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**Literature Review of International Biosimilar Medicines:
Update June – August 2017**

Literature Review of International Biosimilar Medicines: Update June 2017 – August 2017

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Introduction

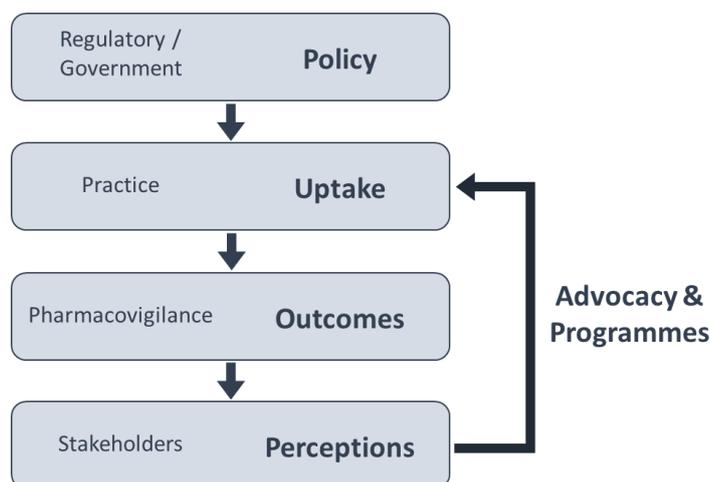
This report provides an update to the comprehensive literature search previously conducted that examined all international and Australian clinical, academic and policy journals and media articles or sources in relation to biosimilar medicines for the purpose of providing evidence which may inform policy development and the communication activities of the Australian Government's Biosimilar Awareness Initiative (the Initiative).

The broad objectives are to provide a review of the literature pertaining to:

- current international policies on biosimilar medicines;
- status of biosimilar use and substitution internationally;
- any current programmes aimed at increasing the uptake or confidence in biosimilars (and an evaluation of their success);
- biosimilar uptake and substitution; and
- impact of biosimilars (if any) on adverse events and health outcomes.

The five stated broad objectives for the review relate to four stages that influence biosimilar use; that is, the national and international regulatory environment that is the foundational determinant of biosimilar availability and associated switching and substitution (Policy); the subsequent uptake of biosimilars by prescribers, pharmacists and patients (Uptake); outcomes resulting from the use of biosimilars outside of the clinical development pathway (Outcomes); and finally the stakeholder perceptions that influence uptake, including the factors that modify these perceptions such as advocacy and associated programmes (Perceptions).

Figure 1: Stages influencing biosimilar uptake and use



In the context of this review it is critical to appreciate that the fundamental central factor to each of these areas is the potential uncertainty that exists in evidence regarding substitution, switching and extrapolation of indication, which is unique to the consideration of biosimilar medicines. This potential uncertainty originates from the highly complex nature of these medicines and the clinical development pathway of biosimilar medicines that extends from initial laboratory-based characterisation (protein structure, pharmacokinetics, etc.) through to the design and conduct of phase III clinical trials to provide evidence of similarity in clinical safety and efficacy in specific patient populations. The considerations involved in each

of these steps are significantly different to those associated with traditional small molecule drugs with which governments, regulators, prescribers, pharmacists and patients are well accustomed. In reflection of this, the following central themes have been identified:

1. Determining Access and Subsidisation: Regulatory, Government and Healthcare Provider Considerations of Biosimilar Medicines
2. Biosimilar Medicine Uptake: Current Practice of Prescribers, Pharmacists and Patients
3. Adverse Events and Health Outcomes of Biosimilar Medicines (Pharmacovigilance): Impact of Substitution, Switching and Extrapolation of Indication
4. Evaluating and Improving Stakeholder Biosimilar Awareness, Confidence, Attitudes and Acceptance of Biosimilar Medicine

Overview of the Published Biosimilar Literature

This report includes literature published between 1 June 2017 and 31 August 2017.

Given the nature of the publications on biosimilars, it is not possible to differentiate articles of an educational nature or those pertaining specifically to biosimilar development from those that specifically seek to contribute new knowledge to the topic, and as such are pertinent to this review, through the use of specific search terms or exclusion criteria. Therefore, filtering of publications relevant to this review through hand-searching was necessary.

Analysis of these manuscripts identifies the following broad types of contributions:

- Education pieces and literature reviews
- Commentaries and individual opinion pieces
- Preclinical characterisation of potential biosimilar medicines
- Technical/methodological development
- Clinical trials of potential biosimilar medicines
- Investigator-initiated studies and case series

Consistent with the observations of the prior review, within the time period encompassed by this update there has continued to be a significant number of papers published that were of an educational or review nature. As discussed previously, these manuscripts have not specifically sought to extend or expand the knowledge base in this area but instead restate what is already known or identified as uncertainties in order to inform the reader of these issues. Some manuscripts provide a broad, relatively superficial, overview of biosimilar medicines. Other manuscripts provide an in-depth review of specific biosimilar medicines reporting only on previously published data but not contributing new information. In the context of this review, these papers do not contribute meaningfully to the specific aims of the Initiative; however, they play an important role in propagating the general understanding within the broader scientific and medical communities. A list of manuscripts of this nature published during the period encompassed by this update is provided in Appendix 1.

