

What is the Role of HTA for Biosimilars?

Jorge Mestre-Ferrandiz and Adrian Towse,
Office of Health Economics

This Briefing contains a summary of the main points and conclusions from a roundtable organised and facilitated by the Office of Health Economics, together with a summary of the briefing material provided to the participants. The Roundtable was funded by an unrestricted research grant from Amgen. The views reproduced here are the authors' synthesis of the discussions at the Roundtable (in which they participated). Accordingly, the arguments and views presented in the text, unless stated otherwise, cannot be attributed to any one of the Roundtable participants or to them all collectively. Any recommendations offered by the authors are their own and do not represent the views of the Roundtable participants. The authors are grateful for the comments received by Virginia Acha, Martin Buxton, Emir Cevro, Julia Earnshaw and Arran Shearer on earlier drafts. A first draft of this Briefing was shared with the participants of the Roundtable, who had the opportunity to comment on it. Their feedback was then incorporated in the final version. All errors and omissions remain the responsibility of the two authors.

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Abbreviations

ABPI	Association of the British Pharmaceutical Industry
AWMSG	All Wales Medicines Strategy Group
CMA	cost minimisation analysis
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPO	erythropoietin
FDA	Food and Drug Administration
GCSF	granulocyte-colony-stimulating-factor
HGH	human growth hormones
HTA	health technology assessment
INN	International Nonproprietary Name
MAbs	monoclonal antibodies
MHRA	Medicines and Healthcare products Regulatory Agency
MTA	multiple technology appraisal
NICE	National Institute for Health and Care Excellence
OHE	Office of Health Economics
RMP	risk management plan
SMC	Scottish Medicines Consortium
SmPC	summary of medicinal product characteristics
STA	single technology appraisal
TA	technology appraisal
TNF	tumour necrosis factor

Executive Summary

Introduction

- Biotherapeutic medicines are medicines whose active ingredients are or are derived from proteins (such as growth hormone, insulin, antibodies) and other substances produced by living organisms (such as cells, viruses and bacteria). They are larger and more complex than chemically-synthesised medicines. Examples of biotherapeutic medicines include the blood-production stimulating protein erythropoietin (EPO), the growth-stimulating hormone, biosynthetic human insulin and its analogues and monoclonal antibodies (MAbs). There has been a rapid worldwide increase in the number of biological medicines that have received regulatory approval.
- Biosimilar is the term used to refer to a biological medicine that is developed to be similar to an existing off-patent innovative biological medicine (the “reference product”). A number of biosimilars have already been approved in Europe – in the area of EPOs, Granulocyte-Colony-Stimulating-Factor (GCSFs) and growth hormones, and more recently the first two MAbs biosimilars of infliximab. A number of important, top-selling biological medicines have lost, or will be losing patent protection over the next five years.

Objectives of this work

- The Association of the British Pharmaceutical Industry (ABPI) published a position paper in 2013 on biosimilar medicines including seven recommendations covering areas where it believes action is needed by regulators, HTA agencies, NHS commissioners and NHS healthcare professionals who prescribe or dispense originator biologics and biosimilar medicines. Recommendations 1, 2, 3 and 4 of the ABPI position paper are, respectively:
 1. “All biologic / biosimilar prescriptions should be written by brand name and not by International Nonproprietary Name (INN)”;
 2. “A biologic or biosimilar must only be substituted with the knowledge and consent of the treating physician”;
 3. “Patients should be kept fully informed about their medication and should be consulted if any changes to their treatment are made”; and
 4. “The summary of medicinal product characteristics (SmPC) should clearly indicate the source of information contained within it, such as relevant clinical studies or that it has been derived from evidence about the originator product”.

- Recommendation 5, which is the most important for the purposes of this Briefing, states that:
 5. “Biosimilar medicines should be subject to Health Technology Assessment (HTA) processes in the UK”.
- Amgen provided the Office of Health Economics (OHE) with an unrestricted research grant to explore the appropriateness of Recommendation 5, in particular, what HTA processes are required to allow an appropriate assessment of value to be made whilst meeting regulatory and safety requirements.

Methodology

- We have undertaken two main tasks. First, we conducted a literature review to explore what has been written about biosimilars generally in terms of regulatory processes and their drivers of competition and specifically about biosimilars and HTA. Second, we held a Roundtable (on 25th February 2013) with ten stakeholders (representatives from MHRA, NICE, SMC, AWMSG and ABPI, with the addition of several academics with expertise in the area) to discuss the appropriate use of HTA for biosimilars in the UK.
- Our approach was as follows. First, we prepared a short background note (based on the literature review) that was shared with all attendees in advance of the Roundtable. This note contained six key questions that were used to frame the debate during the Roundtable. Second, we held the Roundtable, chaired by one of the authors, Adrian Towse. Third, we prepared a first draft of this Briefing, which was sent for comments and review to all attendees. Fourth, we revised the draft accordingly based on the feedback received, and the final outcome is this OHE Briefing.
- This OHE Briefing presents the results of combining the literature review and the Roundtable.

Current use of HTA for biosimilars in the UK

- The Scottish Medicines Consortium (SMC) has a policy position on biosimilars (published in 2010 and will be revisited in 2015). It requires a full submission for all new biosimilar medicines that details a comparison with the biological reference product. The SMC does not state a preference for the type of economic analysis. The SMC has to date reviewed eight biosimilars: four filgrastims, three EPOs and one growth hormone, seven of them after full submissions. All of the economic cases have been cost minimisation analysis. All seven were accepted for use. Thus, it seems that cost minimisation analysis has been more than sufficient to demonstrate the economic value of biosimilars in Scotland. In a number of

occasions the SMC has stated that showing clinical equivalence has been key to accept cost minimisation analysis as the method of analysis.

- The All Wales Medicines Strategy Group (AWMSG) appraises biosimilar products in terms of clinical and cost-effectiveness and they fall within the AWMSG criteria for appraisal and require a full HTA submission. The AWMSG states that cost-minimisation analyses are appropriate for biosimilars only when the reference product has been recommended by NICE or AWMSG for the intended indication; or when the reference product is already in widespread use for the indication (evidence of this would be required). When the reference product has not been recommended by NICE/AWMSG for the intended indication, or if the reference product is not in widespread use, a cost-utility analysis is required, comparing the biosimilar against some other relevant comparator, using clinical data relating to the reference product, if necessary. The AWMSG has, to date, appraised seven biosimilars under a full submission: four filgrastims and three EPOs (although the EPO decisions, including for the reference product Eprex, have now been superseded by subsequent NICE's guidance). Out of the seven decisions, four were positive recommendations, one implied a restricted use and two were rejected. The economic analysis provided was cost minimisation, cost savings or budget impact (versus the reference product).
- NICE does not have a separate policy for biosimilars – although at the time of sending the manuscript for publication, it had just announced its HTA position paper on biosimilars for targeted consultation with key stakeholders (deadline for response is 17 April 2014). To date NICE has appraised one biosimilar in one multiple technology appraisal (for growth hormones) but it was not treated differently to the other products included.

Key issues to consider moving forwards with HTA for biosimilars

- Our Roundtable was structured around six questions. The questions discussed, and the summary of the discussions, were as follows:

Q1. On what basis, if any, should biosimilars continue to be subject to HTA in the UK (in contrast to chemical generics)?

Three issues determine the answer to this first question; whether: (1) Is the effectiveness evidence for the biosimilar as compared to the reference product likely to be different to the pre-launch efficacy evidence? (2) Has the reference product been appraised? and (3) Is the reference product the standard of care?

First, most of the attendees agreed that the logic for an HTA body to consider reviewing a biosimilar would be whether an efficacy/effectiveness gap might emerge post launch i.e. whether or not the biosimilar will treat patients in the same way as the reference product. It would need to be clear what particular circumstances might give rise to this gap, because it is not obvious that there would

be an efficacy/effectiveness issue. Safety issues should be taken into account by the regulator in assessing similarity.

If we expect no differences for the biosimilar as compared to the reference product, then the case for an HTA assessment is reduced. We do, however, need to consider whether the reference product has been appraised and/or is it the standard of care? When the reference product has either not been recommended by the HTA agency, or has received a restricted recommendation – and thus, the reference product would not necessarily be part of the standard of care - the case for biosimilars being subject to HTA was stronger. If the originator had not fully satisfied the HTA body in respect of its effectiveness and/ or cost-effectiveness, the comparator for the HTA assessment should then be the standard of care, not the reference product.

Q2. On what basis should NICE assess biosimilars, for example, under STAs or MTAs or both? Are there any important considerations for NICE if biosimilars are a comparator technology?

There might be a need to do something different if the biosimilar is not introduced in isolation but in the context of other developments within that therapeutic area, including whether there are different presentations available, and what else is needed for the management of a condition – which is more relevant for MTAs and guidelines. Thus, under these circumstances MTAs could be more relevant than STAs for biosimilars.

Q3. In certain circumstances the SMC and AWMSG currently accept cost-minimisation for considering biosimilars. NICE's reference case requires cost-utility analysis. If biosimilars have shown same efficacy as the reference product in the full indication under appraisal, should they be subject to cost-minimisation analysis, or should they always be subject to cost-utility analysis?

First, if there was an efficacy/effectiveness issue (i.e. the biosimilar will not treat patients in the same way as the reference product) then that logically would require cost-utility analysis. The issue, as highlighted above, is what would be the circumstances in which that might arise, given that the regulator will have approved the biosimilar as similar to the reference product, and no more evidence was likely to be available to the HTA body than to the regulator (see below)? Second, if the reference product had been rejected or restricted earlier by the HTA body, or it is not the standard of care, then that would require again a cost-utility analysis for the biosimilar. The comparator, in this case, will not be the reference product.

If the HTA body does decide to review a product in which no differences in effectiveness are expected with the reference product and the reference product has been reviewed and is the standard of care, then a cost minimisation analysis would be sufficient.

Q4. How do we address long term outcomes (i.e. certainties/uncertainties) when trials for biosimilars generate only short-term safety and efficacy results, often in relatively small studies? Would this be enough to meet HTA agencies' evidence standards?

If HTA bodies were satisfied with the evidence from the reference product, and the biosimilar produces similar evidence (in terms of the short-long term relationship), the HTA body should be satisfied with the biosimilars' evidence. But if the evidence for the originator did not satisfy the HTA body then the biosimilar should be treated with the same degree of scepticism.

Q5. How should naming, safety and pharmacovigilance requirements of biosimilars be integrated within the HTA decision making process and subsequent guidance? What safeguards could be put in place to ensure that recommendations and guidance do not inhibit or conflict with these requirements (e.g. is guidance that "the medicine with the lowest acquisition cost should be used" consistent with the need for safeguards)?

The majority view expressed at the Roundtable was that it is important to be explicit about the regulatory advice which recommends prescription by brand, and thus no substitution without the agreement of the clinician (in the UK generic substitution is in any case not permitted). Prescribing by brand is particularly important to enable products to be traced in the event of a safety issue. A recommendation to prescribe the medicine at its lowest acquisition cost should not therefore override the need to prescribe by brand name or the requirement for the clinician and patient to consent to any substitution.

Q6. The EMA only allows extrapolation of indication if the totality of evidence justifies the determination; when should it be permissible for HTA bodies to extrapolate efficacy data from one clinical condition specifically studied to another clinical condition not studied for the biosimilar product?

Given this extrapolation into a number of therapeutic indications, the availability of data on which to do a technology assessment could be problematic. This might be especially relevant for future biosimilars (for example MABs which often have more than one indication); if the research that is conducted on a biosimilar is for one indication, the ability to do an HTA on a different indication will be limited.

Conclusions

- In terms of HTA, the majority view wanted flexibility in the choice of processes and methods to consider whether or not to assess biosimilars from a health economics perspective. Nevertheless, it will be important that, if biosimilars are treated on a case by case basis, the selection process is transparent and based on clear, consistent, criteria. The NICE topic selection process could facilitate this, and NICE has alternatives to HTA, such as Evidence Summaries and clinical guidelines. It is less clear how this would be achieved for the SMC and AWMSG, as they currently review all medicines (barring generics), although they do have different categories of submission. The majority view supported that any recommendations resulting from HTAs should be cognisant of regulatory and safety recommendations from the EMA and MHRA (such as prescribing by brand name and no automatic substitution).

