Regulation of biosimilar medicines and current perspectives on interchangeability and policy

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Acknowledgements

This work was supported by the Health Products Regulatory Authority (HPRA), Regulatory Science Ireland and University College Cork. Brendan T. Griffin is also supported in part by the Irish Pharmaceutical Healthcare Association (IPHA) in the form of a research grant to support regulatory science research

The authors wish to thank the following for advice with this study: Una Moore (HPRA), Sandra Bright (HPRA) and Maeve Lally (HPRA).

Conflict of Interest

Joan O'Callaghan, Sean P. Barry, Brendan T. Griffin, J. Michael Morris and Margaret Bermingham declare that they have no conflict of interest. This paper represents solely the views of the authors and should not be understood or quoted as being made on behalf of or reflecting the position of the Health Products Regulatory Authority or Regulatory Science Ireland.

Abstract

Background

Competition arising from the increasing availability of biosimilar medicines has resulted in healthcare savings and has provided greater patient access to high cost therapeutics in Europe. The biosimilar market in the United States is relatively new so the full impact of biosimilar availability remains to be seen. Educational initiatives relating to the use of biosimilar medicines are currently being undertaken by regulators, policy makers and industry. The debate on biosimilars has moved on from the appropriateness of the regulatory framework which governs their approval, to the practice of interchangeability. Interchangeability is an important issue for healthcare professionals but different definitions and regulatory frameworks exist in the US and Europe. In the US an interchangeable biological product is a biosimilar which may be substituted by a pharmacist, subject to local State policies. The interchangeability of a biosimilar with its reference medicine will be evaluated by the United States Food and Drug Administration (FDA) in cases where approval as an 'interchangeable product' is sought. In contrast, the European Medicines Agency (EMA) does not assess or make recommendations on interchangeability, therefore, in Europe interchangeability does not mean substitution but is generally physician-led or driven by national policy. This paper provides an overview of the regulation of biosimilar medicines. Challenges associated with the demonstration of interchangeability and practical considerations relating to switching are also discussed. Finally, we present policies that have been adopted to date in several European countries, the US and Australia, which aim to promote the use of biosimilar medicines.

1.0 Introduction

Biosimilar medicines

Biological medicines have provided effective treatment options in a number of clinical specialities including gastroenterology, rheumatology, dermatology and oncology. Biologicals are expensive and their increasing use has contributed to escalating healthcare costs globally [1, 2]. The market exclusivity periods for some originator biological medicines have expired, meaning competing manufacturers can sell 'copies' of these medicines. These copies are

known as biosimilars. While biological medicines, such as monoclonal antibodies, have revolutionised treatment of many conditions, their costs are placing an ever increasing strain on national healthcare systems. Market competition for biologicals would free up healthcare resources allowing investment in new innovative treatments. In Europe the first biosimilar, somatropin marketed as Omnitrope®, was launched in 2006. The increasing availability of biosimilars since this time has led to significant healthcare savings and provided greater patient access to high cost therapeutics [3]. In contrast, the biosimilar market in the US is in its infancy; the first biosimilar (filgrastim-sndz marketed as Zarxio®) was only launched in 2015[4]. Consequently the full impact of biosimilar availability in the US remains to be seen.

Biological medicines contain substances, typically proteins, derived or extracted from living organisms. The biological activity of a protein is dictated by both its primary amino acid sequence and its higher order structure [5]. The structural complexity of proteins combined with the sensitivity of their manufacturing process to environmental conditions means that a degree of variability from batch to batch (manufacturing variability) is a typical feature of all biological medicines. The abbreviated regulatory approval pathway which currently applies for chemically synthesised generic medicines, is not suitable for 'copies' of biological medicines. Approval as a generic is possible once an identical molecular structure to the originator (reference) medicine has been confirmed and bioequivalence has been demonstrated [6]. However, due to the nature of their larger molecules, it is generally not possible to make an identical copy of a biological substance using a different manufacturing process. Therefore, a more tailored regulatory evaluation is required for 'copies' of biological medicines. Regulatory guidelines published by the EMA and FDA lay down robust science-based criteria for the approval of biosimilars [7, 8]. Regulatory explanations of the term 'biosimilar' are provided in Table S1 (supplementary material).