Within this quarter there has again been a significant number of manuscripts published that focus upon fundamental and technological issues relating to the production and characterisation of biological agents, including the statistical approaches to these assessments. The regulatory pathway for biosimilar

medicines is built upon the rigorous and extensive characterisation of the physicochemical (e.g. amino acid sequence, glycosylation pattern) and pharmacological properties (e.g. target binding) of the potential biosimilar medicine in comparison with the reference product. Due to the highly detailed and technical nature, the specific content of which is outside of the scope of the communication aims of the Initiative, these manuscripts will not be discussed in greater detail in this review. A list of manuscripts of this nature published during the period encompassed by this update is provided in Appendix 2. However, the results of this extensive characterisation and comparison process provides the critical foundation upon which potential biosimilar medicines can then be subjected to further clinical evaluation in the phase I and phase III trials that are reported upon in Theme 1 of these reviews.

THEME 1: Determining Access and Subsidisation: Regulatory, Government and Healthcare Provider Considerations of Biosimilar Medicines

In the development and regulatory evaluation process of potential biosimilar medicines, compounds that demonstrate appropriate results in the extensive physicochemical and pharmacological characterisation are then subjected to clinical evaluation in phase I studies to compare their pharmacokinetic (PK) characteristics with those of the reference product. As these studies are specifically designed to assess pharmacokinetic endpoints these studies are typically conducted in healthy volunteers but may be conducted in patients depending upon a range of factors such as the potential risks associated with the use of the agent.

During the current update period, three phase I pharmacokinetic studies comparing a potential biosimilar medicine with a reference product were reported. In addition, a phase III trial incorporating a comparative pharmacokinetic component was published. In each of the trials reported, the potential biosimilar met the pre-specified acceptance criteria for the relevant pharmacokinetic/pharmacodynamic parameter endpoints. A summary of the results of these studies are presented in the table below (Table 1). An additional two trials were conducted as follow-on studies to a previously conducted phase I trial that established the similarity of a single course of CT-P10 and originator rituximab; these follow-on studies are also summarised below.

Table 1: Summary of phase I pharmacokinetic studies of potential biosimilar medicines

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
Adalimumab						
SB5 (Samsung Bioepis Co Ltd)	US and EU Humira 40mg	Randomised, single-blind, single dose, three arm, parallel group study (1:1:1)	Healthy volunteers (n=189)	90% CI for the ratio of treatment means for area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_{last}), area-under-the-curve from time zero extrapolated to infinite time (AUC_{inf}) and maximal plasma concentration (C_{max}) were within the pre-specified limits of 80-125% for the comparisons of SB5 with US Humira and SB5 with EU Humira, as well as for US and EU Humira.	Twelve subjects were ADA positive at baseline (n=5 SB5; n=2 EU Humira; n=5 US Humira). ADA were detected in 185/189 subjects after treatment administration, with 68.3%, 73.0% and 65.1% of patients in the SB5, EU Humira and US Humira groups, respectively, exhibiting positive ADAs on Day 15 and 96.8%, 93.7% and 98.4% of patients in the SB5, EU Humira and US Humira groups, respectively, exhibiting positive ADAs on Day 71. The incidence of ADA development was not significantly different between the treatments.	[1]
Bevacizumab						
BI695502 (Boehringer Ingelheim)	US and EU Avastin 1mg/kg	Randomised, single-blind, single dose, three-arm, parallel group study (1:1:1)	Healthy male volunteers (n=90)	90% CI for the ratio of treatment means for area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_{0-tz}), area-under-the-curve from time zero extrapolated to infinite time ($AUC_{0-\infty}$) and maximal plasma concentration (C_{max}) were within the pre-specified limits of 80-125% for the comparisons of BI695502 with US Avastin and BI695502 with EU Avastin, as well as for US and EU Avastin.	Not reported.	[2]

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
Rituximab						
GP2013 (Sandoz)	Rituxan (US) and MabThera (EU) 1000mg	Randomised, double-blind, two dose, three-arm, parallel group study (1:1:2)	Adult rheumatoid arthritis patients (n=312)	<p>90% CI for the ratio of treatment means for area-under-the-curve from time zero extrapolated to infinite time ($AUC_{0-\infty}$) and maximal plasma concentration (C_{max}) were within the pre-specified limits of 80-125% for the comparisons of GP2013 with Rituxan and GP2013 with MabThera, as well as for Rituxan vs MabThera.</p> <p>Area-under-the-curve from time zero to the last quantifiable concentration was not assessed.</p> <p>90% CI for the ratio of treatment means for peripheral CD19 positive B-cell count relative to baseline up to the second infusion on Day 15 (AUE_{CO-14d}) were within the pre-specified limits of 80-125% for the comparisons of GP2013 with Rituxan and GP2013 with MabThera, as well as for Rituxan vs MabThera.</p>	The rate of binding ADAs was 16.5% in the GP2013 group compared with 15.1% in originator rituximab treated patients. Five patients in the GP2013 arm and one patient in the originator rituximab arm exhibited neutralising ADAs. No differences in immunogenicity profiles between the treatments were noted.	[3]
CT-P10 (Celltrion, South Korea)	Rituxan 375mg/m ²	Randomised, double-blind, chronic dosing, two-arm, parallel group study (1:1)	Adult advanced-stage follicular lymphoma patients (n=121)	<p>90% CI for the ratio of treatment means for area-under-the-curve over the dosing interval (AUC_t) and steady-state maximal plasma concentration (C_{maxSS}) were within the pre-specified limits of 80-125%.</p> <p>B-cell kinetics over the 24 weeks of the induction period were similar in the two treatment groups.</p>	Five patients (n=3 CT-P10, n= 2 rituximab) had at least one positive ADA result at post-treatment visits during the induction period. All patients with an ADA positive result at post-treatment visits had positive results in neutralising antibody tests, with the exception of one patient in the CT-P10 treatment group.	[4]

