

# Safeguarding patients as biosimilar medicines enter clinical practice

As more biosimilar products are approved for use, safeguards will need to be put in place to protect patients, a group of MPs warned last week.

**Tom Moberly** looks at the group's recommendations and some of the other issues raised by this new wave of medicines

Over the coming years, an increasing number of follow-on biotechnology products will come onto the market as the patents on originator products expire. Unlike generic versions of small-molecule drugs, these biosimilar medicines will not be identical to the originator products and may have different clinical effects.

In recognition of the fact that biosimilars are not identical to originator products, the mechanism for gaining European approval for a biosimilar differs from that for a generic medicine. In particular, it requires significant clinical evaluation in order to demonstrate that a biosimilar medicine has comparable safety and efficacy to those of the innovator product. The term "biosimilar medicine" comes from EU legislation governing the approval process, but these products are also known as "similar biological medicinal products", "follow-on biologics" and "biogenerics".

To date, the only biosimilars approved for use the EU have been preparations of the recombination growth hormone somatropin and of epoetin alfa, but several more biosimilars are currently being assessed.

The European Generic Medicines Association believes that biosimilar medicines could improve access and reduce cost pressures on health systems. "Biosimilar medicines now offer a major opportunity to provide greater access to affordable healthcare for several life-saving medicines, at least equally significant to the emergence of generic medicines over the past two decades," it says.

The European Medicines Agency (EMA) has recommended that "the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional".

Jayne Lawrence, the Royal Pharmaceutical Society's chief scientific adviser, stresses that biosimilars cannot be considered in the same way as small-molecule generics. "They are not generics and must be treated differently," she says. "At this stage in the development of some types of biologics I believe more information is needed to safely make the decision to substitute a biosimilar product."

A number of countries, including France, Spain, the Netherlands and Norway, have already introduced measures to prevent substitution of biopharmaceutical products. And last week a group of MPs, led by Brian Iddon (Lab, Bolton South East) urged the UK Government to do the same (see Panel).

The MPs argued that biotechnology prod-

ucts should always be prescribed by brand, rather than by their generic name, that patients should be maintained on the specific medicines on which they started treatment and that substitution of one product for another should be banned.

The Government has previously said, in response to Parliamentary questions from Mr Iddon, that when biologics are prescribed they should be "clearly identified and prescribed by brand name to ensure that patients receive the exact product prescribed and that their use can be properly monitored".

The Government has also said that the Medicines and Healthcare products Regulatory Agency encourages manufacturers to give biosimilar products a brand name "so that there is no possibility that the pharmacist can substitute another biosimilar product when dispensing the doctor's prescription".

## Complexity

Biologics are large molecules and so complex to produce, Professor Lawrence explains. Biologics include agents used in a wide range of therapies, such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues and recombinant therapeutic proteins.

They can be composed of sugars, proteins or nucleic acids, or complex combinations thereof, or in some cases may even be cells and tissues. And their production may involve isolating molecules from biological sources or growth in cells. The complexity of biologics means that biosimilar products will almost certainly use different starting materials or different manufacturing processes to those used for the originator biologic.

The characterisation of biologics is also extremely complex, Professor Lawrence adds. A whole range of sophisticated techniques, both physico-chemical and biological, are required to gain a picture of a biologic. In fact, different tests may be needed for different biologics.

"The complexity of characterising biologics means it is not possible to prove that the biosimilar is identical to the reference product," she says. "Therefore biosimilars can only be considered as similar to the reference product — hence the name.

## Clinical differences

"It is also possible for biosimilars to exhibit different clinical characteristics that cannot be detected by standard physico-chemical and biological testing and which might lead to rare adverse events, especially immune-mediated events. All these factors mean that more information is needed about a biosimilar to make a substitution than is needed to substitute a small-molecule drug"

However, Professor Lawrence points out that some biologics have been safely substituted for years, including human growth factor and insulin. In fact, the panel of MPs suggests that the safety of biosimilars could be assured once sufficient clinical data exist, suggesting their recommendations are limited to new biologics coming onto the market.

"If there is a ban on substituting biologics, I would hope that after sufficient wide spread use of biosimilars the situation would be reviewed to see if it were possible to substitute biosimilars," Professor Lawrence says. "A suitably qualified review panel would be needed to consider the therapeutic evidence on biosimilars to remove the ban to substitute," she adds.

## Parliamentary review

A group of five MPs, led by Brian Iddon, conducted a review of the issues surrounding the introduction of biosimilars into clinical practice, hearing oral evidence from seven witnesses. The review was funded by biotechnology company Amgen. In the report that followed the review (*PJ*, 5/12 January, p6), the MPs recommended that a number of safety measures be introduced "to ensure that prescribing and pharmacovigilance procedures are sufficient to safeguard best practice and offer patient protection".

The British Generic Manufacturers Association argues that the evidence taken by the MPs was biased. "Though [the report] is designed to look like an official parliamentary committee document, it is not," the association says. "The BGMA was not asked to contribute to the report. Neither to our knowledge was any representative of the biosimilars industry. The 'evidence' taken was thus not balanced." Nevertheless, a number of the MPs' recommendations already apply to biosimilars, the association says.

However, the Medicines and Healthcare products Regulatory Agency has said it is considering the recommendations in the report and that the Government will be responding to it.

Further information about the report is available from the office of Brian Iddon, House of Commons, London SW1A 0AA or by telephoning 020 7219 2096.