Prescribing biosimilars
Slow adoption is costly

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Generic formulations of small molecules are usually as effective as originators, have similar harms, and are cheaper to prescribe. The same should be true of biosimilars, which are generic equivalents of originator biological medicines (biologics). A

Two years ago2 we cited an article in the Financial Times,1 the author of which claimed that the UK had been slow to adopt biosimilars. Here we provide evidence that that is so, based on the limited publicly available information on NHS prescribing of biosimilars.

Biosimilars are biological medicines that are highly similar to other already approved drugs and are themselves approved according to the same standards of pharmaceutical quality, safety, and efficacy. They are not necessarily identical. Consider, for example, monoclonal antibodies. Although a biosimilar is likely to preserve the primary amino acid sequence of the originator, differences in glycosylation, deamination, oxidation, or three dimensional structure can occur. These can affect interactions with target molecules, which could lead to differences in benefits, harms, or both, between biosimilars and the corresponding originators. This may be the case, for example, with epoetins.3 4

Clinicians face two problems: choosing between an originator or a biosimilar when starting therapy and whether to switch from one to the other during established therapy. There are principles to ensure that biosimilars are similar enough, and US and European regulators demand that biosimilars should be “highly similar to the reference medicinal product in physicochemical and biological terms.” This includes, for example, pharmacokinetic and pharmacodynamic similarity and being used in the same doses as the originator product. Furthermore, “any observed differences have to be duly justified with regard to their potential impact on safety and efficacy.” The principles are included in guidance from the US Food and Drug Administration, and the UK’s National Institute for Health and Care Excellence (NICE) has provisions for recommending biosimilars when appropriate.10

There is some reassuring evidence of equivalence. For example, two infliximab biosimilars, Remsima and Inflectra11 13 are identical to the originator, Remicade, in pharmaceutical form, strength, composition, and route of administration. The biological actions of Remsima are essentially identical to those of Remicade, apart from minor pharmacodynamic differences that seem to be clinically insignificant.14 The pharmacokinetics are almost identical, and clinical markers of disease activity respond equally well to originator and biosimilar products in rheumatoid arthritis and ankylosing spondylitis.12 15

The World Health Organization plans to prequalify biosimilars for cancer therapy, giving them a global stamp of approval.16 Comparability of quality, safety, and efficacy will make them eligible for procurement by UN agencies. This should increase assurance of equivalence.

However, showing that two products are of equal efficacy does not prove that switching them maintains the balance of benefits and harms in individual patients. For example, in an 18 month study in inflammatory bowel disease, switching from originator infliximab to a biosimilar did not affect efficacy, but 13 of 143 patients dropped out because of adverse events.17 A systematic review of 58 studies, including 12 clinical trials, mostly involving infliximab or etanercept, suggested that the expected cost savings of switching outweighed the risks of harms.18 A later review of 57 studies, covering a wider range of compounds (infliximab and etanetumab, etanercept, filgrastim, follicle stimulating hormone, genotropin, insulin glargine, and rituximab), reported that safety and efficacy were mostly unchanged after switching. However, the data were limited, and the authors commented that well powered and appropriately analysed clinical trials and pharmacovigilance studies, with long term follow-up and multiple switches between originators and biosimilars were needed.

We sought evidence about UK prescribing of biosimilars in two publicly accessible sources: OpenPrescribing.net, which contains detailed current data on all prescribing in individual English general practices, and the NHS Medicines Optimisation Dashboard, which contains a limited number of prespecified

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measures at the individual NHS trust level.20 Insulin glargine is commonly prescribed in primary care, and detailed data are available through OpenPrescribing.net. The originator, Lantus, still accounts for 90% of GP prescriptions (fig 1); the biosimilar Abasaglar accounts for around 60% of the new prescriptions for insulin glargine since it was licensed in September 2015. This suggests that 40% of new patients are still receiving the originator, which has an NHS indicative price that is 7% higher, and that switching is rare.

No other biosimilars are commonly prescribed in primary care, and hospital prescribing data are limited: from the large number of biosimilars now available (table 1), the Medicines Optimisation Dashboard gives information on only three: etanercept, infliximab, and rituximab. The median percentages of these drugs prescribed as biosimilars in January 2018 were 76% (interquartile range 60-90%), 90% (85-98%), and 60% (42-76%) respectively. Uptake of biosimilars by formularies of UK acute trusts and health boards has also been poor.21

Reasons for the poor uptake of biosimilars may include lack of familiarity, therapeutic inertia, concern about patient confusion over different brand names and different looking formulations, perceived lack of efficacy, and the nocebo effect.22 This may have substantial cost implications, because prices are high and originators typically cost about 10% more than biosimilars.23

When a biosimilar has been licensed, there should be no concerns about starting treatment with it rather than the originator. And switching to a cheaper product in a patient who is already taking an originator can also be recommended when there is high quality evidence of equivalence of the benefits and harms, provided progress is carefully monitored.

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### Table

#### Table 1 | Examples of biosimilars currently approved in the EU or US

| Generic name | Originator brand name | Examples of biosimilar brand names |
|--------------|-----------------------|-----------------------------------|
| Adalimumab*  | Humira                | Imraldi                           |
| Darbepoetin† | Aranesp               | Retacrit, Silapo (both epoetin zeta) |
| Epoetin alfa†| EpoGen/Eprex/Procrit  | Abseamed, Binocrit                |
| Etanercept‡  | Enbrel                | Brenzys, Benepali Erelzi          |
| Filgrastim†  | Neupogen              | Biogstlim, Filgrastim Hexal, Grastofil |
| Infliximab*  | Remicade              | Flixabi, Remiflexis, Remsima, Inflecta, Flammegis |
| Insulin glargine§ | Lantus                | Abasagrall, Basaglar, Senlglee    |
| Rituximab*   | MabThera, Rituxan     | Truxima, Blitzima, Rituxama, Rituzena |
| Teriparatide§ | Forteo, Forstero     | Movymia, Terosa                   |
| Trastuzumab* | Herceptin             | Ontruzant                         |

* Monoclonal antibodies; †Glycoproteins; ‡Fusion protein; §Polypeptide hormones.