- The majority of the views expressed at the Roundtable supported the first three ABPI recommendations. In terms of Recommendation 4, the regulatory view is divergent from the ABPI view. The regulator argues that the summary of medicinal product characteristics for the biosimilar should be the same as the originator's (with some exceptions); the ABPI's argues that it should be explicit if the information was obtained from either studies investigating the biosimilar product or data derived from evidence about the originator product.
- In terms of Recommendation 5, the majority of the views expressed at the Roundtable thought it would be useful to have the option for biosimilars to be subject to HTA processes but not necessarily to always conduct an assessment. Three issues would determine whether or not to conduct the assessment: (1) Will the effectiveness evidence for the biosimilar, as compared to the reference product, likely to be different to the pre-launch efficacy evidence? (2) Has the reference product been appraised? and (3) Is the reference product the standard of care? If we expect no differences for the biosimilar as compared to the reference product, and the reference product is the standard of care, an HTA process should not be needed for biosimilars at launch.
- An HTA assessment should focus on value, either through a cost-minimisation analysis or a cost-utility analysis. When products are assumed comparable, and the reference product is already the standard of care, then cost-minimisation analysis is relevant, if the HTA body wants to conduct an assessment. When the reference product is not the standard of care, either because it was originally rejected or restricted, then cost-utility analysis is more appropriate; and the comparator for the HTA should be the different standard of care and not the reference product.
- When a biosimilar of a first generation reference product is being compared to a second generation product – potentially with different methods of administration – cost-utility analysis will be more appropriate, as the biosimilar has not been shown to be comparable (or similar) to the second generation product.

1. Objectives of this Paper

The Association of the British Pharmaceutical Industry (ABPI) published a position paper on biosimilar medicines (ABPI, 2013) including seven recommendations covering areas where it believes action is needed by regulators, HTA agencies, NHS commissioners and NHS healthcare professionals who prescribe or dispense originator biologics and biosimilar medicines.

Recommendations 1, 2, 3 and 4 of the ABPI position paper are, respectively:

1. "All biologic / biosimilar prescriptions should be written by brand name and not by International Nonproprietary Name (INN)";

2. "A biologic or biosimilar must only be substituted with the knowledge and consent of the treating physician;
3. "Patients should be kept fully informed about their medication and should be consulted if any changes to their treatment are made"; and
4. "The summary of medicinal product characteristics (SmPC) should clearly indicate the source of information contained within it, such as relevant clinical studies or that it has been derived from evidence about the originator product".

Recommendation 5, which is the most important for the purposes of this Briefing, states that:

5. "Biosimilar medicines should be subject to Health Technology Assessment (HTA) processes in the UK".

Under Recommendation 5, the accompanying paragraphs state that: "Biosimilar products should be subject to health technology assessment in order that they can be assessed for clinical and cost effectiveness using the appropriate evidence base. It should be stated clearly in the main section of resultant HTA guidance that is issued that the medicine appraised is a biosimilar.

Biosimilar products should be recorded on UK PharmaScan by companies as soon as they enter Phase III clinical trials or within three years of their expected launch date so they can be reported upon by the NHS horizon scanning agencies for HTA topic selection purposes.

The Scottish Medicines Consortium (SMC) and All Wales Medicine Strategy Group (AWMSG) (where appropriate) should routinely appraise biosimilar medicines and the NICE topic selection process should be used to identify those biosimilars which should be subject to NICE appraisal" (ABPI, 2013, page 5).

Amgen provided the Office of Health Economics (OHE) with an unrestricted research grant to explore the appropriateness of Recommendation 5, in particular, what HTA processes are required to allow an appropriate assessment of value to be made whilst meeting regulatory and safety requirements (as stated in Recommendation 1-4 above).

We have undertaken two main tasks. First, we conducted a literature review. The objective of this review was twofold, to review what had been written about: (1) biosimilars – both in terms of regulatory processes and their drivers of competition; (2) biosimilars and HTA. Appendix 1 contains the details of our approach and the papers identified and reviewed.

Second, we held a Roundtable (on 25th February 2013) with ten stakeholders to discuss the appropriate use of HTA for biosimilars in the UK. There were representatives from MHRA, NICE, SMC, AWMSG and ABPI, with the addition of several academics with expertise in the area. Our approach was as follows. First, we prepared a short background note that was shared with all attendees in advance of the Roundtable. This note was based on the literature review (albeit shorter than all the

material presented in this Briefing). The note finished with six key questions that were used to frame the debate during the Roundtable. Second, we held the Roundtable, chaired by one of the authors, Adrian Towse. A transcriber was used to record the discussion. Third, we prepared a first draft of this Briefing, which was sent for comments and review to all attendees (plus two members of OHE's Editorial Board). Fourth, we revised the draft accordingly based on the feedback received, and the final outcome is this OHE Briefing. Appendix 2 lists the Roundtable attendees and the six questions.

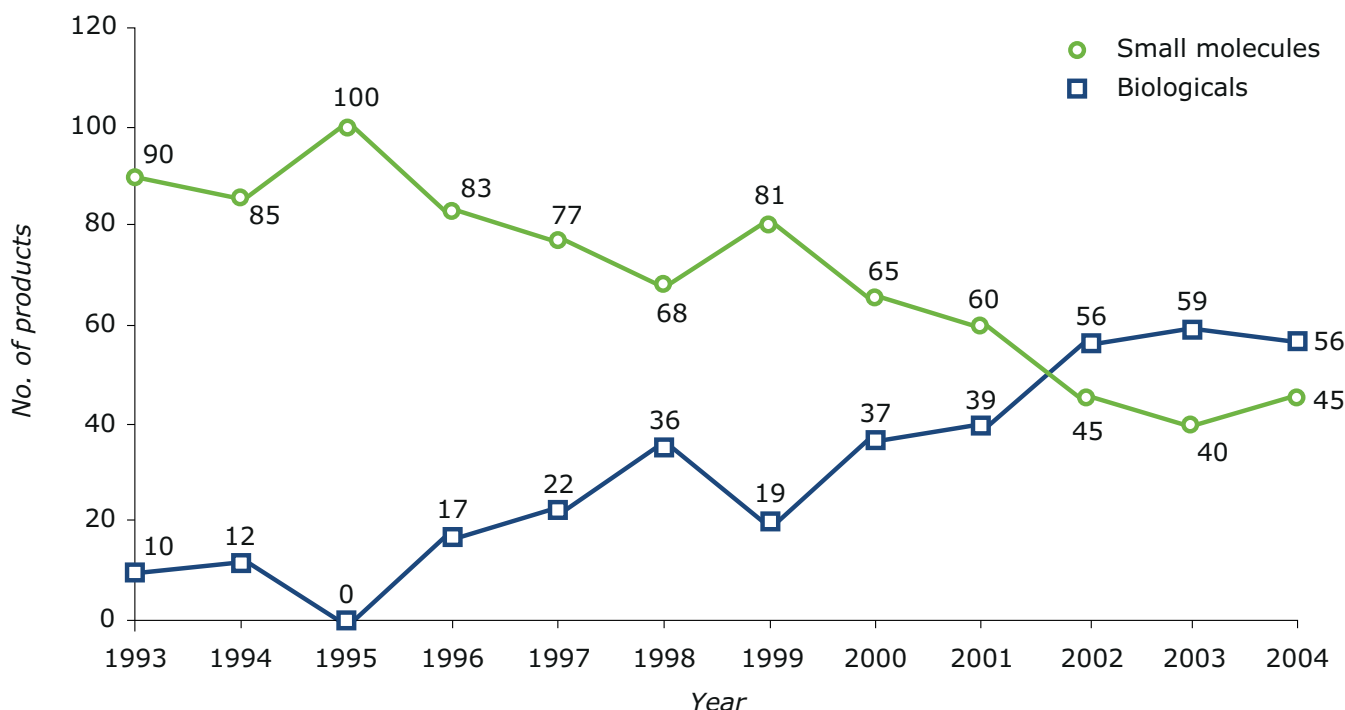
The structure of this Briefing is as follows. We:

- outline the key characteristics of biosimilars, and relevant differences from chemically-processed small molecule generic medicines (Appendix 3 discusses the economics of biosimilars);
- provide an overview of the current processes regarding regulatory and HTA, focusing in Europe for the former (Appendix 4 summarises recent reforms in other geographies), and referencing, where appropriate, the UK's MHRA position on biosimilars, and the UK for the latter;
- summarise the key issues discussed during the Roundtable;
- set out conclusions.

2. Introduction and Context

According to the global pharmaceutical industry trade association "Biotherapeutic medicines are medicines whose active ingredients are or are derived from proteins (such as growth hormone, insulin, antibodies) and other substances produced by living organisms (such as cells, viruses and bacteria). They are larger and more complex than chemically-synthesised medicines and their characteristics and properties are typically dependent on the manufacturing process itself. Biotherapeutic medicines can also be referred to as biologics, biological medicines and biopharmaceuticals" (IFPMA, 2012). Examples of biotherapeutic (or also termed 'biological' in this Briefing) medicines include the blood-production stimulating protein erythropoietin (EPO), the growth-stimulating hormone, biosynthetic human insulin and its analogues and the group of medicines termed monoclonal antibodies (MAbs). Over the past 10 years there has been a rapid worldwide increase in the number of biological medicines that have received regulatory approval – for instance, in the US, from fewer than 15 biological agents in the early 1990s to over 55 by the middle of the last decade, surpassing small molecules (Figure 1).

Figure 1. Products receiving FDA approval



Source: *Dranitsaris et al. (2011)*

Global sales of biologics were \$93bn in 2009, representing 11% of the world pharmaceutical market of \$828bn (IMS, World Executive Review, 2012). Approximately 30% of the pharmaceutical and biotechnology industry R&D pipeline is composed of biologics. By 2016, ten of the global top 20 best-selling drugs will be biologics (McCamish and Woollett, 2011) and sales from biological medicines by 2018 are set to increase to 49% by revenue of the world’s top 100 drugs (Strickland and Raeside, 2012).

In the European Union (EU), granting marketing authorisations (MA) for biological medicines derived from biotechnology processes falls under the authority of the European Medicines Agency (EMA) and the European Commission (EC) under the centralised procedure. However, once authorised through these channels, individual Member States (MS) are responsible, as in the case of chemically-synthesised small molecule medicines, for policies and processes regarding the prescription, delivery, reimbursement and use of biologicals.

Biosimilar is the term used to refer to a biological medicine that is developed to be similar to an existing off-patent innovative biological medicine – the reference product. In Europe, the granting of a MA for a biosimilar, as a biological medicine, is subject to regulatory approval by the EMA and the EU. As stated by the EMA, “A biosimilar medicine is a biological medicine that is developed to be similar to an existing biological medicine (the ‘reference medicine’). Biosimilars are not the same as generics, which have simpler chemical structures and are considered to be identical to their reference medicines” (EMA, 2012a). The standard ‘generic’ approach (that is, demonstration of bioequivalence in comparative bioavailability studies, established for chemical small molecules) is therefore not sufficient for the development, regulatory assessment and licensing of a biosimilar.

The term biogeneric is scientifically incorrect and should not be used for a biosimilar (Weise et al., 2011). IMS (2011) shows that the EU presents the most advanced market for biosimilars, accounting for 80% of global spending on these molecules.

A number of important, top-selling biological medicines have lost, or will be losing patent protection over the next five years – especially tumour necrosis factor (TNF) inhibitors (anti-TNFs) for rheumatoid arthritis (RA), MAbs for oncology and insulins for diabetes. These categories include drugs such as Herceptin, Enbrel, Humalog, MabThera, Remicade and Aranesp (IMS, 2011) significantly increasing the potential biosimilars market. By 2016, approximately \$US64 billion worth of biological therapies globally will be going off patent and be open to biosimilar competition (Dranitsaris et al., 2011). In the US alone, by 2015, sales of biosimilars are expected to total between US\$1.9-2.6 billion, up from US\$378 million for the year to the first half of 2011, going up to US\$11-25 billion by 2020 (IMS, 2011). The wide range for 2020 is due to uncertainty as to how this segment might evolve. Another projection suggests that the global market for biosimilars is expected to reach US\$18 billion by 2017 (GIA, 2012).