- ❖ Yoo et al, 2017: Efficacy, Safety and Pharmacokinetics of Up to Two Courses of the Rituximab Biosimilar CT-P10 Versus Innovator Rituximab in Patients with Rheumatoid Arthritis: Results up to Week 72 of a Phase I Randomized Controlled Trial [5]

This study is a follow-on of a previously conducted phase I study that examined the similarity of biosimilar rituximab CT-P10 and originator rituximab in patients with rheumatoid arthritis. In the phase I study, 154 patients were randomised 2:1 to receive 1000mg CT-P10 (n=103) or 1000mg originator rituximab (n=51) at weeks 0 and 2 and followed for 24 weeks and established similarity of the two treatments with respect to pharmacokinetics, efficacy, immunogenicity and safety. The present study recruited a sub-group of patients (n=83) from the original phase I trial who required retreatment between weeks 24 and 48 (biosimilar rituximab n=60; originator rituximab n=23). Patients were followed for 24 weeks after the retreatment and were evaluated for comparative pharmacokinetics, efficacy, immunogenicity and safety. Whilst no formal comparative analysis of pharmacokinetics was conducted, parameters were comparable between treatments. Efficacy, safety and other clinical data were also similar between CT-P10 and originator infliximab.

- ❖ Park et al, 2017: Efficacy and Safety of Switching from Innovator Rituximab to Biosimilar CT-P10 Compared with Continued Treatment with CT-P10: Results of a 56-Week Open-Label Study in Patients with Rheumatoid Arthritis [6]

This study reports an open-label extension study of the above-mentioned phase I and follow-on clinical trials and examined the safety and efficacy of CT-P10 in patients who had received CT-P10 from the outset (i.e. maintenance group) and in patients who had received originator rituximab in the previous study/ies and were switched to CT-P10 in this open-label extension (i.e. switch group). A total of 87 patients were enrolled in the study, of which 38 patients comprised the maintenance group and 20 patients comprised the switch group; the remaining patients had stable disease and did not require ongoing treatment. The study demonstrated comparable efficacy and safety profiles between the two groups and concluded that *“switching from RTX [originator rituximab] to CTP10 had no notable impact on the efficacy or safety of treatment in this population of patients with RA [rheumatoid arthritis]”*.

Potential biosimilar medicines that demonstrate appropriate pharmacokinetic parameters in phase I studies are then subject to phase III clinical trials to evaluate efficacy and safety outcomes in comparison with the reference product. Within the update period there were six reports.

- ❖ Bae et al, 2017: A phase III, multicentre, randomised, double-blind, active-controlled, parallel-group trial comparing safety and efficacy of HD203, with innovator etanercept, in combination with methotrexate, in patients with rheumatoid arthritis: the HERA study [7]

This phase III, multicentre, randomised, active-controlled, parallel-group aimed to evaluate the equivalence in efficacy and compare the safety of a potential etanercept biosimilar, HD203 (Hanwha Chemical Biologics), with originator etanercept (reference etanercept) when used in combination with methotrexate in patients with rheumatoid arthritis. Patients were randomly assigned to receive HD203 25mg or reference etanercept 25mg (1:1), administered subcutaneously (SC) twice weekly for 48 weeks. The primary end-point was the proportion of patients achieving a 20% improvement from baseline in the American College of Rheumatology core set of measurements (ACR20) at week 24. Secondary end points included ACR20 at weeks 12 and 48; ACR50 and ACR70 at weeks 12, 24 and 48 and change in Disease Activity Score 28 (DAS28) and DAS28 remission. Therapeutic equivalence of HD203 and reference etanercept was specified as containment of the 95% confidence interval of the difference in ACR20 at 24 weeks between HD203 and reference etanercept entirely within the equivalence margin of $\pm 20\%$.

A total of 294 ethnically Korean participants were randomised to HD203 or ETN (n=147 each) with 240 completing the study (120 in both groups). With regards to the primary end-point, there were no significant differences in the proportion of patients achieving ACR20 at week 24 with HD203 as compared with reference etanercept (Per-Protocol Set: 83.48% vs 81.36%, Full analysis set: 79.10% vs 75.56%, respectively). The 95% CI of the difference in ACR20 at 24 weeks between HD203 and ETN was 2.12% (95% CI -7.65% to 11.89%) and 3.55% (95% CI -6.45% to 13.55%) for the per-protocol-set and full analysis set respectively which was within the predefined equivalence criteria. There were no statistically significant differences in the proportion of patients achieving ACR20 or ACR70 responses at any time point. However, the proportion of patients who achieved an ACR50 response was significantly higher in the HD203 group than the reference etanercept group at week 24 and week 48 in the per-protocol set (treatment difference; week 24 = 12.68, 95%CI:0.15% to 25.20%; week 48 =13.72%, 95%CI:1.04% to 26.40). The authors note that this study was not powered for this secondary end-point and that *“because ACR20 and ACR50 response groups are not mutually exclusive, there is a greater chance of a type I error when analysing ACR50 and ACR70 response rates at the same time as analysing ACR20 rates”*. Overall, 76.9% of patients in the HD203 group and 78.1% of patients in the reference etanercept group experienced an adverse event of which less than 40% were considered to be drug related (34.7% HD203, 37.0% reference etanercept). There were no major differences in adverse events identified between groups with infection the most common (37.4% HD203 v 41.1% reference etanercept). Anti-drug antibodies developed in eight participants (3 neutralising) in the HD203 arm and three (one neutralising) in the reference etanercept arm over the 48 weeks. Details regarding the timing and duration of anti-drug antibody positivity are not provided.

