Biosimilars: what are they and why do we need to know?

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As several widely used biological agents are due to come off patent the market for biosimilars is likely to grow. Here we analyse the implications for primary care.

Up to now most non-specialists have been able to ignore biosimilars as the only ones that were around were used for niche indications in oncology and endocrinology. For many years they have been prescribing curios – of passing interest to the average prescriber but of no relevance. But this is about to change as several widely used biological agents are due to lose patent protection in the next few years. This will result in the introduction of new biosimilars with huge implications for NHS spending and access to treatment.

Biologics and biosimilars

Biological agents are compounds that are manufactured using living organisms – examples include monoclonal antibodies (trastuzumab, infliximab), soluble receptors (etanercept) and recombinant DNA technology products such as analogue human insulins and growth hormone. They are typically large molecules with complex three-dimensional structures that require close control during manufacture to achieve a consistent product. They may need careful transportation and storage. They are usually administered parenterally and adverse immunological reactions are a major concern in some cases.

A biosimilar is more than a copy or a simple generic version of a biological. The EMA defines it as ‘...a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise’.

Copies of widely prescribed biologics are available in some markets (eg China, South America), but they have not undergone the process of regulatory approval that confers the title ‘biosimilar’ and their comparability with the reference product is therefore unknown.

Figure 1. Number of changes in the manufacturing process of biological agents after regulatory approval

![Figure 1](prescriber.co.uk)
The importance of biosimilars

Biosimilars are expensive. For example, when NICE recommended biosimilars for rheumatoid arthritis after failure of anti-TNF therapy in 2010, the basic NHS cost of adalimumab (Humira) was over £9000 per patient per year. In 2012, monoclonal antibodies accounted for six of the top 10 NICE-approved drugs prescribed in NHS hospitals in England, or 20 per cent of all drug spending (see Table 1). With cost escalation in secondary care at 11 per cent (2012 figures) compared with overall drug price inflation at 1.5 per cent, there will clearly be pressure to save money on prescribing expensive drugs.

Manufacturers have to recover their investment in research and development of new compounds and make a profit within the period of patent protection. In the case of conventional drugs, generic competition then drives prices down. This can be a very effective mechanism, for example the advent of generic atorvastatin (Lipitor) saw annual NHS expenditure fall by £250 million between 2011 and 2013. It can also increase access to treatment by bringing the drug below the NHS cost-effectiveness threshold. In the case of conventional drugs, generic atorvastatin when previously simulated, the absolute savings is expected to save US$25 billion between 2009 and 2018.

The difference between biosimilars and biologicals

It is not widely acknowledged that a biological agent is not a single, pure compound in the way that a conventional small drug molecule can be. Its exact structure – the extent of glycosylation, for example – is determined by the manufacturing process. No two batches of one biological agent are identical, a property known as microheterogeneity. Further, manufacturers continually refine their production processes (see Figure 1) and this ‘iterative change’ introduces small structural alterations that may or may not affect the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the drug and its safety. The regulatory authorities must be satisfied that iterative change does not have significant clinical impact, so manufacturers carry out a comparability exercise based on physicochemical analysis, biological assays and sometimes non-clinical and clinical assessments to demonstrate that the effects of the biological agent are essentially unaltered by changes in manufacturing.

Regulatory assessment

If the original manufacturer cannot produce a biological agent that is always identical, it follows that a second manufacturer will not be able to produce an exact copy. But, by meeting regulatory standards that enforce consistency, it can produce a closely similar agent.

As with generic drugs, biosimilars undergo an accelerated regulatory assessment. The EMA led the world in recognising the significance of biosimilars when it enacted its first regulatory guideline in 2005. It has now developed ‘over-arching’ guidelines on the quality and safety of biosimilars. Draft guidance recommends that clinical comparability between a biosimilar and the reference biological is established via a stepwise procedure involving PK and, if feasible, PD studies ‘followed by clinical efficacy and safety trials or, in certain cases, confirmatory PK/PD studies for demonstrating clinical comparability.’ The guidance specifies how immunogenicity should be assessed and requires the manufacturer to have a postmarketing pharmacovigilance strategy to detect rare adverse events. There are also guidelines covering the non-clinical and clinical development of specific drugs.

Prescribing biosimilars

There is disagreement between the research-based manufacturers of originalator brands and those of biosimilars about nomenclature. One side maintains that biosimilars are different from the original drug and should therefore have a different International Nonproprietary Name (INN). The other believes that biosimilars are essentially no different from the original drug, which itself undergoes minor structural changes in its life cycle, in which case they should share an INN.

Clearly, different INNs could obstruct substitution of a biosimilar for an original biological – something which the UK pharmaceutical industry opposes, in line with its advocacy of brand prescribing. The EMA has so far accepted a single INN, consistent with the wishes of most EU member states.

In the NHS there is brand prescribing of biological in all but name. Clinicians need to record the brand prescribed because the MHRA needs to know the brand and batch number of any biological – original or biosimilar – that is linked to an adverse event report. It also recommends giving these details to the patient.
Conclusion
Biosimilars are expected to deliver huge savings to healthcare systems and increase access to treatment in the coming years as expensive biological drugs lose patent protection. Regulatory requirements ensure that a biosimilar and the original biological are in all essential respects the same. Small structural differences may affect immunogenicity, therefore the brand and batch number of a biosimilar, as with any biological agent, should be recorded at the point of prescribing and safety should be closely monitored.

References

Declaration of interests
None to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics.