synthesised drug – an antihypertensive, lipid lowerer or bronchodilator, for instance – is relatively cheap, quick and easy. Biopharmaceuticals are made by, or extracted from, living cells, which makes developing a biosimilar expensive, protracted and complex.

Developing a small-molecule generic costs between $1 million and $2 million, takes about two years[2] and the regulatory requirements are relatively straightforward. In contrast, developing a biosimilar costs between $10 million and $40 million.[2] Moreover, companies producing biosimilars often need to develop a bespoke genetically engineered cell line and a unique production process, often with sparse data in the public domain from the originator company. So, the manufacturing investment can be between $250 million and $450 million. This, combined with the robust regulatory requirements, means that developing a biosimilar typically takes between five and eight years.[2]

Nevertheless, developing a conventional pharmaceutical can cost between $92 million and $884 million in cash terms at 2009 prices.[3] "As a result, biosimilars are markedly cheaper than the originator," says Paul Fleming, technical director at the British Biosimilars Association (BBA). "The competition stimulated when a biosimilar enters the market leads to marked discounting. The savings are not on the same scale as generics, which typically attract a 90% discount. However, a biosimilar is typically 20% to 25% less than the reference price. The launch of a biosimilar brings competition, usually leading to further price reductions over time." The Royal College of Physicians suggested that using biosimilar infliximab for inflammatory bowel disease reduces the annual treatment cost from about £10,000 to less than £5000 per patient.[4]

Such opportunities to make savings on the biosimilar bill are increasing rapidly. The patents of several expensive biopharmaceuticals will expire over the next few years. For instance, trastuzumab and bevacizumab will probably face biosimilar competition by 2020 in the EU and USA.[2] The BBA expects, for example, two to three biosimilar launches over the next two years for cancer alone. Indeed, more than 300 biosimilars are in development in the Asia-Pacific region as well as 50 in the USA and EU.[5]

Despite the economic benefits, the BBA reports that uptake of biosimilars is uneven across the UK. "The early adopters rapidly found a place for biosimilars," Mr Fleming reports. "But uptake has been much slower in some parts of the country, for reasons that are not fully understood. There is a need to share best practice to show the benefits and to encourage trust in biosimilars."

But encouraging trust means addressing lingering concerns over the potential impact of the subtle differences between brands, such as the production of neutralising antibodies and immunotoxicological reactions including allergy, anaphylaxis and serum sickness. However, difficulties with pharmacovigilance mean that uncovering any risk might not be easy.

Subtle differences

A chemically synthesised generic is interchangeable with the original brand. Generic captopril is chemically identical to Capoten, for example. Because excipients and release characteristics might differ, a few generics are prescribed by brand. In contrast, rather than being interchangeable, prescribers should consider biosimilars 'individual therapeutic alternatives'.[6] Indeed, the Medicines and Healthcare products Regulatory Agency (MHRA) recommends prescribing all biopharmaceuticals, including biosimilars, by brand. So, unlike generics, a pharmacist cannot substitute an alternative. "Prescribers control the brand of a biopharmaceutical that the patient receives from the start to the end of treatment," Mr Fleming notes.