2.0 Regulation of biosimilar medicines

Biosimilar development

Biosimilar development follows a stepwise approach which can be described as tailoring, fitting, comparison and confirmation (Figure 1). The biosimilar manufacturer does not have knowledge of the originator manufacturing process, therefore tailoring involves extensive analysis of the structural, physicochemical and biological characteristics of the reference medicine, enabling the biosimilar manufacturer to establish 'goal posts' for their own product [2]. The biosimilar manufacturing process is adjusted so the quality attributes of the biosimilar fit the range of the reference medicine as much as possible. A stepwise comparability exercise commences with extensive analytical studies. Up to 20-40 different testing methods can be used to examine all relevant aspects of the molecule's structure and function. In order to establish biosimilarity, these studies must demonstrate that the primary amino acid sequence is identical to the originator protein and that there is similarity in terms of higher order structure, purity, biological activities and protein content. This means that for each analytical test, the results for the biosimilar must be shown to be within the tested range of the reference product. Minor differences in quality attributes (*e.g.* glycosylation, certain process related imputities) may be permitted once it is demonstrated that such differences are not clinically meaningful [8, 9]. Comparative *in vitro* assays provide a detailed comparison of relevant functional effects. *In vivo* testing may be used in the assessment of pharmacokinetics (PK), pharmacodynamics (PD) and toxicology [10]. However, the relevance of animal testing has been questioned by the EMA as unexpected toxicities in patients are unlikely once close similarity has been established through physiochemical and functional testing [11]. Many animal models generally lack the required sensitivity to detect potential relevant differences between a biosimilar and reference product. In addition, immunogenicity assessment in animal models is not usually predictive for immunogenicity in humans [12].

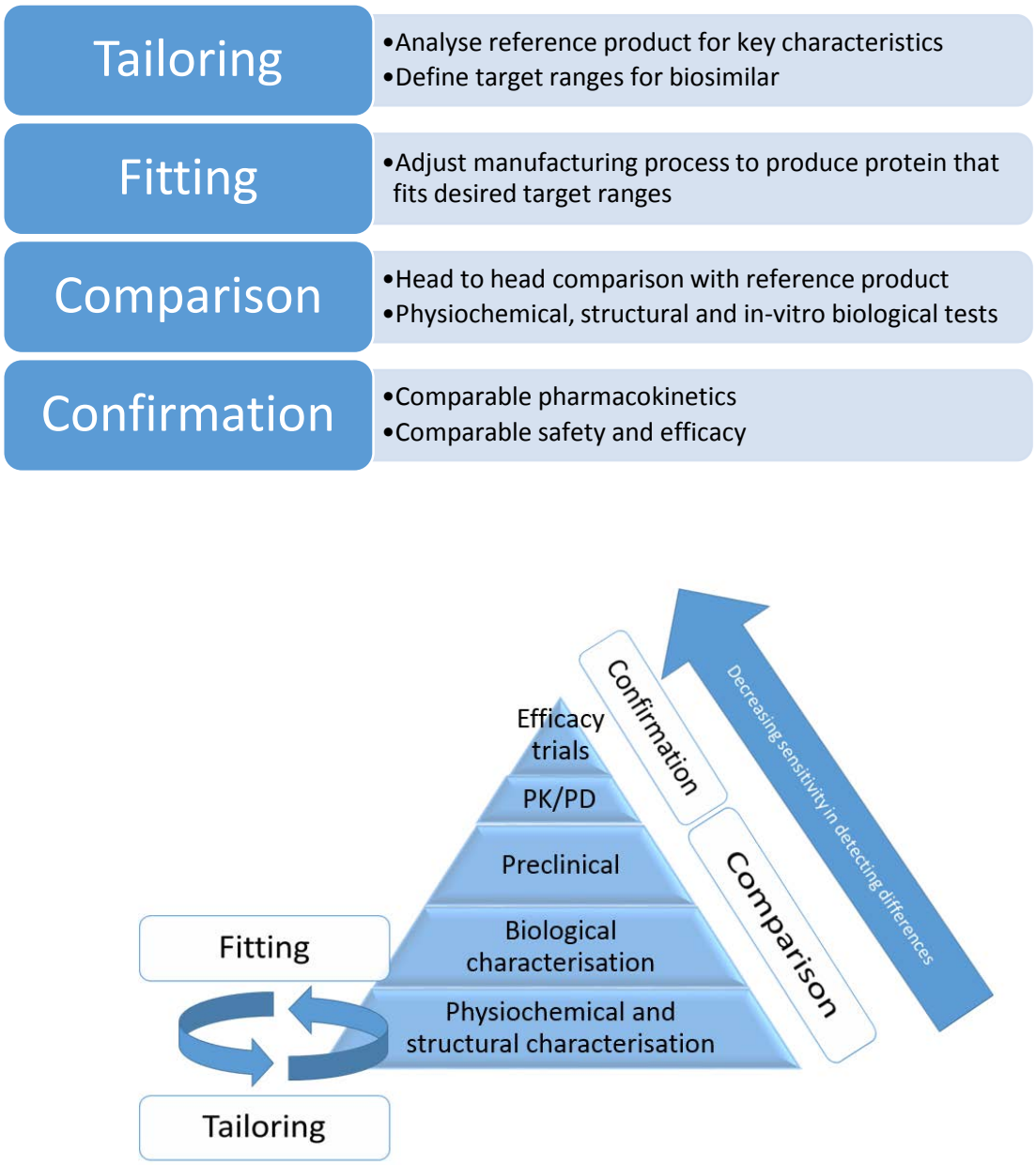

Figure 1: Summary of biosimilar development

PK; pharmacokinetics, PD; pharmacodynamics

Modified from [2]

The clinical comparability step confirms that the reference and biosimilar medicine have comparable clinical performance. A homogeneous patient population, sufficiently sensitive to detect potential differences between the biosimilar and reference, should be used for the clinical studies. Equivalence design is recommended and comparability margins must be justified and represent the largest difference in efficacy that would not be significant in clinical practice [13]. Early clinical studies are concerned with comparison of the PK and PD characteristics of the

biosimilar and reference. Later stages of clinical development should demonstrate comparable efficacy and safety [14]. Comparative immunogenicity data is usually required. If the incidence of immune response is rare and unlikely to be captured during clinical studies, a post-marketing study may be required [13]. In some cases PK/PD studies may be sufficient to demonstrate clinical comparability and this usually depends on the availability of a relevant PD marker which can be used to accurately predict patient outcome (e.g. absolute neutrophil count is a PD measure for filgrastim).

Indication extrapolation – not a new concept

For the approval of biosimilars, clinical studies demonstrating equivalent efficacy and safety in a single indication is usually sufficient to grant approval for all registered indications of the reference product. This is known as 'indication extrapolation'. The mechanism of action across the different diseases being extrapolated must be the same to the extent that it is known. In addition, existing clinical experience with the reference medicine, the extent of functional characterisation, and any differences in safety/immunogenicity profile that may be present across the different indications are all considered in any regulatory decisions concerning indication extrapolation [15].

Previous research suggests some physicians have misconceptions about biosimilar medicines or are not fully confident in their use [16-19]. A number of medical societies have also expressed reservations about indication extrapolation [20-22]. However, the concept of indication extrapolation is not a new one. Indication extrapolation is an inherent part of the comparability exercise, and has been the basis of regulatory evaluation of manufacturing process changes for biological medicines for many years [23]. Manufacturing changes are common [24] and are often required for the purposes of product improvement, scale-up or to meet new regulatory requirements [24-26]. In such cases a comparability exercise is conducted with the pre- and post-change product. As biochemical analytical data is considered more sensitive in detecting potential product changes than clinical trial data [27], comparability is generally supported by quality (physicochemical and biological) studies alone [23, 24, 27]. However, supporting non-clinical and clinical data coupled with continued safety monitoring may be required when quality data is insufficient in assuring that the change will not impact

the safety and efficacy of the medicine [23]. In Europe, it has never been necessary to repeat clinical trials in all indications after a biological medicine has undergone a major manufacturing process change [15]. Table S2 (supplementary material) provides some examples of cases where extrapolation was approved following significant changes to already authorised products and for which clinical trials were required.

Pharmacovigilance

All biological medicines including biosimilars have specific considerations applicable to their pharmacovigilance including immunogenicity and manufacturing variability [28]. For example, in the case of manufacturing process changes, analytical comparability data and supportive clinical studies (if available) may not always be able to predict rare adverse effects which could arise from altered immunogenicity [29]. Although rare, there are incidences where serious safety issues have emerged following such changes [30]. Additionally, in the case of biosimilars, it is important that clinical safety is monitored on an ongoing basis after approval as clinical trials are usually insufficient to detect rare adverse effects [12]. Both originator and biosimilar medicines are therefore subject to 'dynamic quality profiles' with potential for serious new risks to emerge throughout their lifecycles [28]. Consequently, European legislation requires brand name and batch number to be included in Adverse Drug Reaction (ADR) reports for all biological medicines [31].

3.0 Interchangeability

Defining Interchangeability

A key issue for the medical community is whether biosimilars should be reserved for those commencing biological therapy for the first time or whether it is appropriate for patients already receiving treatment with a reference medicine to be changed to a biosimilar [32-34]. In other words, there are questions over whether biosimilars are 'interchangeable' and whether practices such as 'switching' or 'substitution' are appropriate. According to the EMA, interchangeability refers to the 'possibility of exchanging one medicine for another that is

expected to have the same clinical effect'. Replacement can be done by 'switching' or 'substitution' (see Table 1) [35].

In the US an 'interchangeable product' is a biosimilar which has met additional regulatory standards relating to interchangeability, including dedicated clinical switching studies (Table 1). 'Interchangeable products' may be substituted for the reference product by a pharmacist, without intervention of the original prescriber, once the relevant state legislation permits this practice. Although FDA guidance on interchangeability has only recently been published, most US states have already enacted the relevant state legislation in anticipation of pharmacy substitution of biosimilars [36]. In contrast, the EMA does not make recommendations on the interchangeable use of biosimilars [35]. Instead, decisions concerning interchangeability are made nationally at member state level where the responsibility for local healthcare policy decisions resides.

Table 1: Comparison of the term 'interchangeability' in Europe and United States

Region	Explanation of the term 'interchangeability'	Reference
Europe	'Interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another. Replacement can be done by: Switching, which is when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent Substitution (automatic), which is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber'	[35]
United States	'…FDA will determine the biological product to be interchangeable with the reference product if FDA determines that the information submitted in the application or supplement is sufficient to show that the biological product "is biosimilar to the reference product" and "can be expected to produce the same clinical result as the reference product in any given patient" and that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without alternation or switch".	[37]

FDA: United States Food and Drug Administration;

Concerns regarding Interchangeability

The medical community have expressed some reservations about interchangeability and switching [20-22, 38]. One of the most frequently raised concerns is the risk of immunogenicity arising from a switch [39-41]. The most widely cited example of immunogenicity related to the use of biologicals was the occurrence of anti-epoetin antibody induced Pure Red Cell Aplasia (PRCA) in patients with chronic kidney disease. An increase in the incidence of PRCA was observed in patients after they changed to a new version of an

originator epoetin-alfa product (Eprex®) that had undergone reformulation [30]. Although this example is often used to underpin arguments against switching, it is better suited to highlight how product quality contributes to the immunogenicity of a medicine and how in very rare cases manufacturing process changes can adversely alter immunogenicity profile. Such risks are inherent to all biological medicines and not just biosimilars.

Regulatory opinion in Europe is that undesirable immunogenicity is unlikely to be triggered by a switch to a biosimilar unless the biosimilar is of inferior quality (i.e. not truly comparable) to the reference [42]. This is unlikely to be the case in highly regulated regions such as Europe, as (i) the biosimilar is highly similar to the reference medicine in terms of physicochemical characteristics and biological function, (ii) an immunogenicity testing programme compares the incidence, persistence, titre and neutralising capacity of reference and biosimilar anti-drug antibodies, (iii) the biosimilar and reference medicine have an identical primary amino acid sequence and so share the same linear T-cell epitopes (strong immune responses would require a new T-cell epitope), (iv) potentially immunogenic impurities and aggregates are tightly controlled at release and (v) information on the immunogenicity of the reference medicine is already available, thus enabling biosimilar manufacturers to address immunogenicity risks in their pharmacovigilance activities [42, 43].

Numerous biosimilar 'switching studies' have been conducted [33, 42, 44-46]. Indeed, pre-authorisation clinical trials for biosimilars often incorporate a single switch from the reference to the biosimilar. Although switching studies are not a regulatory requirement in the Europe, European Public Assessment Reports, which are available on the EMA website, include switching data for biosimilars of somatropin, epoetin alfa, filgrastim, insulin glargine, adalimumab, etanercept and rituximab [47]. A recent review identified 90 studies on switching between reference and biosimilar products conducted prior to 30 June 2017. Randomised clinical trials and observational studies of varying size and timeframe enrolled 14,225 individuals and covered 7 biological substances across 14 disease indications. The authors concluded that the vast majority of studies did not report any differences in safety, efficacy or immunogenicity after switching from a reference product to its biosimilar [45].

The majority of switching studies have been carried out with an infliximab biosimilar CT-P13, which was the first biosimilar monoclonal antibody to be approved in Europe (2013) and the US (2016) [48, 49]. The clinical trial data, submitted as part of the licence approval, included open label single extension studies which demonstrated that switching from the reference (Remicade®) to the biosimilar had no impact on safety and efficacy in patients with rheumatoid arthritis or ankylosing spondylitis compared to those on maintained treatment with the reference [50, 51]. The first published randomised blinded infliximab switching study (NOR-SWITCH) showed that switching patients from reference infliximab (Remicade®) to the biosimilar was not inferior compared to continued treatment with reference infliximab (pre-specified non-inferiority margin of 15%). The study covered all licensed indications of the reference and biosimilar products, but was not powered to show non-inferiority in individual diseases [52].

Most switching studies conducted to date address a single switch from reference to biosimilar. However, 3 recent publications highlight clinical trial designs which have incorporated multiple or 'back and forth' switching, whereby patients who have undergone a sequence of treatment switches between the biosimilar and reference are compared to patients whose treatment remains unchanged. Alternating filgrastim biosimilar and reference product in breast cancer patients every treatment cycle for six cycles did not reveal any clinically meaningful differences compared to continued treatment with the reference product [53]. In the EGALITY study, patients with moderate to severe chronic plaque-type psoriasis underwent a sequence of three treatment switches between reference etanercept and its biosimilar, and equivalent efficacy and comparable safety and immunogenicity were demonstrated between the switching and non-switching arms [54]. A recent study found that there was no detectable impact on efficacy, safety or immunogenicity when patients with moderate to severe plaque psoriasis were switched between reference adalimumab and its biosimilar up to four times [55].

It is clear that evidence to support interchangeability is increasing, however, the demonstration of interchangeability is associated with major scientific and practical challenges. There are calls for switching studies to include designs that incorporate multiple switches between the biosimilar and reference products [39, 40, 56]. Although this would provide reassurance to healthcare professionals, there are several limitations with this approach. Switching studies

incorporating multiple switches are likely to add to costs associated with the development of biosimilar medicines. In addition, the availability of switching data between reference and biosimilar will not necessarily inform decisions related to switching between different biosimilars of the same reference (Fig 2). As increasing numbers of biosimilar medicines become available it will be difficult to design switching studies that will address all possible clinical scenarios that may occur. Healthcare professional expectations for routine switching studies seem unnecessary as the growing body of evidence on switching, coupled with stringent regulatory requirement for biosimilars provides assurance that the practice of switching does not negatively impact the safety and efficacy of a patient's treatment. It should also be borne in mind that there is currently a scarcity of studies supporting switching patients between different originator biological medicines for treatment of the same indication [43]. This is despite the fact that switching is sometimes recommended or is an established medical practice [57-60].

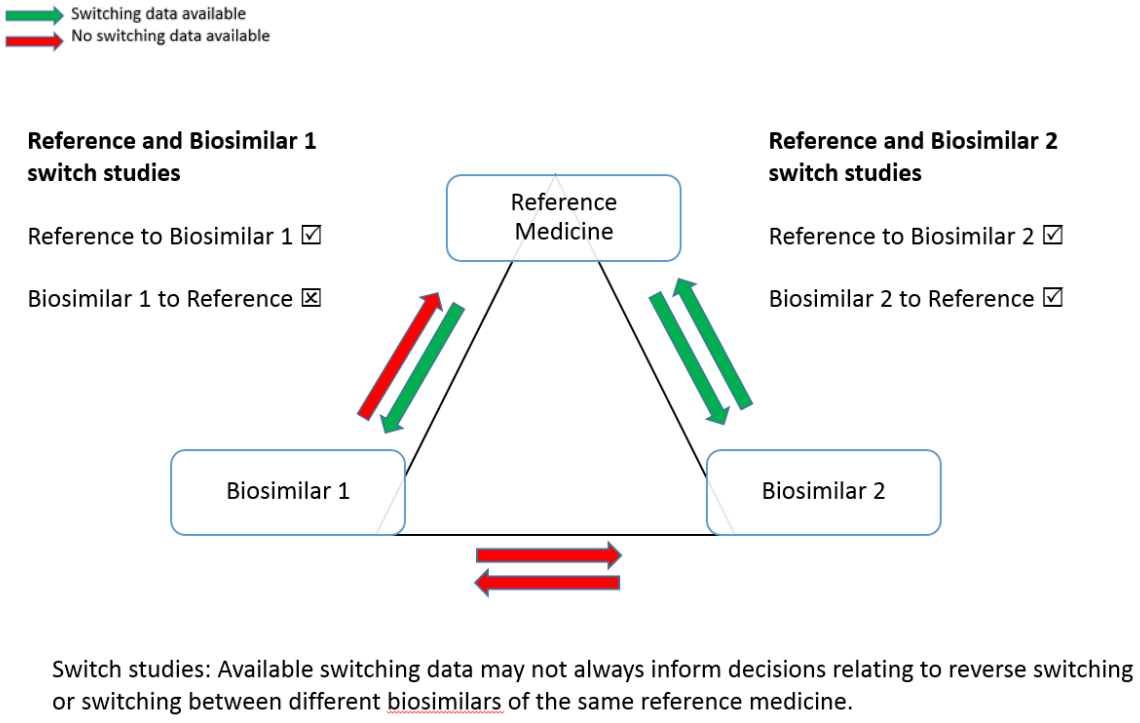

Figure 2: Available switching data may not always inform decisions relating to switching from biosimilar to reference (reverse switching) or switching between different biosimilars of the same reference medicine

United States v's Europe

In the US it is intended that the FDA will conduct regulatory evaluation of interchangeability. It is also the case that, 'interchangeability' is synonymous with pharmacist-led substitution. US legislation permits pharmacists to substitute reference medicines with biosimilars that have been approved as 'interchangeable products' and substitution may occur on multiple occasions. According to draft FDA guidance, the demonstration of interchangeability should be supported by at least one switching study which assesses the impact of at least three switches on clinical PK, PD (if available), safety and immunogenicity in a switching arm verses a non-switching reference arm. Post-marketing data may also be required and in the case of products that are administered by patients or carers, any differences in devices should not impact the user's ability to administer the product [37]. The biosimilar market in the US is relatively new and to date no interchangeable products have been approved. The difference in regulatory requirements for interchangeability between Europe and the US reflect the fact that in Europe pharmacist-led biosimilar substitution is currently not general practice [61]. Furthermore, although EMA grants marketing authorisations for biosimilars, it does not make decisions on interchangeability. Instead the decision has to be made at the individual member state level due to the different national health systems and associated national or regional budgets. Therefore, decisions to switch are made by physicians or are policy driven at a local level.

Biosimilar switching in practice

Biosimilars differ from generic medicines, so specific considerations for their interchangeable use exist. Appropriate clinical monitoring and surveillance should be maintained after any switch. Traceability to brand level is imperative so that any ADRs can be attributed to the correct medicine. In the case of medicines intended for administration by patients or carers, necessary training on devices will be required. The 'nocebo effect', (the negative equivalent of the placebo effect), must also be addressed in light of the fact that switching is generally carried out for cost saving reasons. Negative treatment expectations are known to reduce a medicine's effectiveness or increase side effects experienced by patients [62, 63]. In the case of generic medicines, negative viewpoints held by healthcare professionals can impact on a patient's own viewpoint [63]. Such an effect is also likely to apply to the use of biosimilars. A recent study found that 12.5% of rheumatology patients (n=125) who had undergone an

infliximab switch experienced a nocebo effect [64]. Unexplained high dropout rates observed among patients in several switching studies have also been attributed to the nocebo effect [65-67]. Therefore, healthcare professionals must be informed and confident about the use of biosimilars and be in a position to address patient queries. Healthcare professional provision of clear information and avoidance of unintended negative suggestions is likely to inspire confidence in patients and may help alleviate the nocebo effect [62]. Successful switching programmes in the past have recognised the importance of education and patient involvement [68]. Appropriate patient information materials [69, 70] and practical guidance on how best to introduce biosimilars into healthcare practice should also be utilised [71].

4.0 International policies

Market penetration of biosimilars throughout Europe is variable. For example, in 2016, the share of biosimilar anti-tumour necrosis factor (anti-TNF) inhibitors verses their reference products varied from 5% (Ireland, Belgium) to 90% (Denmark) [3]. Efforts are being made globally in order to improve uptake of biosimilars. Some countries have implemented biosimilar policies, many of which address their interchangeable use. Policies involving the use of (i) tendering, (ii) healthcare professional incentives and (iii) substitution are summarised in Table 2.

Table 2: Example of policies being used to promote the use of biosimilar medicines

Policy	Types	Examples	Ref
Tendering	Hospital, regional or national tenders	Norway and Denmark have tendering systems that are implemented nationally	[72, 73]
Healthcare professional incentives	Prescription quotas	Quotas in place in Germany, Hungary, Italy and Sweden	[74-78]
	Gain-share agreements	Savings from the use of biosimilar medicines are reinvested at a local level	[68, 79]
	Guidance	Positive guidance from medical societies and practical advice on implementation of biosimilars	[71, 80, 81]
Pharmacist led substitution	Treatment initiation only	Legislation passed in France, not yet implemented	[61, 74]
	Payer decision	PBAC in Australia can recommend biosimilars as brand equivalents allowing pharmacists to substitute the biosimilar with its reference and with other biosimilars	[82]
	Regulatory decision	In the United States an interchangeable biological product can be substituted for its reference medicine by a pharmacist	[36]

PBAC; Pharmaceutical Benefits Advisory Committee

Tendering

National tendering processes for biologicals have helped to generate significant savings. In Norway, the Norwegian Drug Procurement Cooperation (LIS) negotiates prices with pharmaceutical companies, enabling LIS to produce a list of recommendations which are implemented in hospitals. Biosimilar infliximab entered the annual tendering process for anti-anti-TNF inhibitors in 2014 [72]. This resulted in a discount of 39% compared to the reference in 2014, increasing to 69% in 2015 [52]. The Norwegian government actively supports biosimilar adoption and sponsored the NOR-SWITCH study in order to confirm the safety of switching from the reference to biosimilar infliximab [52].

The Danish Council for the Use of Expensive Hospital Medicines (RADS) organises tendering and issues recommendations on high cost medicines which are implemented in Danish hospitals. In April 2015 the biosimilar infliximab, Remsima® won the tendering process and was supplied to all Danish hospitals. The biosimilar was given to all patients commencing and already receiving infliximab therapy. By early 2016 the biosimilar had acquired 97% market share [73]. A similar situation occurred with the etanercept biosimilar Benepali® [83]. A Danish 'action plan' on biologicals has been implemented This plan includes more stringent requirements relating to the traceability of biologicals and the development of information materials [73].

Healthcare professional incentives

Prescriber incentives have been used to promote biosimilar uptake [74, 75]. In Germany, the implementation of prescription quotas has resulted in high uptake of epoetin biosimilars with 67% of total sales in 2014/2015 being attributable to biosimilar products [76, 77]. Quotas have since been implemented for infliximab and etanercept biosimilars [78]. Quotas are complemented by information campaigns and local guidelines [76, 78]. Biosimilar prescription quotas are also in place in Hungary, Italy and Sweden [74].

Gain-share agreements enable healthcare professionals and patients to benefit directly from savings achieved through the use of biosimilar medicines. In the United Kingdom, an

agreement negotiated with a local clinical commissioning group, enabled a gastroenterology team in a Southampton hospital, to directly reinvest some of the savings achieved from adoption of biosimilar infliximab, back into their clinical practice [68]. In a Swedish hospital, paediatric patients were switched from reference to biosimilar somatropin and resultant savings were reinvested in the hospital clinic [79]. Positive guidance from medical societies and pharmacist organisations [71, 80, 81] may also result in healthcare professionals becoming more open to the use of biosimilars in their practice.

Substitution

Although biosimilar substitution is generally not practised in Europe there are some exceptions including France and Poland [61, 74]. In France, legislation which has been introduced but not yet implemented, allows substitution on treatment initiation. The prescriber may veto this on the patient's prescription by indicating that substitution is not allowed. Products eligible for substitution must be included on a list drawn up by the French Regulatory Agency [61]. In Poland, there are no specific regulations against biosimilar substitution so substitution does occur in practice [74]. Substitution policies have also been established in the United States and Australia.

In the United States, a pharmacist may substitute an 'interchangeable product' for its reference medicine without prescriber involvement. The first interchangeable product of each active substance will benefit from a year of market exclusivity. This exclusivity only applies against other interchangeable products, therefore, the manufacturer must still compete against non-interchangeable biosimilars of the same reference medicine. Rules governing substitution of interchangeable products are passed at individual State level. Once interchangeable products become available, prescribers will generally have the discretion to prevent substitution (e.g. by stating 'dispense as written' on the prescription) and pharmacists will be obliged to notify the prescriber of the identity of the dispensed biological after an allowable substitution has been made. The time permitted for notification varies by State. In the majority of States patients must be informed that a substitution has been made although in a small number of States patient consent will be necessary[36].

The Australian government is engaged in a drive to increase the use of biosimilar medicines [84]. Substitution of certain biological medicines is possible. The Pharmaceutical Benefits Advisory Committee (PBAC), whose primary role is to recommend medicines for government subsidy [85], can endorse medicines as brand equivalents. Brand equivalents may be substituted by a pharmacist at the point of dispensing [82, 86], however certain caveats apply. Prescribers, pharmacists and patients are all involved in the final decision on which medicine the patient receives. Prescribers may indicate on the prescription form that brand substitution is not permitted [87]. Pharmacists too can use their discretion in choosing which medicine is to be dispensed. The Australian Pharmaceutical Society advise that pharmacists 'endeavour to be consistent' in brand selection for patients on long term therapy [82]. Finally, the patient must agree on any decision to substitute. Patients wishing to remain on the reference brand do not have to pay additional fees [87]. Details of reference and biosimilar medicines which may be substituted in Australia (August 2018) are provided in Table S3 (supplementary material). .

Need for policy

Robust regulatory frameworks for biosimilar medicines have ensured that lower costs can be achieved without compromising quality, safety and efficacy. However, regulatory approval pathways for biosimilars in themselves do not guarantee access to biosimilar medicines. Rather, biosimilars are generally adopted following establishment of local policies concerning their use. Policies which clearly address the interchangeable use of biosimilars are required so that maximum cost savings can be achieved. Some countries have remained passive on biosimilar policy to date. For instance, lack of national guidance and incentives to switch may be a reason why a survey of medical specialists in Ireland found that more were likely to prescribe a biosimilar on treatment initiation rather than switch to a biosimilar once treatment had been initiated with the originator [18]. Current attitudes and prescribing practices relating to biosimilars might reflect earlier attitudes and behaviours relating to generic medicines. Ireland, for example has implemented policies and information campaigns on generic medicines, with the result that healthcare professionals in Ireland now view generic medicines more favourably than they did previously [88-91]. Implementation of specific policies on biosimilars are necessary to drive biosimilar uptake and maximise healthcare savings.

5.0 Conclusions

The advent of biosimilar medicines has resulted in price competition with a resultant decrease in the cost of some expensive biological therapies. Lack of familiarity with biosimilars and unease with the concept of indication extrapolation are being addressed through the peer-reviewed literature [13, 15, 92], provision of information materials [35, 93] and regulatory discussions with medical societies [94]. As such, the debate on biosimilars has moved on to the practice of interchangeability and the policies which are in place to promote this practice.

The EMA does not make recommendations on interchangeability. Rather, the concept of interchangeability is ensured by the 'state-of-the-art' demonstration of biosimilarity, together with intensified post-market surveillance [42]. In the United States, the term 'interchangeable' is a legal term synonymous with pharmacy-led substitution of a biosimilar and its reference product. Evidence from switching studies does not suggest that switching from a reference to biosimilar will adversely affect safety and efficacy. Concerns about interchangeability remain theoretical and the scientific rationale behind these concerns remains unclear. Switching studies are unlikely to address questions such as whether it is safe to switch from one biosimilar to another. There are no regulatory requirements in Europe to carry out switching studies as part of the biosimilar approval process. Nonetheless, there is an expectation from some prescribers that switching studies are necessary before moving a patient from the reference product to the biosimilar. However, having a requirement for switching studies which would cover all scenarios seen in clinical practice may very well negate cost savings associated with the development of biosimilar medicines and may even discourage entrants to the biosimilar market. Moreover, in countries where the biosimilar becomes the market leader, there may be an absence of switching studies to support switching from the biosimilar back to the reference or switching from the market leading biosimilar to the next biosimilar. Having a requirement for switching studies may mean that the first biosimilar could become dominant in the market for a considerable period of time, thereby reducing competition and ultimately cost savings.

Switching should be carried out in a controlled manner with due regard to continued monitoring, traceability, patient engagement and training on administration devices. In this sense, it is imperative that interchangeability of biosimilars is embraced by healthcare

professionals. The alternative scenario (maintaining patients on their original prescription and prescribing biosimilars on treatment initiation only) could become logistically impractical especially as more biosimilars of the same reference medicine become available over time. Healthcare professionals and policy makers must weigh their uncertainty around interchangeability against the benefits of increased access to medicines for patients in a market that has full competition for biosimilars. The benefit/risk must be viewed not only on the individual patient basis but on the basis of society as a whole. Healthcare savings arising from biosimilar competition must be weighed against the unsubstantiated theoretical risk that an individual patient will experience reduced efficacy or immunogenicity following a switch. While healthcare costs have been steadily rising for decades, the recent advent of personalised medicines may represent a paradigm shift in healthcare spending, as patients demand greater access to these revolutionary but costly treatments. In order to afford these new medications in an era of limited healthcare funding, cost savings must be gleaned from other areas of the healthcare system. The embracing of biosimilar interchangeability, supported by robust scientific evidence, should be a key part of this discussion.

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