- ❖ Cohen et al, 2017: Efficacy and safety of the biosimilar ABP 501 compared with adalimumab in patients with moderate to severe rheumatoid arthritis: A randomised, double-blind, phase III equivalence study [8]

A randomised, double-blind, active comparator-controlled equivalence study designed to demonstrate clinical similarity between ABP 501 (Amgen) and reference adalimumab (randomised 1:1) in adalimumab-naive adult patients with moderate to severe RA who had an inadequate response to MTX. Participants were required to have active RA (≥ 6 swollen joints and ≥ 6 tender joints) and have received methotrexate for at least 12 consecutive weeks with a stable dose of 7.5–25mg/week for at least 8 weeks. Participants were excluded if they had used two or more bDMARDs or previous exposure to adalimumab. The primary efficacy endpoint was the risk ratio of achieving a 20% improvement from baseline in the American College of Rheumatology core set of measurements (ACR20) at week 24 with equivalence defined by comparing the 2-sided 90% confidence interval (CI) to the predefined equivalence margin of 0.738-1.355. Secondary efficacy endpoints included assessments of Disease Activity Score 28-joint count-CRP (DAS28-CRP), the risk ratio for ACR20, ACR50 and ACR70 responses. Safety endpoints included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and incidence of anti-drug antibodies (assessed at baseline and weeks 4, 12 and 26).

A total of 526 patients were randomised (ABP 501 =264; reference adalimumab=262) of whom 494 (93.9%) completed the study (ABP 501=243, Reference adalimumab=251). With regards to the primary endpoint, 74.6% (194/260) of participants in the ABP 501 arm and 72.4% (189/261) of participants in the reference adalimumab arm achieved an ACR20 response resulting in a risk ratio of 1.039 (0.954, 1.133) which is within the predefined equivalence margin of 0.738-1.355. The secondary endpoint of the percentage of participants achieving an ACR20, ACR50 and ACR70 were considered comparable at all time points (eg. ACR20 at week 2: ABP 501=35.4%, reference adalimumab=24.5%; ACR20 at week 8: ABP 501=63.5%, reference adalimumab=62.5%). The percentage of participants reporting TEAEs and SAEs were similar between those in the ABP 501 and reference adalimumab arms, 50.0% versus 54.6% and 3.8% versus 5.0%, respectively. At baseline 11 participants tested positive to anti-drug antibodies (ABP 501=5, reference adalimumab=6). A total of 201 (38.2%) participants tested positive for binding antibodies (ABP 501=101, 38.3%; reference adalimumab=100, 38.2%) of which 53 (10.1%) were neutralising (ABP 501=24, 9.1%; reference adalimumab=29, 11.1%). The authors conclude that *“Data from this study indicate that the clinical efficacy, safety and immunogenicity of ABP 501 are similar to that of adalimumab in patients with moderate to severe RA.”*

- ❖ Jamshidi et al, 2017: A phase III, randomized, two-armed, double-blind, parallel, active controlled, and non-inferiority clinical trial to compare efficacy and safety of biosimilar adalimumab (CinnoRA) to the reference product (Humira) in patients with active rheumatoid arthritis [9]

In this randomized, double-blind, non-inferiority trial, a total of 136 patients with active RA were randomized in a 1:1 ratio to receive 40-mg subcutaneous injections of either biosimilar adalimumab (CinnoRA®, CinnaGen Co., Iran) or the reference product (Humira®, AbbVie Inc., USA) every other week along with methotrexate (15 mg/week), folic acid (1 mg/day), and prednisolone (7.5 mg/day) over a period of 24 weeks. The primary end-point was the percent of patients achieving good and moderate disease activity score (DAS)-based EULAR response. Secondary end-points included the proportion of patients achieving ACR criteria for 20% (ACR20), 50% (ACR50), and 70% (ACR70) improvements after 24 weeks of treatment.

Based on the per-protocol population (64 patients in each treatment group), non-inferiority of CinnoRA compared to Humira was demonstrated for the primary end-point, with 42% and 38% of patients at week 12, and 55% and 52% of patients at week 24 fulfilling moderate and good DAS-based EULAR response criteria after administration of CinnoRA and Humira respectively. No statistically significant differences were observed between the treatment arms at either the 12- or 24-week timepoints for any of the secondary end-points. The authors conclude that “*CinnoRA®*, as a biosimilar adalimumab, was shown to be non-inferior to Humira® in the treatment of adult patients with active RA”.

Commentary

Statistical power for this study was based on a clinically relevant non-inferiority margin of $\delta = -0.18$ with 90% power and a 0.025 one-sided significance level, and thus the sample size selected was deemed sufficient to detect a difference in the primary end-point. However, it should be noted that the power to detect a meaningful difference in the secondary end-points is not clear.

It should also be noted that ‘biogenerics’ (the terminology used in Iran) approved in Iran might not have been authorized following the same strict regulatory process required for approval of biosimilars in the EU, and thus it is not clear if CinnoRA meets the standard requirements for classification of a biosimilar.

- ❖ Jurczak et al, 2017: Rituximab biosimilar and reference rituximab in patients with previously untreated advanced follicular lymphoma (ASSIST-FL): primary results from a confirmatory phase 3, double-blind, randomised, controlled study [10]

This manuscript reports the outcomes of a phase 3 randomised, active-controlled, double-blind, multicentre, parallel-group confirmatory study of a potential biosimilar of rituximab (GP2013) or originator rituximab (MabThera) in adults with previously untreated, advanced stage follicular lymphoma. Participants received eight cycles of rituximab (GP2013 or MabThera, randomised 1:1) in combination with cyclophosphamide, vincristine, and prednisone (CVP) followed by rituximab monotherapy maintenance in responders for up to 2 years. The primary endpoint was comparability in overall response, defined as patients whose best overall disease response was either complete or partial response during the combination treatment phase, with equivalence concluded if the entire 95% confidence interval was within a margin of -12% to 12% . Secondary end-points included descriptive assessments of best overall response of complete response, partial response, stable disease, and progressive disease during the combination treatment period, and progression-free survival and overall survival.