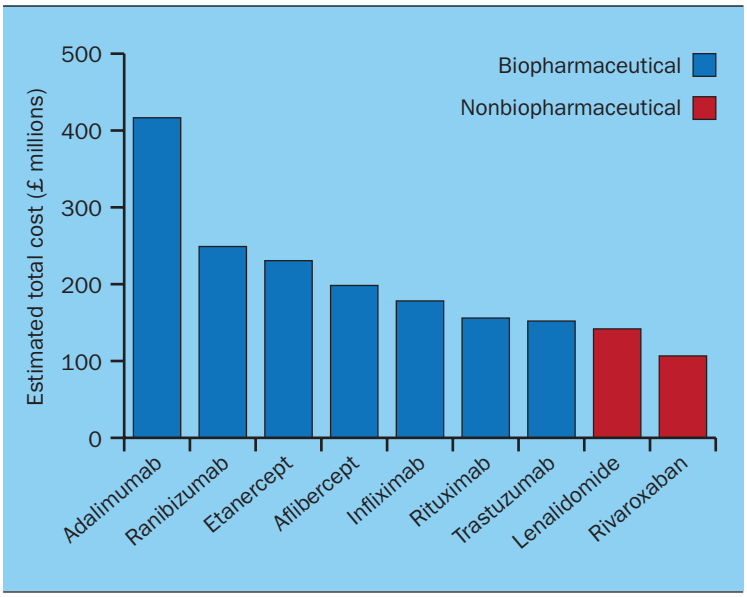

Figure 1. Top 10 medicines by estimated prescribing cost for medicines positively appraised by NICE and prescribed or issued in all sectors in 2015/16. Source: Health and Social Care Information Centre

The specific manufacturing process can influence the biopharmaceutical's characteristics, such as its three-dimensional structure and the carbohydrate side chains attached to the amino acid backbone (glycosylation).[7] Both are critical to the biopharmaceuticals' clinical effects. For example, changes in glycosylation (specifically increased N-glycan branching and sialylation) seem to increase the potency of epoetin, primarily by altering half-life.[6] In another example, a biosimilar manufacturer used a genetically engineered yeast to produce growth hormone. The original product was derived from genetically engineered *Escherichia coli*. The different production methods probably accounted for several differences in the precautions and warnings required by regulatory authorities in the USA between the brands.[8]

Moreover, as biopharmaceuticals derive from living systems, they are inherently more variable than conventional drugs. Living cells often produce a cocktail of variants (isoforms) rather than a single product, which includes differences in glycosylation (glycoforms).[6] Indeed, several factors contribute to variability between batches of a biopharmaceutical including their complexity and size.[9] The typical biopharmaceutical is between 100 and 1000 times larger than that of a chemically synthesised drug. Aspirin, for example, has a molecular weight of 180 Daltons, compared to 19,000 Daltons for interferon-beta.[8] Furthermore, the three-dimensional structure of a biopharmaceutical is more convoluted and fragile than a chemically synthesised drug.

To complicate matters further, the production process for many biopharmaceuticals undergoes several modifications during the drug's lifecycle. NICE notes, for instance, that the manufacturing process for Remicade (infliximab) has undergone 40 changes since the original authorisation in 1999.[9] Mr Fleming notes that each change requires regulatory scrutiny similar to, but less extensive than, that needed by biosimilars. Moreover, a company needs to collect data on various batches to demonstrate the biosimilar's consistency over time.

Nevertheless, even small changes can be clinically significant. Between 1998 and 2004, for example, 175 renal patients taking epoetin alfa developed pure red cell aplasia (PRCA) caused by neutralising antibodies against recombinant erythropoietin. Patients developed severe anaemia requiring blood transfusions, immunosuppressants and kidney transplants. These cases of PRCA emerged about 10 years after epoetin's launch and seemed to be associated with one formulation in which polysorbate 80 and glycine replaced human

Active substance	Brand names	Date of authorisation	Therapeutic indications
adalimumab	Amgevita Solymbic	22/03/2017 22/03/2017	Ankylosing spondylitis, rheumatoid arthritis, ulcerative colitis, psoriasis, psoriatic arthritis, Crohn's disease
enoxaparin sodium	Inhixa Thorinane	15/09/2016 15/09/2016	Venous thromboembolism
epoetin alfa	Abseamed Binocrit Epoetin Alfa Hexal	28/08/2007 28/08/2007 28/08/2007	Anaemia, cancer, chronic kidney failure
epoetin zeta	Retacrit Silapo	18/12/2007 18/12/2007	Anaemia, cancer, chronic kidney failure
etanercept	Benepali	14/01/2016	Psoriatic arthritis, rheumatoid psoriasis
filgrastim	Ratiograstim Tevagrastim Filgrastim Hexal Zarzio Nivestim Grastofil Accofil	15/09/2008 15/09/2008 06/02/2009 06/02/2009 08/06/2010 18/10/2013 18/09/2014	Cancer, neutropenia
follitropin alfa	Ovaleap Bemfola	27/09/2013 27/03/2014	Anovulation
infliximab	Inflectra Remsima Flixabi	10/09/2013 10/09/2013 26/05/2016	Psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriasis, ankylosing spondylitis
insulin glargine	Abasaglar Lusduna	09/09/2014 04/01/2017	Diabetes
rituximab	Truxima	17/2/2017	Wegener granulomatosis, microscopic polyangiitis, rheumatoid arthritis, leukaemia, non-Hodgkin lymphoma
somatropin	Omnitrope	12/04/2006	Pituitary dwarfism, Prader-Willi syndrome, Turner syndrome
teriparatide	Movymia Terrosa	11/01/2017 04/01/2017	Osteoporosis

Table 1. Biosimilars approved by the European Medicines Agency (EMA), date of EU marketing authorisation and therapeutic indications. Source: EMA, http://www.ema.europa.eu

serum albumin.[2,8,10] Although PRCA was "extremely rare", this much-cited high-profile case underscores that "small differences and changes in the production process can… have major implications on the safety profile of biologicals".[10]

"The experience with erythropoietin represented a landmark in our understanding of biosimilars," Mr Fleming says. "Partly in response, the regulatory environment has changed dramatically in the last decade and it continues to evolve as we gain experience. Biosimilars undergo increasingly robust regulatory review."

Robust tests

According to NICE, the "active substance of a biosimilar and its reference medicine is essentially the same". So, a biosimilar manufacturer does not need to show a clinical benefit. However, a biosimilar is not identical. As a result, the manufacturer needs to show that the biosimilar's intrinsic variability and any differences compared with the reference do not influence safety or effectiveness,[9] which means undergoing a much more robust series of tests than a chemically synthesised generic.

"In general, a generic needs to show that its pharmacokinetic profile is the same as the original product. So, many generics are approved based on a single cross-over study that enrolled 40 or 50 healthy volunteers," Mr Fleming explains. In general, provided the 90% confidence intervals for the important pharmacokinetic parameters, such as the maximum serum concentration of a drug (C_{max}) and the area under the serum drug concentration-time curve (AUC; a measure of drug exposure), fall between 80% and 125% of the reference, the generic is deemed bioequivalent and approved.

"In contrast, a biosimilar undergoes a long list of tests before approval," says Mr Fleming who previously worked for the MHRA. "These include pharmacokinetic and immunogenicity tests, comparisons of the amino acid sequence and three-dimensional structure, and clinical trials. Overall, biosimilars undergo more than 20 tests – including analytical tests, bioassays and human trials. Unlike a generic, a biosimilar is approved only for specific indications where there is clinical evidence rather than for all those covered by the originators." Indeed, the regulatory tests are helping biologists understand factors that drive immune responses to drugs, such as the relationship between protein structure and biological function.

Not surprisingly, given the complexities, a biosimilar's manufacturing process comes under more scrutiny than is typically the case with conventional generics. "Approval of a biosimilar includes a wide range of variables, many of which are bespoke to the product and the indication," Mr Fleming explains. "The regulatory authorities consider all these data in the round."

Pharmacovigilance concerns

Despite the stringent regulatory oversight, prescribers need to be vigilant for differences in safety and efficacy once the biosimilar reaches the market. In particular, the rapidly growing choice for many biosimilars underscores the need for vigilance. Studies of a biosimilar are performed against the originator, rather than against competing biosimilars, which might mean there is no direct evidence to inform switching.

"In theory, biosimilars should be sufficiently similar that they have almost identical adverse events profiles," says Professor Loke. "However, it is difficult to judge the effects of subtle modifications, when the trials might have included only a few hundred patients, yet the clinical user base could encompass tens of thousands. So, pharmacovigilance is essential. Unfortunately, however, there are major challenges in pharmacovigilance that are not easy to overcome."