In the UK, O'Neill et al. (2013; 2014) have projected sales of biosimilars for 2018 to be around £600m, out of a total projected medicines bill of £17.4bn (representing nearly 3.5% of the total medicines spend).

As of December 2013, the EMA has authorised 18 biosimilars to be marketed under different brand names in four specific therapy areas (EPOs for treating anaemia caused by renal dialysis, GCSFs for lowered white blood cell counts after chemotherapy, human growth hormones (HGH) and treatment of fertility disorders) plus a monoclonal antibody used for a number of diseases. Of the 18, 16 are currently marketed in Europe (five EPOs, seven GCSFs, one growth hormone, one treatment for fertility disorders and two monoclonal antibodies). Two marketed biosimilars (one G-CSF brand and one growth hormone biosimilar) were subsequently withdrawn by the manufacturer for commercial reasons. EMA announced in July 2013 their recommendation to approve the first two monoclonal antibody biosimilars of infliximab (Remicade): Remsima (applicant: Celltrion Healthcare Hungary Kft) and Inflectra (applicant: Hospira UK Limited). Both are recommended for authorisation in the same indications as Remicade, covering a range of autoimmune diseases such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis (EMA, 2013). Remsima and Inflectra subsequently received European Commission (EC) approval on 10 September 2013. Since the pathway was initiated, two biosimilars were rejected (a recombinant human interferon alfa-2a and an interferon beta-1a)¹. Table 1 shows the 18 biosimilars which were approved for MA in the EU (including the two withdrawn) and the biosimilars rejected.

¹ We also understand that there have also been six insulin dossiers submitted and withdrawn pre-authorisation.

Table 1. EU biosimilars and reference product

Medicine Name	Active Substance	Marketing Authorisation Holder	Status	Authorisation date	Reference product
Abseamed	epoetin alfa	Medice Arzneimittel Pütter GmbH & Co. KG	Authorised	28/08/2007	Eprex/Erypo
Binocrit	epoetin alfa	Sandoz GmbH	Authorised	28/08/2007	Eprex/Erypo
Epoetin Alfa Hexal	epoetin alfa	Hexal AG	Authorised	28/08/2007	Eprex/Erypo
Retacrit	epoetin zeta	Hospira UK Limited	Authorised	18/12/2007	Eprex/Erypo
Silapo	epoetin zeta	Stada Arzneimittel AG	Authorised	18/12/2007	Eprex/Erypo
Biograstim	filgrastim	AbZ-Pharma GmbH	Authorised	15/09/2008	Neupogen
Filgrastim ratiopharm	<i>filgrastim</i>	<i>Ratiopharm GmbH</i>	<i>Withdrawn</i>	<i>15/09/2008</i>	<i>Neupogen</i>
Ratiograstim	filgrastim	Ratiopharm GmbH	Authorised	15/09/2008	Neupogen
Tevagrastim	filgrastim	Teva Generics GmbH	Authorised	15/09/2008	Neupogen
Filgrastim Hexal	filgrastim	Hexal AG	Authorised	06/02/2009	Neupogen
Zarzio	filgrastim	Sandoz GmbH	Authorised	06/02/2009	Neupogen
Nivestim	filgrastim	Hospira UK Ltd.	Authorised	08/06/2010	Neupogen
Grastofil	filgrastim	Apotex Europe BV	Authorised	18/10/2013	Neupogen
Ovaleap	follitropin alfa	Teva Pharma B.V.	Authorised	27/09/2013	GONAL-f
Inflectra	infliximab	Hospira UK Limited	Authorised	10/09/2013	Remicade
Remsima	infliximab	Celltrion Healthcare Hungary Kft.	Authorised	10/09/2013	Remicade
Alpheon	<i>recombinant human interferon alfa-2a</i>	<i>BioPartners GmbH</i>	<i>Refused</i>	-	<i>Roferon-A</i>
Biferonex	<i>interferon beta-1a</i>	<i>Biopartners</i>	<i>Refused</i>	-	<i>Avonex</i>
Omnitrope	somatropin	Sandoz GmbH	Authorised	12/04/2006	Genotropin
Valtropin	<i>somatropin</i>	<i>BioPartners GmbH</i>	<i>Withdrawn</i>	<i>24/04/2006</i>	<i>Humatrope</i>

Source: EMA. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac0580281bf0 (accessed 20 December 2013)

Sandoz has dominated the European biosimilars market since 2007, and now has seven Phase III clinical trials across five biosimilar molecules (Sandoz, 2013). Whilst Indian companies, such as Biocon, Dr Reddy, Ranbaxy and Cipla (some of which are generic companies) dominate the Indian market (Grant Thornton, 2013), the EMA has not yet approved any regulatory application for a follow-on biological agent submitted by an Indian manufacturer. Some innovator companies have announced involvement in the biosimilars field, including Amgen (Berkrot, 2013). Biotech and generics firms are partnering to gain access to biosimilar expertise lacking in-house, also involving the most powerful generic companies (Grant Thornton, 2013); Dranitsaris et al., 2011). However, there are also some examples that show that there are still some important uncertainties about the future of biosimilars, related to regulatory issues and profit margins being lower than expected (Dimond, 2013). There are also examples of functionally enhanced biologics, such as pegylated, long-acting formulations, and originators have sought to establish these newer versions as the standard of care.

3. Current Processes

3.1 Regulatory Process - Europe

Our focus is the European market, and for this reason we provide a more detailed description of the EU regulatory process. Appendix 4 briefly outlines recent changes in the regulatory process in other jurisdictions.

The first guidelines for the EMA's pathway for approving biosimilars were published in 2005. The evaluation is a comparison of the biosimilar with its reference medicine and is intended to show that there are no clinically significant differences between them. Stringent criteria are applied to the evaluation of studies comparing the quality, safety and efficacy of the two medicines. The studies on quality include comprehensive comparisons of the structure and biological activity of their active substances, while the studies on safety and efficacy are intended to establish that there are no significant differences in their clinical efficacy and safety compared to the reference product, including the risk of immune reactions. In addition to general guidance for biosimilars the EMA has issued a number of product specific guidelines (for EPOs, somatropin, GCSF, recombinant human insulin, low-molecular weight- heparins, recombinant interferon alpha and monoclonal antibodies)². The most critical safety concern relating to biological medicines (including biosimilars) is immunogenicity (i.e. the ability of a substance to trigger an immune response in the patient).

The EMA states that "in case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. In certain cases it

²For more information on EMA documents, please refer to: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c. The product-specific guideline for MAbs has been in force since December 2012.

may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product. Justification will depend on e.g., clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications” (EMA, 2006, page 3)³.

Assessing Comparability

An extensive comparability exercise is required in order to demonstrate that the applicant biosimilar medicine and reference product have similar profiles in quality, safety and efficacy. The comparability exercise is typically performed through a “stepwise procedure” that begins with pharmacokinetic and pharmacodynamic studies, followed by clinical safety and efficacy trials, or, where scientifically justified, additional pharmacokinetic/pharmacodynamic studies to demonstrate clinical comparability. Different amounts of pre-clinical and clinical data are required on a case-by-case basis to ascertain the safety and efficacy of biosimilars.

Interchangeability and Substitutability

Assessments of the substitution and interchangeability of the biosimilars with the originator product are not part of the scientific evaluation leading to the granting of a MA (EMA, 2012a). The EMA states that for questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist. Interchangeability and substitutability decisions are taken at Member State (MS) level. Substitution of biologicals (including as between an innovator and a biosimilar) by a pharmacist without the permission of the prescribing doctor is either not allowed or advised against in the vast majority of EU countries (including France, Italy, Spain, UK, Netherlands, Sweden and Germany). This includes countries that do allow (chemical) generic substitution.

Ebbers et al. (2012) provide the only analysis we have identified exploring the effects of switching, for human recombinant growth hormones, EPOs and GCSF agents. These authors reviewed data from clinical trials, pharmacovigilance databases and an overview of the literature on the frequency of switching between these products. The review covers both switching between innovator products within the same product class and switching to and from biosimilars. Data on the frequency of switching in clinical practice is scarce, but it seems most frequent for EPOs. Ebbers et al. (2012) found no evidence from clinical trial data or post marketing surveillance data that switching to and from different biopharmaceuticals leads to safety concerns. Nevertheless, these authors argue that care must be taken to interpret this data. For instance, most clinical trials included in their analysis were not designed to identify switching related adverse events, while spontaneous reporting systems may also not be well equipped to identify any adverse events associated with switching between biologicals. The studies identified and reviewed by Ebbers et al. (2012) do not

³The EMA’s “Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues” is under consultation. The consultation period finished on 30 November 2013.

show repeated switches.

According to the FDA, interchangeability means that for a biological product that is administered more than once to an individual, the safety and reduced efficacy risks of alternating or switching⁴ are no greater than with repeated use of the reference product without alternating or switching (Sherman, 2012). Thus, it seems that the FDA will expect to determine the appropriateness of interchangeability based on repeated switches.

Pharmacovigilance/Risk Management

Clinical safety of biosimilar medicines must be monitored closely on an on-going basis during the post-approval phase including continued benefit–risk assessment (Zuñiga and Calvo, 2010). The need for pharmacovigilance with biologics can be highlighted with two examples (a biosimilar and an innovator) where changes in the manufacturing process led to some (unexpected) adverse effects; for instance, two patients suffered an unexpected side effect⁵ in a clinical trial requested by the EMA as a condition of the approval of a subcutaneous route of administration for the biosimilar HX575 (epoetin alfa). After some investigation, the issue was traced to the interaction of HX575 with tungsten residuals from the drug product container (Seidl et al., 2012). In the earlier innovator Eprex case there was a spontaneous increase in the incidence of PRCA and the only explanation consistent with available data is that a small change in formulation decreased protein stability, leading to increased aggregate formation (Owens et al., 2012). Although this occurred with the reformulation of an innovator's product, it highlights the potential for differences in formulations to cause problems, given that a biosimilar by definition does not use an identical formulation to the innovator's product.

Biosimilar medicines are approved with a formal risk management plan (RMP) that must be delivered/executed by the MA holder (as with all new medicines). This RMP lists a number of adverse events that must be formally monitored along with the mechanisms by which they should be monitored.

⁴ The concept of interchangeability includes switching and alternating. Switching is when there is a switch from one biologic product to another; alternating is when there is a switch from one biologic product to another and then a switch back to the original biologic product (Chow, 2013).

⁵ Two patients in the trial had neutralising antibodies, with one confirmed case of pure red cell aplasia (PRCA) (out of 177 patients being studied).

Naming, Prescribing and Traceability

Naming for biologics, including biosimilars, is particularly important in order to enable appropriate pharmacovigilance/risk management monitoring (MHRA, 2008). WHO's "Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)" states that biosimilars "should have a unique brand name" and that "the provision of the lot number is essential as this is an important part of production information and is critical for traceability in cases where problems with a product are encountered" (WHO, 2009). The current INN policy for biosimilars follows two different approaches, one for those that are glycosylated and one for those that are not. Non-glycosylated biosimilars are considered to have highly similar post-translational modifications and receive the same INN, whilst those that are glycosylated are considered comparable but distinct; they get the same INN name but are further qualified by a Greek letter suffix.

During the WHO's 55th Consultation on International Nonproprietary Names for Pharmaceutical Substances (WHO, 2012), WHO INN guidance was discussed. Several options were considered⁶, and it was agreed that "the present situation is not satisfactory and that action is required...to investigate ways in which the present system might be improved and to consider guidance or recommendations for regulatory authorities in dealing with issues that biosimilars raise after they are placed on the market" (page 4). It was also mentioned that a further complication with biosimilars is that the INN Programme cannot force a company to apply for an INN, and if it chooses not to, it can still use an INN based on comparability studies.

In November 2012, the MHRA issued a Drug Safety Update that states that "When prescribing biological products, it is good practice to use the brand name" (MHRA, 2012). In the UK, this is endorsed by the British National Formulary (BNF)⁷ in its general guidance on prescribing and by the National Prescribing Centre (NPC, 2011). This will ensure that substitution of a biosimilar product does not occur when the medicine is dispensed by the pharmacist. The EU Pharmacovigilance Directive highlights the need for accuracy in medical records to ensure effective pharmacovigilance: "Member States should operate a pharmacovigilance system to collect information that is useful for the monitoring of medicinal products" (EC, 2010, page 348).

3.2 Health Technology Assessment

We now discuss the relationship between HTA and biosimilars. In order to do so, this section is divided into two main sections. First, we discuss the current HTA environment in the UK for biosimilars (based on official documents and the Roundtable). Second, we summarise the key findings from the relevant literature.

⁶ Four options were discussed: (1) continue with the status quo; (2) treat all SBPs as unique products and provide them with a unique INN; (3) create a biosimilar 'identifier' to be used for all SBPs (and not just glycosylated ones), e.g. use the original INN and add a fantasy code suffix; (4) encourage regulatory authorities to provide an 'identifier' under the guidance of WHO. The first two options were considered as not viable.

⁷ <http://www.medicinescomplete.com/mc/bnf/current/PHP60-general-guidance.htm>

3.2.1 Current HTA Environment in the UK for Biosimilars

All Wales Medicines Strategy Group (AWMSG)

The AWMSG states that, in general, economic evaluations should take the form of cost utility analyses, with results expressed as incremental costs per quality-adjusted life-year (QALY) gained. Exceptions where cost-minimisation analyses may be acceptable include where there are no clinically meaningful differences in the distribution of effects between the medicine and its comparator(s) (AWMSG, 2013a). The AWMSG states that “biologically produced medicines (biosimilars) cannot be assumed to be therapeutically equivalent to (and therefore substitutable for) any other approved biologic medicine” (AWMSG, 2013b⁸). Therefore, the AWMSG appraises biosimilar products in terms of clinical and cost-effectiveness and they fall within the AWMSG criteria for appraisal and require a full HTA submission (AWMSG, 2013a⁹). A limited submission¹⁰ is only allowed for a biosimilar when it is identical to an existing product (i.e. produced on the same production line in the same factory) but with a different product licence (AWMSG, 2013a).

The AWMSG argues that “cost-minimisation analyses (CMA) are appropriate for biosimilars only when the reference product has been recommended by NICE or AWMSG for the intended indication; or when the reference product is already in widespread use for the indication (evidence of this would be required)” (AWMSG, 2013a, page 9). However, “when the reference product has not been recommended by NICE/AWMSG for the intended indication, or if the reference product is not in widespread use, a cost-utility analysis is required, comparing the biosimilar against some other relevant comparator, using clinical data relating to the reference product, if necessary” (AWMSG, 2013a, page 9). Prescription by brand name to avoid automatic substitution and support pharmacovigilance is explicit and provided upfront in guidance on biosimilars’ appraised by AWMSG.

The AWMSG has to date appraised seven biosimilars: four filgrastims and three EPOs (although the EPO decisions, including for the reference product Eprex, have now been superseded by NICE’s guidance (TA 142 - Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia, published in May 2008)). Out of the seven decisions, four were positive recommendations, one implied a restricted use and two were rejected. The biosimilar somatropin was not appraised because the manufacturer did not make a submission. AWMSG has not appraised Genotropin, the reference product for somatropin.

The AWMSG has recommended the four biosimilar filgrastims (note that a fifth biosimilar filgrastim was not assessed¹¹) under a full submission. Some of them used CMA and others just presented cost savings or a budget impact analysis versus the reference product (Neupogen). The AWMSG (or

⁸ This 2013 document updates a version of October 2012, but contains the same wording as the October 2012 one.

⁹ A full submission is required for a new medicine (new chemical entity/new biosimilar medicine) or patient access scheme (PAS) submitted; for a new licensed therapeutic indication (New Target Disease).

¹⁰ A limited submission is required for a significant new formulation of existing medicine (including biosimilars) when there is a clear case for equivalence, superiority, or non-inferiority and cost pro-rata is equivalent or lower than comparator, or the cost difference is deemed insignificant; or for new minor licensed extension (e.g. paediatric indications) to medicines previously recommended by NICE/AWMSG or medicines already in widespread use or license predates AWMSG and the impact deemed is not significant by AWMSG Steering Committee

¹¹ Filgrastim Hexal met the exclusion criteria and was not assessed.

NICE) has not appraised the reference product for the biosimilar filgrastims (Neupogen) – what we do not know is whether Neupogen was considered at the time to be in widespread use, in which case it would still be consistent with AWMSG approach (as outlined above).

AWMSG appraised Eprex (reference product) in 2003 and the decision was not to support the use of erythropoietin in the treatment of anaemia associated with cancer due to the lack of evidence of cost-effectiveness. Out of the three biosimilar EPOs that were originally appraised by AWMSG, one received a restricted recommendation (Binocrit (August 2010) in accordance with NICE Clinical Guideline 39 for the treatment of symptomatic anaemia associated with chronic renal failure in adult and paediatric patients¹²) and two were rejected (biosimilar epoetin beta (NeoRecormon) and a biosimilar epoetin zeta (Retacrit)). Binocrit was compared against Eprex, epoetin beta (NeoRecormon) and darbepoetin alfa (Aranesp). AWMSG states that the model comparators are appropriate although the analysis fails to consider methoxy polyethylene glycol beta (Mircera) which had been recommended earlier by AWMSG as a treatment option for use within NHS Wales for the treatment of adults with symptomatic anaemia associated with chronic kidney disease. However, there is no explicit mention in this decision that the reference product (Eprex) was not recommended in the original decision and the implications this might have in the type of economic analysis (which was CMA).

NeoRecormon and Retacrit were both originally rejected by the AWMSG. NeoRecormon was assessed (in March 2004) for the treatment of symptomatic anaemia in adult patients with non-myeloid malignancies receiving chemotherapy and its use was not supported due to the lack of evidence of cost effectiveness. Retacrit was not recommended in April 2010 for use within NHS Wales for the treatment of anaemia associated with chronic kidney disease, reduction of transfusion requirements in adult patients receiving chemotherapy or to increase the yield of autologous blood from patients in a predonation programme, because its cost effectiveness case had not been proven. In November 2011, the AWMSG issued a Statement of Advice for Retacrit for the reduction of exposure to allogeneic blood transfusions in adult non-iron deficient patients prior to major elective orthopaedic surgery; there was no submission from the holder of the marketing authorisation so the AMWSG could not endorse its use within NHS Wales¹³.

Based on our review of AWMSG decisions on biosimilars, it seems this body is following their biosimilar-specific policy. The appraisals when the reference product had not been appraised before, however, are not stating explicitly if they are assuming this product is already in widespread use. Nevertheless, the AWMSG tends to comment on the appropriateness of the comparators used by the manufacturers in their economic analysis.

¹² This NICE Clinical Guideline, which has now been updated and replaced by NICE Clinical Guideline 114 (February 2011) states that regarding the choice of erythropoiesis-stimulating agents, there is a need to discuss this choice with the patient when initiating treatment and at subsequent review, and that there is no evidence to distinguish between erythropoiesis-stimulating agents in terms of efficacy.

¹³ As of 9 December 2013, there is no additional information on AWMSG advice for Eprex, NeoRecormon and Retracrit other than the final decision and a comment that these decisions have been superseded by NICE Guidance (TA 142).

Scottish Medicines Consortium (SMC)

The SMC has two types of submission: 'full' and 'abbreviated'. The full submission needs the clinical and economic case. The SMC will consider an abbreviated submission in some circumstances, which may be appropriate when the product is not a new active substance, for example for a new formulation of an established product. One of the requirements for an abbreviated submission is that the medicine is expected to have minimal impact on the NHS Scotland medicines budget, thus no economic evidence is required.

The SMC has a policy position on biosimilars, which arose from a short-life Working Group created in 2008 to consider the types of submissions required for biosimilars. The Group had representatives from SMC, the New Drugs Committee and industry. There was a consensus around the conclusions. A key outcome was the recognition of the need to be cautious about biosimilars. The SMC was clear that it wanted to see them in clinical practice and observe the extent to which potential cost savings were realised. The Working Group recognised that there might be key differences around the efficacy and safety between a biosimilar and its reference product. In particular, there was concern about the immunogenic reactions and neutralising antibodies and whether they could affect the efficacy of a biosimilar. Other issues highlighted by this Working Group were the need for biosimilars to be prescribed by brand and for non-interchangeability. In addition, there was a feeling that the SMC, as a consortium of the Area Drugs and Therapeutics Committees in Scotland's 14 Health Boards, should give leadership to the Health Boards. The Health Boards' perspective was that they wanted an SMC assessment to be carried out so that they could see their advice document and get a feel for what the medicine would offer. The main recommendation, published in 2010, was to go for full submissions for biosimilars, with a review of the policy position. The policy position now states that in 2011 a decision was made to extend the review date for this policy until SMC has further experience in the assessment of biosimilar medicines, and that it will be revisited in 2015¹⁴.

The SMC states that "biosimilars are fundamentally different from chemically derived medicines in terms of their production, complexity of chemical structure, purity and immunogenicity". The SMC also states that "by definition, biosimilar medicines are not generic medicines (and are therefore not interchangeable), since it could be expected that there may be subtle differences between biosimilar medicines from different manufacturers or when compared with the reference product. These variations may affect the efficacy and safety of the biosimilar medicine (e.g. increased risk of allergic reactions when compared with the reference product)".

Regarding substitution and prescribing, the SMC states that "the clinical profile of biosimilar medicines must be monitored closely on an ongoing basis during the post-approval phase, including continued risk-benefit assessment. In order to support pharmacovigilance monitoring, biosimilar medicines should be prescribed by brand name. If the specified biosimilar medicine is unavailable during dispensing, automatic substitution for the reference product is inappropriate. Substitution should only be considered if the prescribing physician gives prior consent".

¹⁴ Available at: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Biosimilar_Medicines (accessed 9 December 2013).

The SMC believes that “the managed introduction of biosimilar medicines into clinical practice in NHS Scotland is desirable. To facilitate this process, SMC requires a full submission for all new biosimilar medicines that details a comparison with the biological reference product. In line with the licensing process, SMC will accept extrapolation of clinical data for a single indication for the biosimilar medicine to the wider licensed indications of the biological reference” (SMC, 2012).

Similar to AWMSG, SMC references the BNF and states that it is good practice to prescribe biosimilars by brand name and explicitly states upfront in the guidance if the product being appraised is a biosimilar.

The SMC position, however, does not refer explicitly to the appropriate type of economic analysis (either cost-utility or cost-minimisation) under the situation when the reference product has not been accepted by the SMC – contrary to the AWMSG position. This was discussed during the Roundtable.

The SMC has to date reviewed eight biosimilars: four filgrastims, three EPOs and one growth hormone, seven of them after full submissions¹⁵. All of the economic cases have been CMA. All seven were accepted for use.

The four filgrastim were compared against their reference product, Neupogen. We did not find an SMC decision for Neupogen. The three biosimilar EPOs were compared to the reference product (Eprex) and other EPOs. Again, we did not identify an SMC decision for Eprex. The biosimilar growth hormone was compared to the reference product, Genotropin. Genotropin had been assessed by SMC (recommended for restricted use).

As an example to illustrate some of the details of these assessments, the SMC accepted Ratiograstim (biosimilar filgrastim) for use within NHS Scotland for the prevention of febrile neutropenia in 2009 (SMC, 2009). The manufacturer submitted a CMA comparing two filgrastim products Ratiograstim and its reference product Neupogen. This SMC recommendation states that “Ratiograstim is a biosimilar product and has demonstrated equivalency in terms of efficacy and safety to a reference GCSF (filgrastim (Neupogen))” and that “The British National Formulary advises that it is good practice to prescribe biological medicinal products by brand name”. It is also stated in this SMC recommendation that the assumption of clinical equivalence is critical both for licensing and for the choice of CMA as the economic evaluation technique. The SMC remarked that no data had been submitted comparing the biosimilar with the second generation biopharmaceutical, pegfilgrastim.

Within the EPOs, the SMC approved the use of Retacrit (epoetin zeta) for the treatment of anaemia associated with chronic renal failure in patients on haemodialysis and adult patients on peritoneal dialysis. It was also recommended for the treatment of severe anaemia associated with kidney disease in patients not yet undergoing dialysis (SMC, 2008). As two phase III trials showed clinical equivalence for epoetin zeta when compared with epoetin alfa for the surrogate endpoints of correction and maintenance of haemoglobin concentration, the economic evaluation took the form

¹⁵ The only abbreviated submission was for TevaGastrim as it is manufactured at the same production site and is identical to the biosimilar product filgrastim (Ratiograstim), previously accepted for use by SMC.

of a CMA. The evaluation compared epoetin zeta with three other EPO stimulating agents and concluded that epoetin zeta would yield equivalent efficacy at similar or lower costs.

Likewise, Binocrit's manufacturer presented a cost-minimisation analysis comparing Binocrit with epoetin alfa (Eprex), darbepoetin alfa (Aranesp), epoetin beta (NeoRecormon) and epoetin zeta (Retacrit), across all indications as covered by the licence. Two of the indications covered by the licence had previously been assessed for use in NHS Scotland (treatment of anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy)), so only the chronic renal failure and autologous predonation indications were considered for review by SMC.

The growth hormone biosimilar appraised by the SMC, in 2010, was Sandoz's somatropin (Omnitrope), which was compared against the reference recombinant human growth hormone (somatropin (Genotropin)) and another somatropin (Norditropin). The manufacturer presented a CMA comparing Omnitrope against these two somatropins. Genotropin was assessed by the SMC in 2006 and was recommended for 'restricted' use, where the restriction was that treatment should be initiated and monitored by a paediatrician with expertise in managing childhood growth disorders and growth hormone therapy.

Based on the SMC experience to date with biosimilars, and as raised during the Roundtable, one area of concern is around the extrapolation by indication - although recognising that the SMC would absolutely not stray into regulatory authority territory.

Similarly to AWMSG, the SMC seems to be following their policy position. Nearly all biosimilars appraised have gone through the full submission route - and all have used CMA. SMC's approval rate for biosimilars to date has been 100%, so it seems that CMA has been more than sufficient to demonstrate the economic value of biosimilars in Scotland. In a number of occasions the SMC has stated that showing clinical equivalence has been key to accept CMA as the method of analysis.

NICE

NICE does not have a separate policy for biosimilars¹⁶. Under NICE's criteria for topic selection for technology assessment (AWMSG and SMC's remits are to look at all medicines) biosimilars have not so far emerged as a high priority for assessment, for various reasons. This includes NICE's focus on issuing guidance for new technologies targeting new patients (rather than substitution of patients - which is more relevant for biosimilars) and the level of discounting already going on in the biosimilar market. NICE focuses on comparative clinical and cost effectiveness, which seem less relevant

¹⁶ At the time of sending the manuscript for publication, NICE had just announced its HTA position paper on biosimilars for targeted consultation with key stakeholders. There will be a six-week consultation period for stakeholders to respond to the NICE position paper and the deadline for response is 17 April 2014.

for biosimilars, which tend to be associated with CMA. Under NICE's "Technology appraisals topic selection", there is a reference for biosimilars that states that "The National Institute for Health Research Horizon Scanning Centre will notify NICE of all new biosimilar indications as per standard topic selection procedures. Biosimilars are different to generic drugs. Any guidance on biosimilars will use brand names as substitutability and interchangeability cannot be assumed and ultimate decision making on biosimilars versus originator biologic must rest with the responsible clinician."¹⁷

To date, NICE has appraised one biosimilar in one Technology Appraisal, "Human growth hormone (somatropin) for the treatment of growth failure in children", TA 188 (NICE, 2010). TA 188 was a review of an earlier TA (TA 42, Human growth hormone for the treatment growth failure in children). The biosimilar was Omnitrope. Omnitrope was not treated differently to the other products included. Within TA 188, it states that the active substance of a biosimilar medicine is similar but not identical to the biological reference medicine, although the references to the biosimilar included in the TA are stated as a footnote (footnote 1) and in two paragraphs (4.3.4 and 4.3.5). TA 188 says that making specific recommendations around the safety of a drug is outside the remit of NICE¹⁸, and there is no reference to the pharmacovigilance requirements for biosimilars e.g. the importance of prescribing by brand name or avoiding automatic substitution.

NICE has also recently considered biosimilars in the context of reviewing TA 142: Erythropoietin (alpha and beta) and darbepoetin for the treatment of cancer-treatment induced anaemia (NICE, 2008). The original TA 142 guidance was issued in May 2008 with a review date of February 2011. In April 2011, it was agreed that NICE would consult on the review plans for this guidance; as a result, in July 2011 a review of the guidance was planned into NICE's work programme. Part of the rationale for the review of this TA is the availability of biosimilars and their lower acquisition cost versus the originator's price used in the original TA¹⁹, as well the availability of results from the EVALUATE study. We understand the review is now underway. A number of future selection topics include three or four biosimilars. It was mentioned at the Roundtable that these have been delayed as NICE is considering the issues around biosimilars.

NICE also makes reference to biosimilars in the comparators section of the recently published revised Guide to the Methods of Technology Appraisals 2013 stating that "Comparator technologies may include branded and non-proprietary (generic) drugs and biosimilar products" (NICE, 2013, page 18).

As an aside, the future important role of the NHS England was also raised during the Roundtable - given that this national group will be responsible for commissioning 85% of medicines appraised by NICE, including cancer and difficult specialised disease areas. Biosimilars for such disease areas will fall into national specialised commissioning - which will also be true for Scotland and Wales. Thus, it was agreed that the NHS Commission Board should also be aware of the issues around biosimilars. The point here is that while NHSEngland will make referrals to NICE, it may have its own policies in

¹⁷ Available at: <http://www.nice.org.uk/getinvolved/topicselection/TechnologyAppraisalTopicSelection.jsp> (accessed 23rd September 2013)

¹⁸ Page 30 of TA 188 states that "The Committee was aware that making specific recommendations around the safety of a drug was outside the remit of NICE" - but no further reason is given as to why this was the case.

¹⁹ See <http://www.nice.org.uk/nicemedia/live/11990/55292/55292.pdf> for more information (accessed 9th December 2013).

relation to biosimilars.

3.2.2 HTA and Biosimilars: Key Findings from the Literature Review

Two papers discuss what could be an appropriate HTA process for biosimilars. Stewart et al. (2010) argue that there is a fundamental discordance in the attitudes of regulatory bodies and HTA authorities towards biosimilars: while regulatory bodies regard biosimilars as sufficiently similar to the reference product to require an abbreviated submission, HTA authorities regard biosimilars as sufficiently different from the reference product to require a full submission, incorporating economic analysis – indeed, and as mentioned above, SMC and AWMSG require full submissions. Stewart et al. (2010) argue that cost-utility analysis is only appropriate for biosimilars when clinical experience shows a difference in rare adverse events or resource utilization between the originator and the biosimilar, or between biosimilars. However, they argue such cases are likely to be exceptional and are likely to emerge, if at all, only when a large number of patients have received the biosimilar. This view is shared by Simoens (2011). Both Stewart et al. (2010) and Simoens (2011) propose that HTA organisations accept pharmacokinetic and pharmacodynamic equivalence between the brand and the biosimilar as a proxy of biological comparability. Stewart et al. (2010) and Simoens (2011) do not discuss the possibility of the reference product not being the standard of care.

Stewart et al. (2010) also state that once approved, biosimilar manufacturers and regulators should maintain rigorous pharmacovigilance to exclude immunoreactivity or other rare adverse events, as well as prescribing by brand, to facilitate pharmacovigilance.

As highlighted in the next section, these issues were debated during the Roundtable.

4. Summary of the Roundtable

The following six questions formed the basis of the deliberations:

1. On what basis, if any, should biosimilars continue to be subject to HTA in the UK (in contrast to chemical generics which are not subject to HTA)?
2. On what basis should NICE assess biosimilars, for example, under STAs or MTAs or both? Are there any important considerations for NICE if biosimilars are a comparator technology?
3. In certain circumstances the SMC and AWMSG currently accept cost-minimisation for considering biosimilars. NICE's reference case requires cost-utility analysis. If biosimilars have shown same efficacy as the reference product in the full indication under appraisal, should they be subject to cost-minimisation analysis, or should they

always be subject to cost-utility analysis?

4. How do we address long term outcomes (i.e. certainties/uncertainties) when trials for biosimilars generate only short-term safety and efficacy results, often in relatively small studies? Would this be enough to meet HTA agencies' evidence standards?
5. How should naming safety and pharmacovigilance requirements for biosimilars be integrated within the HTA decision making process and subsequent guidance? What safeguards could be put in place to ensure that recommendations and guidance do not inhibit or conflict with these requirements (e.g. is guidance that "the medicine with the lowest acquisition cost should be used" consistent with the need for safeguards)?
6. The EMA only allows extrapolation of indication if the totality of evidence justifies the determination; when should it be permissible for HTA bodies to extrapolate efficacy data from one clinical condition specifically studied to another clinical condition not studied for the biosimilar product?

We now take in turn each of the six questions, followed by a final section that summarises other issues discussed that do not relate directly to any of the six questions.

Q1. On what basis, if any, should biosimilars continue to be subject to HTA in the UK (in contrast to chemical generics which are not subject to HTA)?

We need to address three issues when thinking about the appropriate HTA for biosimilars at launch:

1. Is the effectiveness evidence for the biosimilar, as compared to the reference product, likely to be different to the pre-launch efficacy evidence?
2. Has the reference product been appraised? and
3. Is the reference product the standard of care?

On the first point, the literature reviewed has suggested that biosimilar companies would need to collect additional post-launch data (safety and effectiveness) to confirm expectations that the product did treat patients in the same way as the reference product, so reassuring clinicians and any HTA body appraising it. The problem is that when HTA bodies look at products at launch, such additional data is not available. Indeed, given the regulatory requirements for biosimilars, the issue of whether the licensing evidence for the reference product along with that for the biosimilar would be available to HTA bodies is important. At the time of authorisation there will be a public assessment where the regulator summarises the evidence that has been submitted. All biosimilars have a European Public Assessment Report (EPAR), containing a summary of the clinical package that was submitted to the regulator, the regulator's assessment and the regulators' conclusions. Detailed clinical data could be requested from the EMA under an equivalent of the UK's Freedom of Information (FOI) – but as outlined above, the EPAR for biosimilars will not contain the usual safety

and efficacy results found for the innovator biologic (as biosimilars only need to show comparability). However, most innovators have their EPARs where safety and efficacy results are summarised. So, a key issue raised was what exactly can the HTA body do at launch?

The discussion logically followed on whether is there a need to collect effectiveness data for biosimilars post-launch? Two points fall from this question. First, is there a reason to expect effectiveness to be different from efficacy for the biosimilar, as compared to the reference product? Second, what sort of studies post-launch, over what time period, could establish any differences? If the answer to the first question is that we expect no differences for the biosimilar as compared to the reference product, then we need to consider points 2 and 3 above: has the reference product been appraised and/or is it the standard of care? If the reference product was positively appraised by the HTA body and/or is the standard of care, then an HTA process should not be needed for biosimilars at launch. The originator may not be the standard of care because, for instance, it has been rejected or restricted by the HTA body. Under this situation the case for biosimilars being subject to HTA was stronger as the originator had not fully satisfied the HTA body in respect of effectiveness and/or cost-effectiveness. As with any HTA, the appropriate comparator for the biosimilar under this circumstance should be the standard of care. Question 3 below picks up on the type of desired analysis for this scenario.

An option (not mutually exclusive to the one described in the preceding paragraph) could be that HTA bodies take the view that 'We do not think there is any difference between the reference product and the biosimilar but we want to see some data collection in future years – which could mostly be safety but it could extend to other things as well'. There was also some questioning about the sensitivity and likelihood of a post-marketing effectiveness study picking something up even if there was a difference between the reference product and the biosimilar, if nothing had been apparent in the pre-clinical studies conducted pre-launch. Safety issues should be taken into account by the regulator in assessing similarity, and the risk management plan is designed to pick up any issues that might appear post-launch. Regarding safety issues, there might be concerns about the trial population not necessarily being representative of those going to receive the medicine and about longer-term effects. The latter might be important if the regulator's short-term study is making the assumption that whatever outcome measures are used in that trial will be an appropriate surrogate for whatever longer-term outcome measures are for the reference product and it is reasonable to assume that the same things will happen with the biosimilar product.

It is important to ascertain whether or not HTA processes at launch for biosimilars are adding value. It would need to be clear what particular circumstances might give rise to the above-mentioned efficacy/effectiveness gap post-launch, because it is not obvious that there would be an efficacy/effectiveness issue. If the critical issue is safety, then there was agreement that there is reduced scope for the HTA body to add to the evidence assessed by the regulator and post-launch pharmacovigilance requirements will be put in place. Such early HTA assessment could just be lulling the clinical community into a false sense of security around the product by saying it has both the regulatory and HTA approval when the HTA body has, in reality, nothing to add. It was argued at the Roundtable that the HTA assessments done to date for biosimilars at launch have probably not provided additional clinical and cost-effectiveness information compared to the information used

for regulatory approval.

There was also a discussion about whether this efficacy-effectiveness gap is not a particular concern for biosimilars, but applies across the board. There is not enough real world research post launch – but not just for biosimilars.

The broader question of what is the value of an HTA body doing a full assessment and looking at the same evidence used for regulatory approval was also discussed – and not just for biosimilars. HTA bodies end up quite often looking at the evidence that has gone to the licensing body. The implication is that the HTA bodies are asking a different question from that the regulator has asked. Bearing that in mind, a further point discussed which only relates to biosimilars is that the regulatory data provided is not focusing on safety and efficacy, as with other medicines, but that it is a comparability exercise – and HTA bodies need to be aware of that, as they usually review efficacy and safety data but not comparability data.

Post-launch, what could be the role of HTA for biosimilars? At least three options might be available. First, no further review (irrespective of whether there was an HTA at launch). Second, there could be a review of the STA (if there was one done at launch). Third, there could be an MTA if a large number of competing agents and other options are available. This third option would eliminate the need to carry out a large number of STAs in parallel.

Comparing different presentations was also discussed; for instance, if a new presentation of the reference product is available when the biosimilar (of a previous presentation) is launched. The question then followed as to what product is receiving the technology appraisal and which one is used as the comparator. The biosimilar might be assessed and the comparator might be either the original presentation of the reference product or the new presentation. Alternatively, the cost-effectiveness of the new presentation of the reference product might be assessed and a comparator might be the biosimilar version of the original presentation.

Flexibility and choice to appraise biosimilars were deemed as important elements. An option could be that for the first monoclonal antibody (MAb) or anti-TNF biosimilar version there is a full HTA assessment to learn from the experience – and then decide whether full appraisals are required for subsequent biosimilars too. Overall, the majority of the views expressed at the Roundtable supported that “subject to HTA processes” was useful in that it could imply that biosimilars are considered as part of the process but that ultimately are not assessed in detail at a later stage. However, given the differences between HTA bodies in the UK this has different implications for each one.

Within England and Wales, there are a range of options if there is a decision finally not to do a technology assessment (TA). First, there is the possibility of producing “Evidence Summaries: New Medicines” for technologies not selected for TA. The purpose of these is not to provide guidance but to summarise the evidence. Such summaries are done consistently to a NICE process so they should be helpful for making evidence-based decisions. Second, to prepare clinical guidelines; while it was recognised that guidelines might be less relevant for existing biosimilars (perhaps with the exception of clinical guideline CG114 for Anaemia management in people with chronic kidney

disease (NICE, 2011)), they might be more relevant for the MABs and anti-TNFs, where there might be more treatment options (and not just biosimilars). It nevertheless seems that for high-priority topics (in general), there is a general trend to move those towards TAs – in order for NICE to make a recommendation. And so far biosimilars have not been deemed as a too high priority, although biosimilars have been included in two TAs (TA 118 and TA 142).

Evidence summaries are not produced by the other two UK HTA bodies – as the SMC and AWMSG need to review every new drug. There is the possibility of the SMC changing its policy position so as not to need a full submission for biosimilars (but not until 2015). In the extreme, biosimilars could be classified in the same way as 'generics' and thus would fall outside the SMC's remit. But it is also true that given imminent patent expiries for MABs and anti-TNFs, the interest to assess biosimilars in these areas will undoubtedly arise. Nevertheless, the SMC will keep exploring whether HTA assessments for biosimilars provide value added.

There was also discussion about the translation of TA/guidance to local decision making, and from local policy to individual patients. It was argued that the focus, in general, has been on developing the guidance or TA, rather than in these two translations.

Q2. On what basis should NICE assess biosimilars, for example, under STAs or MTAs or both? Are there any important considerations for NICE if biosimilars are a comparator technology?

HTA bodies have tended to assess new technologies individually i.e. assessing a new technology and making a decision whether it should be selected for a TA; for instance, SMC and AWMSG review technologies individually and NICE has STAs. However, a point raised was that perhaps there is a need to do something different if the biosimilar is not introduced in isolation but in the context of other developments within that therapeutic area, including whether there are different presentations available, and what else is needed for the management of a condition – which is relevant for MTAs and guidelines. Thus, under these circumstances MTAs could be more relevant than STAs for biosimilars. Still, even within MTAs biosimilars might not be treated differently to any other products. This is how the MTA for the human growth hormones treated the biosimilar appraised in TA 188.

Q3. In certain circumstances the SMC and AWMSG currently accept cost-minimisation for considering biosimilars. NICE's reference case requires cost-utility analysis. If biosimilars have shown same efficacy as the reference product in the full indication under appraisal, should they be subject to cost-minimisation analysis, or should they always be subject to cost-utility analysis?

The AWMSG uses cost-utility analysis when the reference product has not been recommended by NICE or AWMSG, or the AWMSG has not looked at it. Cost-minimisation analysis is appropriate when the reference product has been recommended by NICE or the AWMSG, or if it has not been appraised by the HTA body but is still the standard of care. The SMC does not have the requirement to have looked at the reference product in order to allow the use of cost-minimisation analysis–

indeed, many of the reference products used for the biosimilars appraisals have not been looked at by the SMC.

An additional scenario was discussed, where the biosimilar comes into the market but the originator was not originally recommended by an HTA body. Under this scenario, it was agreed that cost-minimisation analysis would not be appropriate. It was suggested at the Roundtable that the SMC could not be comfortable with a cost-minimisation analysis for the biosimilar when the SMC had rejected the reference product – and thus, a cost-utility analysis would be more appropriate versus the relevant comparator, which might actually not be the reference product.

Following the discussion around Q1 and the possibility of the reference products not being positively appraised in the first instance, there are two answers to Q3. First, if there was an efficacy/effectiveness issue (i.e. the biosimilar will not treat patients in the same way as the reference product) then that logically would require cost-utility analysis. The issue, as highlighted above, is what would be the circumstances in which that might arise, given that the regulator will have approved the biosimilar as similar to the reference product, and no more evidence was likely to be available to the HTA body than to the regulator (see below)? Second, if the reference product had been rejected or restricted earlier by the HTA body, or it is not the standard of care, then that would require again a cost-utility analysis for the biosimilar. The comparator, in this case, will not be the reference product.

If the HTA body does decide to review a product in which no differences in effectiveness are expected with the reference product and the reference product has been reviewed and is the standard of care, then a cost minimisation analysis would be sufficient.

Q4. How do we address long term outcomes (i.e. certainties/uncertainties) when trials for biosimilars generate only short-term safety and efficacy results, often in relatively small studies? Would this be enough to meet HTA agencies' evidence standards?

It was agreed that this question is revisiting whether the efficacy/effectiveness issue might be reflected in different longer-term outcomes for a biosimilar product as compared to the originator – as long-term safety issues are being addressed by the regulator²⁰. There was a general agreement across the Roundtable participants that overall TAs do not factor in adverse drug reactions very well²¹. The biosimilar should be treated similarly to the reference product when addressing uncertainty as to the relationship between short and long term outcomes. In essence, if HTA bodies were satisfied with the evidence from the reference product, and the biosimilar produces similar evidence (in terms of the short-long term relationship), the HTA body should be satisfied with the biosimilars' evidence. But if the evidence for the originator did not satisfy the HTA body then the biosimilar should be treated with the same degree of scepticism.

²⁰ The Pharmacovigilance Risk Assessment Committee (PRAC) is the committee at the EMA that is responsible for assessing and monitoring safety issues for human medicines and will be doing both post-authorisation safety and efficacy studies (PASS/PAES).

²¹ NICE's latest Guide to the methods technology appraisal does mention throughout the entire document that adverse effects should be identified and built into the economic models (NICE, 2013).

Q5. How should naming safety and pharmacovigilance requirements of biosimilars be integrated within the HTA decision making process and subsequent guidance? What safeguards could be put in place to ensure that recommendations and guidance do not inhibit or conflict with these requirements (e.g. is guidance that “the medicine with the lowest acquisition cost should be used” consistent with the need for safeguards)?

It was argued during the Roundtable that prescribing by brand name should be good practice whether it is for the reference product or the biosimilar. Thus, the majority view at the Roundtable was that it is important to be explicit about the regulatory advice which recommends prescription by brand, and thus no substitution without the agreement of the clinician (in the UK generic substitution is in any case not permitted). Prescribing by brand is particularly important to enable products to be traced in the event of a safety issue. NICE did not make any explicit remarks around naming for the human growth hormone TA (TA 188), which might be important if substitution from the reference product to the biosimilar takes place as a result of NICE’s guidance - noting NICE statement that “Any guidance on biosimilars will use brand names as substitutability and interchangeability cannot be assumed, and ultimate decision making on biosimilars versus originator biologic must rest with the responsible clinician” (see footnote 18). For instance, a recommendation to prescribe the medicine at its lowest acquisition cost (assuming, of course, there are efforts from someone to ensure that prescribers know relative acquisition costs) should not therefore override the need to prescribe by brand name or the requirement for the clinician and patient to consent to any substitution. But it would be important that recommending prescribing by brand should not send the signal that biosimilars are somehow inferior. Based on recent experience as to the lack of effectiveness of recommendations to prescribe anti-epileptics by brand name in England and Wales, it was argued that to get a message across on brand prescribing might require more than a TA.

A key concern of the attendees was whether or not regulators are asking for a heavier risk management plan (RMP) burden for the biosimilar than for the reference product when it was first authorised. It may be that this is unavoidable in some circumstances if regulatory expectations change over time.

Q6. The EMA only allows extrapolation of indication if the totality of evidence justifies the determination; when should it be permissible for HTA bodies to extrapolate efficacy data from one clinical condition specifically studied to another clinical condition not studied for the biosimilar product?

It is always possible for a biosimilar to have fewer indications than the reference product. Theoretically, at least regulators could approve some indications but not others.

For extrapolating indications, the regulator needs to go beyond evidence that the biosimilar and the reference product are comparable in the clinical indication(s) studied. The regulator would need assurance that if the reference product works for several indications, the biosimilar is also going to work for all these indications without requiring additional data. Any extrapolation to other indications also requires assurance of comparability on both safety and efficacy. This should be easier when there is a single mechanism of action relative to a situation with multiple mechanisms

of action, where the regulator is likely to require evidence of comparability in terms of efficacy and safety across these multiple mechanisms of action. The additional evidence required for additional indications will depend on the nature of the product, but analytical and pre-clinical studies are thought to be more sensitive at picking up potential differences between a reference product and a biosimilar than clinical ones.

Given this ability of regulators to accept extrapolation into a number of therapeutic indications, the availability of data on which to do a technology assessment could be problematic. This might be especially relevant for future biosimilars (for example MABs which often have more than one indication); if the research that is conducted on a biosimilar is for one indication, the ability to do an HTA on a different indication will be limited. It was confirmed that if the regulator is in any doubt over the ability to extrapolate to other indications, there are regulatory tools that can be used to ask for additional efficacy studies for those indications. It was argued that this has not been an issue to date, but it is always there as an option if there is a potential need for something in the future for more complicated products.

Other issues

Two further issues, not directly related to the six questions, were also discussed: impact of changing manufacturing lines and the text in the summary of product characteristics (SmPC) for biosimilars (the latter relates to ABPI's recommendation 4).

First, the context for the discussion on the impact of changing manufacturing lines for the reference product and the biosimilar was in order to create a level playing field for both. Reference products themselves can change, batch to batch. Manufacturers need to demonstrate comparability of any intentional changes in their manufacturing lines, and if they involve greater changes, this can even require clinical testing. Batch to batch variability must be contained within an agreed, limited range as part of the approval process. Biosimilars have to do this as well. Fluctuations within a reference product can often be greater than the difference between a reference product and a biosimilar. What the regulator is seeking is evidence of comparability or equivalence, whether it is a manufacturer changing their own manufacturing process or the fluctuations within their own batch release, for example, or a biosimilar.

Changes to the manufacturing process can be classified according to risk and data requirements (Grampp, 2011). For instance, changing the filter supplier could be deemed as a low risk change, with minimal additional evidence requirements (e.g. analytical comparability data and process studies). Site changes could then be classified as 'moderate risk', with the need to provide data on stability in addition to analytical comparability data. High risk changes can include changes in cell line or formulation, and would generally require clinical comparability data. This change applies to biosimilar development.

Second, the regulatory view is divergent from the ABPI view on Recommendation 4. According to the regulator, the summary of product characteristics (SmPC) for the biosimilar should be the same as that of the reference product. The only differences will arise in the quality sections as appropriate

and for the mention that the product is a biosimilar with reference to the EPAR. The only exception would be if the biosimilar does not have all the indications of the reference product. The justification for the regulatory position is that only clinical data are presented in the SmPC while the approval of a biosimilar is firstly based on quality/non-clinical evidence, which is not described in the SmPC. The regulator's view is that the only useful information for the prescriber in the SmPC is the data from the reference product's pivotal trials that support the efficacy and safety in the various indications. Additional clinical data (comparison of the biosimilar and reference product) do not provide any information that is useful for the product's use²².

5. Conclusions

Based on our literature review and the Roundtable with key stakeholders (MHRA, NICE, SMC, AWMSG, academics and industry representatives), we identified challenges and opportunities in the process of undertaking HTA for biosimilars. Experience to date relates primarily to EPOs, GCSFs and growth hormones (as the first two anti-TNF biosimilars were accepted after our Roundtable took place). However, we expect a further wave of biosimilar arriving in the near future for monoclonal antibodies and anti-TNFs – and it appears these molecules may be more complex than the biosimilar medicines licensed to date. The regulatory process is evolving to take this into account. The EMA has issued product specific guidelines for the monoclonal antibodies and already two biosimilar monoclonal antibodies (for the same reference product) have been approved by the EC.

In terms of HTA, the majority view wanted flexibility in the choice of processes and methods to consider whether or not to assess biosimilars from a health economics perspective. Nevertheless, it will be important that, if biosimilars are treated on a case by case basis, the selection process is transparent and based on clear, consistent criteria. The NICE topic selection process could facilitate this, and NICE has alternatives to HTA, such as Evidence summaries and clinical guidelines. It is less clear how this would be achieved for the SMC and AWMSG, as they currently review all medicines (barring generics), although they do have different categories of submission. The SMC and AWMSG currently require a full HTA submission for a biosimilar. Options might be to relax the required type of HTA submission (towards 'limited' and 'abbreviated' for the AWMSG and SMC respectively) or to treat biosimilars in the same way as chemical generics, so that they are not subject to HTA in any form. The premise behind this change is that in an at launch review HTA bodies might add little additional evidence relative to the evidence provided for regulatory approval. NICE does not have a formal public position regarding biosimilars. Underpinning such thinking would be that safety issues are dealt with at regulatory level and that it is not envisaged that there will be an efficacy-effectiveness gap for biosimilars that is different to any arising from use of the reference product. The majority views supported that any recommendations resulting from HTAs should be cognisant of regulatory and safety recommendations from EMA and MHRA (such as prescribing by brand name and no automatic substitution).

²² However, the labelling for current biosimilars have not all followed that approach – it's been a bit of a "pick and mix" approach. The policy for a "generic-style" SmPC has only been implemented now with infliximab biosimilar (we thank Amgen for providing this information).

So, going back to the original ABPI Recommendations, where did the Roundtable discussion take us? The majority of the views expressed at the Roundtable supported the first three recommendations. In terms of Recommendation 4, the regulatory view is divergent from the ABPI view. On the one hand, the regulator argues that the summary of medicinal product characteristics for the biosimilar should be the same as the originator (with some exceptions). On the other, ABPI's recommendation 4 states that the summary of medicinal product characteristics should make explicit if the information was obtained from either studies investigating the biosimilar product or where the data was derived from evidence about the originator product.

In terms of Recommendation 5, the majority of the views expressed at the Roundtable thought it would be useful to have the option for biosimilars to be subject to HTA processes but not necessarily to always conduct an assessment i.e. having the option of assessing and so not treating them as chemical generics (which are never subject to HTA). Three issues would determine whether or not to conduct the assessment: (1) Will the effectiveness evidence for the biosimilar as compared to the reference product likely to be different to the pre-launch efficacy evidence? (2) Has the reference product been appraised? and (3) Is the reference product the standard of care? If we expect no differences for the biosimilar as compared to the reference product, and the reference product is the standard of care, an HTA process should not be needed for biosimilars at launch.

The difference between the regulatory process and the HTA process is that they are looking at different things. HTA bodies do not address safety and comparability issues. These are under the remit of the regulatory process for biosimilars, which seems to be working well; moreover, there is no additional evidence at launch relative to the evidence available for regulatory review. One area for further improvement relates to post-launch studies to reassure prescribers (and patients) about the safety and effectiveness of biosimilars.

An HTA assessment should focus on value, either through a cost-minimisation analysis or a cost-utility analysis. When products are assumed comparable, and the reference product is already the standard of care, then cost-minimisation analysis is relevant. When the reference product is not the standard of care, either because it was originally rejected or restricted, then cost-utility analysis is more appropriate; and the comparator for the HTA should be the different standard of care and not the reference product. When a biosimilar of a first generation reference product is being compared to a second generation product – potentially with different methods of administration – cost-utility analysis will be more appropriate, as the biosimilar has not been shown to be comparable (or similar) to the second generation product.

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Appendix 1 Literature Review

For the purpose of this Briefing Note, we have undertaken a selective literature review – using combinations of the terms “health economics”, “economic evaluation”, “pharmacoeconomics”, “pharmacovigilance” and “biosimilars”. Further references were identified following the review of the relevant papers and subsequently after the Roundtable. The table below lists the papers that we identified and reviewed. In total, 42 papers were reviewed for this literature search. Each column has the hits reviewed under each search term, and in brackets we have the selected hits. For example, for column 1, we have the results for the search “biosimilars and health economics”; we reviewed 20 hits out of a total of 28. In columns 2, 3 and 4 we also highlight those references that also appeared under “biosimilars and health economics”.

I Health economics (20/28 hits)	II Economic evaluation (20/24 hits; 8 in I).	III Pharmacoeconomics (3/3; 2 in I)	IV pharmacovigilance (15/20 hits; 6 identified from before)
<p>1. Hadji P, Kostev K, Schröder-Bernhardi D, Ziller V, Cost comparison of outpatient treatment with granulocyte colony-stimulating factors (G-CSF) in Germany, <i>Int J Clin Pharmacol Ther.</i> 2012 Apr;50(4):281-9</p>	<p>2. Strober BE, Armour K, Romiti R, Smith C, Tebbey PW, Menter A, Leonardi C, Biopharmaceuticals and biosimilars in psoriasis: what the dermatologist needs to Know, <i>J Am Acad Dermatol.</i> 2012 Feb;66(2):317-22</p>	<p>1. Simoens S, Verbeken G, Huys I, Biosimilars and market access: a question of comparability and costs? <i>Target Oncol.</i> 2012 Jan 17</p>	<p>1. Kay J, Feagan BG, Guirguis MS, Keystone EC, Klein AV, Lubiniecki AS, Mould DR, Nyarko KA, Ridgway AA, Trudeau ME, Wang J., Health Canada/BIOTECanada Summit on regulatory and clinical topics related to subsequent entry biologics (biosimilars), <i>Biologicals.</i> 2012 Nov;40(6):517-27</p>
<p>3. Grabowski HG, Kyle M, Mortimer R, Long G, Kirson N, Evolving brand-name and generic drug competition may warrant a revision of the Hatch-Waxman Act, <i>Health Aff (Millwood).</i> 2011 Nov;30(11):2157-66</p>	<p>3. Thompson CA, Forum discusses biosimilars, better biologics, <i>Am J Health Syst Pharm.</i> 2011 Dec 1;68(23):2210</p>		<p>2. Owens DR, Landgraf W, Schmidt A, Bretzel RG, Kuhlmann MK, The emergence of biosimilar insulin preparations-a cause for concern?, <i>Diabetes Technol Ther.</i> 2012 Nov;14(11):989-96</p>
<p>4. NCCN Biosimilars White Paper: regulatory, scientific, and patient safety Perspectives, <i>J Natl Compr Canc Netw.</i> 2011 Sep;9 Suppl 4:S1-22</p>	<p>4. Zelenetz AD, Ahmed I, Braud EL, Cross JD, Davenport-Ennis N, Dickinson BD, Goldberg SE, Gottlieb S, Johnson PE, Lyman GH, Markus R, Matulonis UA, Reinke D, Li EC, DeMartino J, Larsen JK, Hoffman JM, NCCN Biosimilars White Paper: regulatory, scientific, and patient safety Perspectives, <i>J Natl Compr Canc Netw.</i> 2011 Sep;9 Suppl 4:S1-22</p>		<p>3. Ebbers HC, Muenzberg M, Schellekens H, The safety of switching between therapeutic proteins, <i>Expert Opin Biol Ther.</i> 2012 Nov;12(11):1473-85</p>
<p>5. Simoens S, Biosimilar medicines and cost-effectiveness, <i>Clinicoecon Outcomes Res.</i> 2011;3:29-36. Epub 2011 Feb 10</p>	<p>5. Locatelli F, Del Vecchio L. Erythropoiesis-stimulating agents in renal medicine, <i>Oncologist.</i> 2011;16 Suppl 3:19-24</p>		<p>4. Gascon P., Presently available biosimilars in hematology-oncology: G-CSF, <i>Target Oncol.</i> 2012 Mar;7 Suppl 1:S29-34. Epub 2012 Jan 19</p>

7. Gitter DM, Informed by the European Union experience: what the United States can anticipate and learn from the European Union's regulatory approach to biosimilars, Seton Hall Law Rev. 2011;41(2):559-92	7. Hirsch BR, Lyman GH Biosimilars: are they ready for primetime in the United States? J Natl Compr Canc Netw. 2011 Aug 1;9(8):934-42; quiz 943		11. Zuñiga L, Calvo B., Biosimilars approval process. Regul Toxicol Pharmacol. 2010 Apr;56(3):374-7
9. McCamish M, Woollett G Worldwide experience with biosimilar development, MABs. 2011 Mar-Apr;3(2):209-17. Epub 2011 Mar 1	8. Dranitsaris G, Amir E, Dorward K, Biosimilars of biological drug therapies: regulatory, clinical and commercial Considerations, Drugs. 2011 Aug 20;71(12):1527-36		15. Krämer I., Pharmacy and pharmacology of biosimilars. J Endocrinol Invest. 2008 May;31(5):479-88
10. Wiatr C. US biosimilar pathway unlikely to be used: developers will opt for a traditional BLA filing, BioDrugs. 2011 Feb 1;25(1):63-7	12. Blackstone EA, Fuhr JP Jr. Biosimilars and innovation: an analysis of the possibility of increased competition in biopharmaceuticals, Future Med Chem. 2010 Nov;2(11):1641-9		17. Nowicki M., Basic facts about biosimilars., Kidney Blood Press Res. 2007;30(5):267-72
11. Jelkmann, Biosimilar epoetins and other "follow-on" biologics: update on the European Experiences, Am J Hematol. 2010 Oct;85(10):771-80	13. Carroll J Payers begin to make plans for coming wave of biosimilars, Manag Care. 2010 Jun;19(6):7-8, 10		19. Wiecek A, Mikhail A., European regulatory guidelines for biosimilars. Nephrol Dial Transplant. 2006 Oct;21 Suppl 5:v17-20
12. Stewart A, Aubrey P, Belsey J, Addressing the health technology assessment of biosimilar pharmaceuticals, Curr Med Res Opin. 2010 Sep;26(9):2119-26	14. Zuñiga L, Calvo, Biosimilars: pharmacovigilance and risk management, Pharmacoepidemiol Drug Saf. 2010 Jul;19(7):661-9		20. Locatelli F, Roger S., Comparative testing and pharmacovigilance of biosimilars. Nephrol Dial Transplant. 2006 Oct;21 Suppl 5:v13-6
13. Carroll J, Payers begin to make plans for coming wave of biosimilars, Manag Care. 2010 Jun;19(6):7-8, 10	18. Reingold SC, Steiner JP, Polman CH, Cohen JA, Freedman MS, Kappos L, Thompson AJ, Wolinsky JS, The challenge of follow-on biologics for treatment of multiple sclerosis, Neurology. 2009 Aug 18;73(7):552-9		
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17. Hughes DA, Biosimilars: evidential standards for health technology assessment, Clin Pharmacol Ther. 2010 Mar;87(3):257-61	24. Mellstedt H, Niederwieser D, Ludwig H., The challenge of biosimilars, Ann Oncol. 2008 Mar;19(3):411-9. Epub 2007 Sep 14		
19. Simoens S, Health economics of market access for biopharmaceuticals and biosimilars, J Med Econ. 2009 Sep;12(3):211-8			

<p>21. Lamarque V, Merle L, Demarez JP, Generics and substitution modalities: proposed methods for the evaluation of equivalence, traceability and pharmacovigilance reporting, Therapie. 2008 Jul-Aug;63(4):301-9. Epub 2008 Oct 22</p>			
<p>22. Roger SD, Goldsmith D, Biosimilars: it's not as simple as cost alone, J Clin Pharm Ther. 2008 Oct;33(5):459-64</p>			
<p>23. Wenzel RG, Biosimilars: illustration of scientific issues in two examples, Am J Health Syst Pharm. 2008 Jul 15;65(14 Suppl 6):S9-15</p>			
<p>24. Gottlieb S, Biosimilars: policy, clinical, and regulatory considerations, Am J Health Syst Pharm. 2008 Jul 15;65(14 Suppl 6):S2-8</p>			
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Appendix 2 Roundtable Attendees

	Name	Position
HTA bodies		
AWMSG	Rob Bracchi	Chairman, New Medicines Group
NICE	Meindert Boysen	Programme Director Technology Appraisals & PASLU & HST
NICE	Neal Maskrey	Consultant Clinical Adviser, Medicines and Prescribing Centre
SMC	Anne Lee	Chief Pharmacist
Regulator		
MHRA	Ian Hudson	CEO
Academics	Martin Buxton	Professor of Health Economics, Health Economics Research Group, Brunel University
	Paul Declerck	Vice-decaan Faculteit Farmaceutische, Wetenschappen, Katholieke Universiteit Leuven
	Mike Drummond	Professor of Health Economics, Centre for Health Economics, University of York
ABPI	Paul Catchpole	Director of Value & Access
	Esteban Herrero	Head of Regulatory Affairs
Amgen	Virginia Acha	Director, Regulatory Affairs - R&D Policy
(Observers only)	Arran Shearer	Director Value, Access and Policy Amgen UK & Ireland
OHE	Jorge Mestre-Ferrandiz	Director of Consulting
	Adrian Towse (Chair)	Director

Appendix 3 Economics of Biosimilars

Development costs for biosimilars have been estimated to be considerably higher than for chemically-processed small molecule generics, because biosimilars need to conduct pre-clinical and clinical studies. Estimates for biosimilars range from US\$100-250 million if plant development is included or US\$20-100 million for non-plant cost (IMS, 2011), increasing to \$US500 million for more complex MAbs (Dranitsaris et al., 2011). Traditional generics' costs are around US\$1-4 million (IMS, 2011). The developmental time for a generic medicine is around three years, whereas this period increases to between six and nine years for a biosimilar (Mellstedt, 2010). The European Commission's pharmaceutical sector inquiry in 2009 discussed the cost and time differences between generics and biosimilars (EC, 2009).

In addition, while the cost barriers to developing a biosimilars manufacturing capability are not prohibitive, the development of biosimilars involves sophisticated technologies and processes, raising the riskiness of the investment (IMS, 2011). The ongoing costs of manufacturing biologics are also usually higher than those of manufacturing chemical products.

We cannot therefore expect similar levels of price discounting for biosimilars as for chemically-processed small molecule generics because of pre-launch development and manufacturing costs. There are three further issues (Chauhan et al., 2008): (i) manufacturers will need to invest in communicating with prescribers as well as pharmacists, as prescribing is by brand name. Originators have established strong relationships with prescribers, key opinion leaders and patients, based on services, clinical development and investment, which biosimilar-only manufacturers may struggle to replicate (IMS, 2011); (ii) physician (and pharmacist) concerns about comparability may need to be addressed in post-launch studies (Blackstone and Fuhr, 2007) – so it would be unrealistic to expect the same rapid speed of adoption as observed with generics following patent expiry of a chemical reference product; (iii) the number of entrants is a key factor driving price competition in the generics market – the more entrants, the greater the competition (Reiffen and Ward, 2005; Grabowski and Kyle, 2007; Saha et al., 2006). Based on the comments above, we can expect fewer biosimilar entrants (relative to generics). However, the potential market size for some of the future biosimilars, such as the MAbs, is higher than for existing biosimilars. *Ceteris paribus*, this may lead to more biosimilar entrants in the future relative to the experience to date.

These factors (cost structures, potential prescriber concerns, entry hurdles and the degree of competition) help to explain why price differentials including discounts (to date) between biosimilars and their originator reference products have not been as substantial as experienced in the traditional, small molecule generic medicine market. Price discounts for biosimilars relative to the originators in Europe between 2007 and 2009 have been estimated at 10%-35% for biosimilars (Rovira et al., 2011, IMS, 2011); and price reductions in the region of 30% (measured from average ex-manufacturer list price) have been observed. Rovira et al. (2011) point out that their analysis is relative to list prices. Biosimilars' discounts relative to the originators' list price may be high. However, originators may already be discounting prices if there is brand competition from other innovators. And originator companies may respond to biosimilar discounts by offering larger discounts to the most price-sensitive, knowledgeable and high-volume buyers, and so is more likely to be seen in the hospital

segment. For example, in Germany, Eprex lowered its price by 18% during 2008 (after approximately one year of competition from biosimilars), while biosimilar prices declined 9% (Blackstone and Fuhr, 2010).

There is not a clear pattern regarding the magnitude and evolution of prices and discounts across Europe and across different therapeutic areas (Rovira et al., 2011; IMS, 2011). Germany and France account for half the EU biosimilars market by value with a 34% and 17% share respectively, although uptake in Spain and the UK has started to increase (IMS, 2011). Biosimilars penetration has been higher for the G-CSFs and for EPOs as it has been argued that in these two classes there is general acceptance of high similarity between biosimilars and original brands and established experience of their use in Europe (IMS, 2011). Three biosimilars competed in Germany against the branded reference EPO drug Eprex. After one year, by December 2008, the combined market share in units of the three biosimilars was approximately 50% and their prices were approximately 25% less than the pioneer drugs (Blackstone and Fuhr, 2010). This relatively large market share for biosimilars may be due to several generic companies producing biosimilar medicines being based in Germany (Blackstone and Fuhr, 2010).

Looking forward to the evolution of biosimilars in the area of oncology and anti-TNFs, O'Neill et al. (2013) project less intense competition relative to the experience seen to date with the HGH, GCSF and EPOs markets.

Appendix 4 Regulatory Processes in Other Non-EU Regions

In the US, the Public Health Service Act (PHS Act) was modified to set up the details of the abbreviated approval pathway created by the Biologics Price Competition and Innovation Act of 2009 (BPCA) for products that are confirmed to be “biosimilar” to or “interchangeable” with an FDA-licensed biologic. This took effect in March 2010. Under this Act, if a product is highly similar to an existing approved biologic then it is considered as a biosimilar. It allows only minor differences in clinically inactive components in terms of safety, purity and potency. In February 2012, the FDA issued three draft guidance documents on biosimilar product development, which can help the industry to produce biosimilars of approved biologics (Grant Thornton, 2013).

In early October 2010 Teva filed for approval of Neutroval in the US using the full Biologic License Application (BLA) route with supporting clinical data, not the abbreviated BCPA route. Teva has indicated it will do the same with other biosimilar products²³. Neutroval contains a related drug substance to Amgen’s Neupogen (filgrastim). The FDA required a unique INN for this product, in order to minimise medication errors and facilitate safety monitoring; however the FDA also said that it intends to evaluate the need for distinct nonproprietary names on a product-specific basis (Busch, 2012). In Europe, Neutroval was approved in September 2008 under the name TevaGrastim (Wiatr, 2011). At present, there is only one product on the US market that could potentially fit the BCPA description – Omnitrope (somatropin/HGH) which was launched by Sandoz in 2007 under a special ruling (IMS, 2011).

The Therapeutic Goods Administration (TGA) in Australia has followed the EMA approach to approving biosimilars, adopting the European guidelines (TGA, 2013). The TGA will approach each submission on a case-by-case basis, and manufacturers are advised to seek pre-submission meetings in order to clarify the information required to gain approval. Omnitrope has been available in Australia since 2006, before the new approach was set up (Roger, 2010; Dranitsaris et al., 2011).

The Canadian drug regulator, Health Canada, has issued draft guidelines for approving Subsequent Entry Biologics, or biosimilars. The guidelines were subject to a consultation among the different stakeholders and a summary report from the consultation has been issued. The agency plans to issue additional guidance covering specific product classes (Roger, 2010; Dranitsaris et al., 2011). Under the regulatory term Subsequent Entry Biologic, a biosimilar somatropin, a copy of Genotropin, has been approved by Health Canada (Blackstone and Fuhr, 2010).

The Ministry of Health, Labour and Wealth in Japan published in 2008 a guideline to pave the way for a biosimilar regulatory pathway, “Guidelines for the Quality, Safety and Efficacy Assurance of Follow-on Biologics”, based on that in place in Europe (Roger, 2010; Dranitsaris et al., 2011). These guidelines were updated in 2009. A filing in Japan must use a Japanese “Precedent Biotechnology Drug” as the reference. Sandoz’ somatropin was the first Japanese biosimilar approved in 2009, before the current guidelines were implemented. The first biosimilar epoetin (epoetin kappa) has

²³ Partly because of this, in the US, biosimilars are often referred to as “follow-on biologics”.

been ratified according to the new Japanese guidelines as a follow-on product to epoetin alfa (Blackstone and Fuhr, 2010), and currently there are four biosimilars approved, in addition to this epoetin alfa – two filgrastims and one somatropin (GABI, 2013).

Many emerging markets, including India, Brazil and Mexico, have developed or are in the process of developing their own regulatory pathways to manage the approval of biosimilars. It has been argued that “in China and India, the approval pathway for versions of biological drugs is not as thorough as in Europe, and a wide range of agents have already been launched or are under development. However, such agents should not be considered as ‘biosimilars’ to reference products because they have not been adequately tested using rigorous criteria such as those developed by the EMA” (Dranitsaris et al., 2011, page 1533). In South America²⁴, Brazil has led the development of biosimilar regulation, with two distinct pathways, one for more complex molecules such as MAbs and a less rigorous path for simpler molecules such as pegylated interferon and low molecular weight heparin. Other countries have been slower to respond (Azevedo et al., 2012). It is our understanding that the WHO SBP Guidelines (WHO, 2009) have been the reference for the development of guidelines in many emerging markets.

²⁴ For more information on Latin America, see also Ferreira et al. (2013).

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