A total of 629 participants were randomly assigned to GP2013 (n=314) or reference rituximab (n=315). With regards to the primary end-point, overall response during the combination phase was achieved in 271 (87%) participants in GP2013 arm and 274 (88%) participants in reference rituximab arm (per-protocol set) resulting in a difference of -0.40% (95% CI: -5.94 to 5.14) which was within the predefined equivalence interval of -12% to 12% . The descriptive secondary end-point of progression-free survival events were reported in 94 (30%) participants in the GP2013 arm as compared with 76 (24%) in the reference rituximab arm (hazard ratio = 1.31, 95% CI 0.97–1.78) but the authors note that the study “*was not powered to show similarity in progression-free survival or overall survival, and given the high proportion of censored patients and the decentralised assessment, progression-free survival and overall survival results should be*

interpreted with caution". The safety profiles of GP2013 and reference rituximab during the combination phase were considered similar with 289/312 (93%) of participants in GP2013 arm experiencing an adverse event as compared with 288/315 (91%) of those in the reference rituximab arm and resulted in 23 (7%) and 22 (7%) discontinuations respectively. Anti-drug antibodies were detected in five participants in the GP2013 arm three in the reference rituximab arm.

Overall the authors conclude that *"the results of this study confirm the therapeutic equivalence of the biosimilar GP2013 and reference rituximab in this clinical trial in patients with previously untreated, advanced stage follicular lymphoma"*.

- ❖ Kim et al, 2017: Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with rituximab in patients with previously untreated advanced-stage follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial [4]

This manuscript reports on an ongoing, randomised, double-blind, parallel-group, active-controlled study of a potential rituximab biosimilar (CT-P10) in comparison to reference rituximab (Rituxan) in adults with advanced stage follicular lymphoma. Efficacy assessment was based on data from a total of 134 participants that received eight cycles of rituximab (n=66 CT-P10; n=68 originator) in combination with cyclophosphamide, vincristine, and prednisone (CVP). The primary end-point was the proportion of patients achieving an overall response over the 24-week induction period. Overall response was defined as patients who had complete response, unconfirmed complete response or partial response.

Non-inferiority of CT-P10 was demonstrated with respect to the primary efficacy endpoint, with 97% of patients in the CT-P10 treatment group and 93% of patients in the rituximab treatment group achieving an overall response, as judged by a central independent review committee. The resulting difference in the proportion of patients attaining an overall response was 4.3% (one-sided 97.5% CI: -4.25%) which was within the predefined non-inferiority margin of -7%. No notable differences were observed in the treatment groups with respect to safety or immunogenicity assessments.

Based on the findings of this study, the authors indicated that *"CT-P10 showed non-inferiority of efficacy, equivalence of pharmacokinetics, and comparable pharmacodynamics to rituximab up to week 24 in patients with previously untreated advanced-stage follicular lymphoma"*. This phase 3 trial is ongoing, and longer-term data for patients with advanced-stage follicular lymphoma on maintenance therapy will be available in the future.

- ❖ Stebbing et al, 2017: CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial [11]

This randomised, double-blind, active-controlled, phase 3 trial in women with histologically confirmed and newly diagnosed clinical stage I–IIIa, operable, HER2-positive breast adenocarcinoma to investigate the equivalence of a potential trastuzumab biosimilar (CT-P6, Celltrion) as compared with reference trastuzumab. Participants were randomised 1:1 to receive neoadjuvant CT-P6 or reference trastuzumab intravenously in conjunction with neoadjuvant docetaxel or FEC (fluorouracil, epirubicin and cyclophosphamide). Surgery was performed within 3–6 weeks of the final neoadjuvant dose and was followed by an adjuvant treatment period of up to 1 year. This manuscript reports results available at completion of the neoadjuvant phase. The primary end-point was pathological complete response, defined

as the absence of invasive tumour cells in the breast and axillary lymph nodes, at the time of definitive surgery. Equivalence was defined as containment of the 95% confidence interval for the treatment difference within the interval of -0.15 to 0.15 . Secondary endpoints included overall response and breast conservation. Safety endpoints were the prevalence and severity of adverse events, laboratory measures, cardiotoxicity and immunogenicity. Pharmacokinetic end-points included trastuzumab concentration 15 minutes after each infusion and trough concentrations prior to cycles 1–7 and at the end of cycle 8. The per-protocol population included 504 patients (CT-P6=248, reference trastuzumab = 256). With regards to the primary end-point, at the time of surgery 46.8% (95%CI:40.4–53.2) of participants in the CT-P6 achieved a pathological complete response as compared with 50.4% (95% CI:44.1–56.7) for the reference. The resulting estimated difference in pathological complete response proportion between the two groups was -0.04 (95% CI -0.12 to 0.05), which was within the prespecified equivalence margin of -0.15 to 0.15 . The risk ratio estimate for the pathological complete response proportion in the per-protocol population was 0.93 (95% CI 0.78–1.11) which was within the prespecified equivalence margin of 0.74 to 1.35. Within the CT-P6 arm, 6% of participants experienced grade 3 or worse treatment-related adverse events as compared with 8% the reference trastuzumab arm. Treatment-emergent adverse events due to heart failure were reported in five patients (2%) in the CT-P6 arm and three patients (1%) in the reference trastuzumab arm. All post-infusion antidrug antibody tests were negative. There were no notable differences in the pharmacokinetic end-points between groups at any cycle. The authors conclude that this study “*study showed therapeutic equivalence of biosimilar CT-P6 to reference trastuzumab in patients with early stage, operable, HER2-positive breast cancer*”

Once biosimilarity of the new product against the reference has been established through phase I and III trials, it is the national and international regulatory environment that is the foundational determinant of use. Within this quarterly update period, three publications were identified that related to this topic which examined the economic impact of the introduction of a biosimilar within a local region; while these papers do not specifically relate to policy, the cost of treatment is a strong determinate informing policy relating to biosimilar access and use.

- ❖ Kanters et al, 2017: Adoption of Biosimilar Infliximab for Rheumatoid Arthritis, Ankylosing Spondylitis, and Inflammatory Bowel Diseases in the EU5: A Budget Impact Analysis Using a Delphi Panel [12]

This Hospira-funded study examined the budget impact of adopting biosimilar infliximab in the current therapeutic landscape for rheumatoid arthritis, ankylosing spondylitis, Crohn’s disease and ulcerative colitis in the UK, Germany, France, Spain and Italy, using assumptions derived from a Delphi survey of expert clinicians. It is important to note that the predictions of this budget impact study not only accounted for the introduction of biosimilar infliximab, but took into account the overall cost of treatment of the rheumatological and gastroenterological conditions in the context of the availability of biologic alternatives such as vedolizumab. The model utilised current externally available epidemiological, market share and cost data and compared a base-case scenario of a “world with biosimilar infliximab” to a “world without biosimilar infliximab”. In the former, existing patients could stay on their initial biologic therapy or switch to biosimilar infliximab and treatment naïve patients could be allocated to any of the available biological drugs. In the latter, treatment naïve and existing patients were allocated to the currently available

biological drugs according to their market shares. Further secondary scenarios examining the impact of varying price discount for biosimilar infliximab and the introduction of alternate biologics (vedolizumab, biosimilar etanercept, biosimilar rituximab) within the 5 countries were also explored.

With respect to the base-case scenario, the introduction of biosimilar infliximab was projected to result in budget savings for rheumatology (€0.7-3.5 million) after 5 years in all countries except France where a budget increase of €1.3 million would be expected. For gastroenterology, budget savings of €2.7-3.9 million would be expected after 5 years in Spain and Italy, whereas increases of €0.9-65 million were predicted for France, Italy and Germany. In these scenarios, the introduction of biosimilar infliximab was projected to decrease the market share of reference infliximab and also decrease the market shares of other biologics (etanercept and adalimumab); as the total costs for biosimilar infliximab were higher than total costs for etanercept and adalimumab, the budget was therefore predicted to increase. Furthermore, in the UK and Germany the recent availability of vedolizumab was predicted to result in increased budget due to an increase in the market share of vedolizumab, despite its higher cost.

Varying the price discount of biosimilar infliximab was projected to result in substantially higher costs savings in Year 5, with budget decreases of €22-81 million for rheumatology and €12-247 million for gastroenterology with a price discount of 50% of reference infliximab, and €66-289 million for rheumatology and €24-339 million for gastroenterology with a price discount of 75% of reference infliximab. Similarly, the concurrent introduction of biosimilar etanercept or biosimilar rituximab was found to result in cost savings of up to €20 million and €12 million respectively.

Commentary

Whilst the intention of this study was to examine the budget impact of the introduction of biosimilar infliximab, it should be noted that the scenarios explored this within the current therapeutic landscape of the listed conditions within each of the countries; this includes the recent availability of higher-priced vedolizumab within the UK and Germany. As such, the overall projected budgets within the scenarios examined do not only reflect the impact of the introduction of biosimilar infliximab but rather this in combination with a more complex therapeutic environment.

- ❖ McBride et al, 2017: Cost-efficiency analyses for the US of biosimilar filgrastim-sndz, reference filgrastim, pegfilgrastim, and pegfilgrastim with on-body injector in the prophylaxis of chemotherapy-induced (febrile) neutropenia [13]

This cost-efficiency analysis, sponsored by Sandoz Inc., examined the comparative drug acquisition and administration costs of the recently approved biosimilar filgrastim (Sandoz, filgrastim-sndz) with reference filgrastim, pegfilgrastim and a pegfilgrastim injection device for chemotherapy-induced febrile neutropenia prophylaxis within the US. The model utilised 2016 US drug costs and was based on administration of filgrastim (biosimilar and originator) 300 µg for 1-14 days and pegfilgrastim (single injection or single injection via injection device) 6mg. Four scenarios were considered which explored (1) cost of medication only, (2) self-administration of filgrastim or pegfilgrastim by patient and administration of pegfilgrastim-injector by staff on the day of chemotherapy completion, (3) healthcare provider administers first dose of filgrastim (biosimilar and reference) or pegfilgrastim with all subsequent filgrastim doses self-administered by patient, (4) all doses administered by healthcare provider.

Based on drug acquisition costs alone (scenario #1), biosimilar filgrastim was expected to result in a \$65 (1 day of treatment) to \$916 (14 days of treatment) cost reduction per patient, compared to treatment with originator filgrastim. When considering scenario #2 relating to self-administration, relative to pegfilgrastim biosimilar filgrastim results in cost savings per patient ranging from \$834, if 14 days biosimilar filgrastim are administered, to \$3692 if only a single day of biosimilar filgrastim is administered. In the scenario where all doses are administered by a healthcare provider (#4), biosimilar filgrastim is calculated to result in a saving over the pegfilgrastim-injector ranging from \$267 if 14 days of biosimilar filgrastim is administered to \$3649 if only a single day of biosimilar filgrastim is required. The authors concluded that the analysis “shows consistently that filgrastim-sndz is the least expensive and, therefore, economically the most cost-efficient method of prophylaxis for cancer patients at risk for developing (febrile) neutropenia”.