For example, Professor Loke notes that different brands of a biosimilar may be made on the same production line. "Despite their different branding they are exactly the same substance," he points out. "Currently, it is not clear who has formal responsibility for combining two or more datasets."

"Having more than one brand of the same biosimilar doesn't help pharmacovigilance," agrees Mr Fleming. "We need full transparency so that the data sets can be scrutinised by the MHRA." However, the BBA suggests that the increasing use of registries and pharmacovigilance as part of risk management plans will help allay concerns. "The combination of robust regulatory scrutiny and postmarketing surveillance should give prescribers and patients confidence," Mr Fleming adds. "We've seen very few issues with biosimilars."

Issues with switching

A recent review noted that a "large amount of clinical data", mostly from open and observational studies, has been collected in patients with various autoimmune diseases who switched from Remicade (infliximab) to the biosimilar CT-P13, which is available in the UK as Inflectra and Remsima. The authors say that the data show "satisfactory outcomes, sustained efficacy and no sign of increased immunogenicity or any other safety concerns".[11]

Moreover, the *National Clinical Audit of Biological Therapies* in inflammatory bowel disease reported that Inflectra and Remsima showed similar short-term efficacy to Remicade. A response was seen at three months in 84% of adult and 86% of paediatric patients treated with biosimilars. This compared to a response of 85% in both adults and children treated with Remicade. However, the report suggests that the data comparing the efficacy of Remicade with biosimilars in people with inflammatory bowel disease is "relatively sparse". As a result, ongoing audits of effectiveness, safety and appropriateness are needed.[4]

Nevertheless, switching to a biosimilar is not as simple as substituting a generic. "Beginning a treatment-naïve patient on a biosimilar is straightforward and no different from starting any biopharmaceutical," Mr Fleming says. "Switching patients from the originator or between biosimilars requires extra vigilance, especially as some adverse drug reactions don't happen immediately. Patients need to be informed about the change, monitored and a management plan should be in place."

"Switching means that it is hard to judge the cause of an adverse drug reaction when the patient has been exposed to different brands of the biosimilar," Professor Loke points out. "Is the adverse drugs reaction due to the most recently administered biosimilar or is it a carry-over effect from the one given a month ago?"

Switching can raise other issues. Biopharmaceuticals are typically injected and each biosimilar might use a specific device. So, a change of biosimilar might mean training the patient to use the new device.[12] Formulations, containers and other elements of the packaging may differ, which potentially leads to differences in structure and stability between brands.[6]

Furthermore, patients trust their device and biopharmaceutical to control their serious, chronic disease. So, they might find the change disconcerting. "Switching formulations might prove unnerving or psychologically uncomfortable for the patient," Professor Loke adds. "This might result in new subjective symptoms that are reported as an adverse drug reaction, but have nothing to do with the biosimilar. Moreover, many patients taking biosimilars have chronic diseases that may fluctuate in intensity or severity. If the biosimilar happened to be introduced at the time the disease was flaring-up, this might be mistakenly recorded as an adverse drug reaction."

Conclusion

Biosimilars undoubtedly offer considerable savings and, according to a growing body of evidence, most patients do not notice a difference in efficacy or safety. But immunotoxicology remains, if not in its infancy, in its early childhood. We are still some way from, for example, developing assays that reliably predict the spectrum of immune effects that can arise when a genetically and clinically diverse population switches between biosimilars. Nevertheless, prescribers searching for much-needed savings still require the reassurance of effective pharmacovigilance, especially as the number of biosimilars is growing rapidly. Unfortunately, concludes Professor Loke, "pharmacovigilance for biosimilars is very challenging and their use is a difficult area to monitor." While early data are reassuring, we still have, it seems, some way to go before we fully characterise the efficacy profile and safety implications of these increasingly important drugs.

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Declaration of interests

Mark Greener is a full-time medical writer and, as such, regularly provides editorial and consultancy services to numerous pharmaceutical, biotechnology and device companies – including those producing biosimilars and generics – and their agencies. He has no shares or other financial interests.

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