Editorial:

Biosimilars are becoming indispensable in the management of multiple diseases although concerns still exist

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Global expenditure on medicines is rising driven by increased expenditure on medicines for immunological diseases, cancer and orphan diseases[1]. This is principally new biological medicines, often with very high prices and limited health gain[2-4]. This is a concern as it threatens universal healthcare where this exists potentially negatively impacting on the image of biologicals[5-6]. In addition, high prices for biological medicines to treat patients with immunological conditions such as rheumatoid arthritis, inflammatory bowel diseases, and psoriasis, have made them unaffordable for patients in lower- and middle-income countries (LMICs) with typically high co-payments denying them access to effective therapies[7-10]. High prices have also resulted in concerns with their cost-effectiveness in LMICs[11]. The same concerns with affordability for biological medicines for immune diseases are also seen in oncology with medicines such as trastuzumab[12-14], as well as cancer care generally among some LMICs[15]. We are also seeing rising expenditure on medicines generally as a result of ageing populations with an associated increase in non-communicable diseases (NCDs) and changing clinical guidance[2,16]. This is putting further pressure on healthcare systems as they strive to reduce morbidity and mortality of non-communicable diseases (NCDs) as part of the Sustainable Development Goals[17-19], and increased availability of lower cost biosimilars can help address this.

We have seen health authorities across countries introduce a variety of supply-side measures such as pricing regulations and aggressive procurement practices, coupled with demand-side measures such as education of physicians, prescribing targets and financial incentives for physicians, pharmacists and patients, to enhance the prescribing of multiple sourced medicines in a class or related class versus still patented medicines to secure savings without compromising care to help maintain universal healthcare[20,21]. Such multiple activities following the availability of generic omeprazole and simvastatin resulted in expenditure on proton pump inhibitors (PPIs) and statins in Sweden being up to ten times lower than Ireland between 2001 and 2007 with its very limited supply- and demand-side measures when adjusted for population size[20]. Expenditure on PPIs and statins also fell by 58% and 14% respectively in the Netherlands between 2000 and 2010 following extensive measures despite a three-fold increase in PPI utilisation and a 3.8 fold increase in statin utilisation during this period helped by generic omeprazole and simvastatin at just 2% of pre-patent loss prices[22]. A similar situation was seen in Scotland with their multiple initiatives, including very high rates of voluntary international non-proprietary name (INN) prescribing, where there was a 50% reduction in expenditure on lipid lowering medicines between 2001 and 2015 despite a 412% increase in utilization and a 66.7% reduction in PPI expenditure in 2017 versus 2001 despite a 3.06-fold increase in utilisation[16, 23]. However, there have been occasions where pharmaceutical companies and others have challenged the prescribing of generics versus originators. An example was generic clopidogrel which was initially launched with a different salt with concerns from cardiologists and

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others regarding its effectiveness and safety despite health authority educational and other activities[24,25]. The level of disinformation emanating from the Company eventually resulted in a fine from the French Health Authorities[26].

There were also similar concerns regarding the effectiveness and safety of biosimilars versus originators when first launched[27-29]. This is changing with more studies demonstrating similar effectiveness and safety between biosimilars and originators[30-36]. In addition, greater knowledge that originator companies themselves change their manufacturing processes, sometimes quite frequently, without currently needing to undertake additional studies; consequently, new batches can also be viewed as biosimilars to the originators[37-39].

We have also seen issues with oral generic medicines when the first indication loses its patent but not the subsequent indications. This difference impacted on the prescribing of generic pregabalin versus LYRICA across indications in Europe with the neuropathic pain indication still patented[40]. However more recently, this did not seem to apply to either oral generic cancer medicines or biosimilars where there can also be multiple indications[41,42]. This is welcomed given the considerable potential for savings.

Initiatives to obtain low prices for biosimilars, coupled with multiple activities to enhance their use, are necessary to realise appreciable savings from biosimilar availability, alternatively enhance access, which is similar to the situation with oral generic medicines[20,43,44]. We have seen that low prices for biosimilar adalimumab among hospitals in Denmark through procurement and switching activities resulted in an almost total replacement of Humira® with adalimumab biosimilars by December 2018 decreasing overall expenditure by 82.8%[45]. In the UK, expenditure on adalimumab is envisaged to fall by 75% following the availability of biosimilars coupled with indicators and other activities to enhance their prescribing[42,46]. Savings have not always been as high as this with typically biosimilars initially priced only at 10 to 30% below the originator price, which is still the case for biosimilar trastuzumab[6,47,48]. However, even at these reductions, savings can be appreciable given the sales of trastuzumab[47,48].

We have seen a growing increase in the utilisation of biosimilars across countries as a result of ongoing initiatives, and this is likely to continue[39,49-52] enhanced by advice concerning additional initiatives that could be instigated to enhance their use if needed[53]. Education of physicians and patients regarding biosimilars is very important given the nocebo effect in practice else saving goals will not be achieved[54,55]. Such initiatives are likely to grow given the number of biological medicines likely to lose their patent in the near future and the need to enhance the use of biological medicines across countries to improve patient care[56].

As a result of multiple activities in Scotland both regionally and nationally, including target indicators for the prescribing of biosimilars for new or switched patients, prescribing of etanercept and infliximab biosimilars reached 84% and 94% of total prescribing for these biological medicines respectively by December 2017[42]. Prescribing of rituximab biosimilar also rose to 74% of all rituximab by December 2017, its first year of availability[42]. By December 2019, biosimilars had accounted for 92% of all trastuzumab and 87% of all adalimumab[57], with these rates likely to grow given continual pressure on available resources.

However, there are biosimilars where there is still caution regarding their use. This includes insulin glargine where for instance Commissioning Groups in England and Health Boards (Regions) in Scotland recommend prescribing by brand name[58-60] due to concerns that switching between devices could increase the rate of hypoglycaemia[61,62]. This is because medicine substitution is not allowed by pharmacists in the UK when an originator is prescribed[63]. This though typically has limited financial impact with very high rates of voluntary INN prescribing in the UK, with healthcare students taught using the INN name of medicines in universities with initiatives post launch to continue to encourage INN prescribing[16,63,64]. However, it is envisaged new patients should be started on a biosimilar insulin glargine where possible, with such activities likely to grow as more biosimilars are launched with lower prices[65]. We will be researching this further in the future as lower prices through biosimilars are likely to enhance the prescribing of long acting insulin analogues.

In conclusion, we will see growing use of biosimilars across countries as more biological medicines lose their patents to enhance patient access and care, release resources to fund new valued biological medicines, help with the sustainability of healthcare system given ever increasing prices for new medicines as well as provide funding for additional healthcare

professionals[2,39,66]. Such activities will be helped by a growing body of evidence showing no difference in effectiveness and safety between biosimilars and originators. Alongside this, we are also likely to see health authorities re-negotiate potential prices or discounts for still patented biological medicines that used a medicine that is now available as a low cost biosimilar as the reference compound during pricing negotiations given the likely extent of price reductions for new biosimilars with greater competition under value-based pricing approaches to further help with the sustainability of healthcare systems[41,67,68].

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