❖ Kawalec et al, 2017: Pricing and Reimbursement of Biosimilars in Central and Eastern European Countries [14]

This study reviewed the pricing and reimbursement status of currently approved biosimilars in Central and Eastern European countries. Experts from participating countries, including Bulgaria, Czech Republic, Croatia, Estonia, Hungary, Latvia, Lithuania, Poland, Slovakia, and Romania completed a questionnaire based survey that included questions on the pricing and reimbursement of biologics in a given country, as well as providing data on the reimbursement status and level for each individual biologic drug. Data on reimbursement costs of biologic drugs in the years 2014 and 2015 were also collected along with the corresponding data on the total pharmaceutical and public health care budgets.

The reimbursement criteria for biosimilars were generally similar to those for other generic products, and there were no specific criteria exclusively for biosimilars in any of the countries. None of the countries were shown to have a specific price negotiation procedure exclusively for biosimilars, except Lithuania, which applied a specific pricing pathway for outpatient care.

The total expenditure on the reimbursement of biologic drugs in the CEE countries was €397,097,152 in 2014 and €411,433,628 in 2015. On average, 81.8% and 78.7% of the value was covered by the reimbursement of original drugs in 2014 and 2015 respectively. The shares of expenditures on the reimbursement of biosimilars in individual countries ranged from 8.0% in Estonia in 2014 to 38.1% in Lithuania in 2015. On an individual drug basis, share of expenditure varied considerably with biosimilars comprising 100% of the epoetin zeta market and 0% of the etanercept, enoxaparin and teriparatide markets across all studied countries in both years.

THEME 2: Biosimilar Medicine Uptake: Current Practice of Prescribers, Pharmacists and Patients

During the current review update period, a single manuscript was published addressing the theme of biosimilar uptake.

- ❖ Remuzat et al, 2017: Supply-side and demand-side policies for biosimilars: an overview in 10 European member states [15]

The authors of this manuscript previously published a review with the aim of identifying the key drivers of biosimilar uptake within the ten largest EU pharmaceutical markets (Belgium, France, Germany, Greece, Hungary, Italy, Poland, Spain, the UK and Sweden) and to evaluate the impact of incentivisation policies. That manuscript was included in the June 2017 biosimilar awareness literature review quarterly update. The objective of this current literature review was to provide an updated overview up to September 2016 of supply-side and demand-side policies on biosimilars within these markets and to discuss the potential impact of these policies on biosimilar uptake. The key supply side policies related to biosimilar uptake in the member states included internal and external reference pricing, health technology assessment, price linkage, price re-evaluation and tendering processes. The key demand side policies identified affecting uptake included prescription budgets and quotas, financial incentives, switching, substitution, patient co-payment and the provision of information and education. The authors noted that this is a *“very dynamic environment where the practice may sometimes differ from the written rules, and our study relies only on secondary research and did not integrate primary research”*.

THEME 3: Adverse Events and Health Outcomes of Biosimilar Medicines (Pharmacovigilance): Impact of Substitution, Switching and Extrapolation of Indication

Within the period encompassed by this update, there have been 11 publications that specifically examine this theme related to epoetin, filgrastim and infliximab.

In the case of filgrastim there is a focus upon the extrapolated indications related to stem cell transplantation rather than prophylaxis of chemotherapy induced neutropenia. Two studies of biosimilar filgrastim for the prophylaxis of chemotherapy induced neutropenia, focussed on issues such as the appropriateness of prophylaxis, rather than on the biosimilar agent per se [16, 17]. In these studies, limited results are provided regarding the effect of the biosimilar medicine.

Erythropoiesis Stimulating Agents (ESAs)

- ❖ Minutolo et al, 2017: Effectiveness of Switch to Erythropoiesis-Stimulating Agent (ESA) Biosimilars versus Maintenance of ESA Originators in the Real-Life Setting: Matched-Control Study in Hemodialysis Patients [18]

The aim of this retrospective study was to evaluate the efficacy on anemia control of switching from ESA originators to biosimilars in daily clinical practice. Haemodialysis patients receiving stable intravenous ESA doses, and who had not received a blood transfusion in the previous 6 months, were selected from medical records obtained from 12 non-profit Italian centers. Patients switched from originators (epoetin alfa [Eprex], epoetin beta [NeoRecormon] and darbepoetin [Aranesp]) to biosimilars (epoetin alfa [Binocrit] and epoetin zeta [Retacrit]) were matched with those maintained on ESA originators using a propensity score approach. The study duration was 24 weeks, and the primary endpoint was the mean dose difference (MDD), defined as the difference between the switch and control groups of ESA dose changes during the study.

A total of 326 patients (n=163 control, n=163 switch) were matched on a number of demographic and clinical characteristics known to influence response to ESAs. Within the control group 16.6% received darbepoetin compared with 18.4% of those patients who would switch. ESA dose remained unchanged in the control group and progressively increased in the switch group leading to a significant MDD of 2423 IU/week (95% confidence interval [CI] 1615–3321), corresponding to a 39.6% (95% CI 24.7–54.6) higher dose of biosimilars compared with originators.

Commentary

It should be noted that those patients in the switch group who had previously received darbepoetin (18.4%), the change to biosimilar epoetin constitutes a change in their therapy which is associated with uncertainty with regards to dose equivalence. This study utilised a conversion ratio of 1:200; however, this is considered an estimate that requires subsequent dose adjustment based on clinical response. The inclusion of a significant proportion of patients for whom this study represents a change in therapy rather than a change from reference to biosimilar complicates the interpretation of this result. The results specifically for patients that switched from reference to biosimilar epoetin (excluding darbepoetin) is not presented.

Filgrastim

- ❖ Lisenko et al, 2017: Comparison of biosimilar filgrastim, originator filgrastim, and lenograstim for autologous stem cell mobilization in patients with multiple myeloma [19]

This retrospective study of 250 patients with multiple myeloma aimed to compare the peripheral blood stem cell (PBSC) mobilization efficiency of the three G-CSF variants; originator filgrastim (n=74), lenograstim (n=45), and the biosimilar filgrastim (Hexal, n=131) in the context of chemomobilization with CAD (cyclophosphamide, doxorubicin, dexamethasone). The median duration of G-CSF administration until PBSC collection was 5 days in all G-CSF subgroups. All but one patient attained the PBSC collection goal during a median of one (range: one to three) leukapheresis session. There were no significant differences in CD34+ mobilization and collection yields between the filgrastim-mobilized (median, 10.5; range, 2.7-40.4), filgrastim Hexal–mobilized (median, 9.9; range, 0.2-26.0) patients. The authors conclude that *“this study supports the notion that all the three pharmaceutical G-CSF variants mobilize PBSCs equally efficiently without affecting apheresis practices in patients with MM in first-line therapy”*.

- ❖ Nasillo et al, 2017: Effectiveness of originator (Neupogen) and biosimilar (Zarzio) filgrastim in autologous peripheral blood stem cell mobilization in adults with acute myeloid leukemia: a single-center retrospective study [20]

This retrospective study compared peripheral blood stem cell (PBSC) mobilization and autologous haematopoietic stem cell transplant (HSCT) outcomes in patients with acute myeloid leukemia (AML) who received either originator filgrastim (Neupogen) between January 2006 and August 2011 (n=33) or biosimilar filgrastim (Zarzio) between September 2011 and February 2016 (n= 26). There were no statistically significant differences in key PBSC harvest parameters, including number of apheresis procedures and number of CD34+ cells harvested, between those receiving originator and biosimilar filgrastim. PBSC mobilization failed in 6/33 (18.2%) and 5/26 (19.2%) patients receiving originator and biosimilar filgrastim respectively. There was a statistically significant (p=0.03) earlier recovery in platelet count following autologous HSCT in patients mobilized with biosimilar filgrastim (median day of recovery = +12, range 11-18) as compared with originator filgrastim (median day of recovery = +14, range 11–24). The authors note that this analysis should be interpreted in context of *“potentially suffering from historical biases, namely possible changes in clinical practice”* but that *“our findings indicated no difference in key parameters of PBSC mobilization in adult patients affected with AML, with the use of a biosimilar filgrastim, compared with originator, as previously shown for other hematologic malignancies”*.

- ❖ Farhan et al, 2017: Biosimilar G-CSF versus filgrastim and lenograstim in healthy unrelated volunteer hematopoietic stem cell donors [21]

This manuscript describes the outcomes of 313 healthy haematopoietic stem cell donors who were mobilized with originator filgrastim (n=107), biosimilar filgrastim (n=85) or lenograstim (n=121) between October 2014 to March 2016 at the Medical University of Warsaw. The mean number of CD34+ cells/kg collected during the first apheresis was similar between lenograstim, biosimilar filgrastim, and filgrastim (p = 0.06). The authors conclude that *“Biosimilar G-CSF is as effective in the mobilization of hematopoietic stem cells in unrelated donors as original G-CSFs”*.

- ❖ Kobayashi et al, 2017: Comparative study of the number of report and time-to-onset of the reported adverse event between the biosimilars and the originator of filgrastim [22]

The objective of this study utilised the World Health Organization's global individual case safety report (ICSR) database (VigiBase®) to identify the most reported adverse events for originator and biosimilar filgrastim and to compare the time-to-onset distribution of these events. After removal of duplicates, the number of ICSR reports where the suspected drugs were Neupogen® or the biosimilars Zarzio®, Nivestim®, and Tevagrastim® was 1266, 289, 156, and 124, respectively. Bone pain, pyrexia, and dyspnea were most commonly reported for Neupogen® (125, 101, and 55 cases, respectively) as compared with 'drug ineffective' for Zarzio® and Tevagrastim® (37 and 30 cases respectively). The reporting ratio of bone pain with was similar for biosimilar filgrastim (8-9%) as compared with originator (10%). Similarly, the reporting ratios for pyrexia and dyspnea were similar between biosimilar filgrastim (4-7%) as compared with originator (8% and 4% respectively). The time-to-onset of bone pain and pyrexia with Zarzio® (N: 22 and 16, median: 1 and 0.5 days) was significantly shorter than those with Neupogen® (P <0.01, N: 72 and 33, median: 3.5 and 3 days), respectively. The authors state that "*The difference in the TTO might suggest that the AEs of biosimilars were different from those of Neupogen®*" whilst noting that "*there could be reporting practices affecting the TTO (time-to-onset)*" result.

- ❖ Kraj et al, 2017: Efficacy and safety of biosimilar filgrastim in primary and secondary prevention of febrile neutropenia [16]

This manuscript, sponsored by Accord Healthcare, describes a study evaluating the use of biosimilar filgrastim (Accofil, Accord Healthcare) for the primary and secondary prevention of chemotherapy induced febrile neutropenia, and to assess its efficacy and safety. 170 cancer patients (Male 32.9%; mean age 59.5 years [range: 23–82]) were included in this non-interventional phase IV post-marketing study. In the majority of cases six cycles of chemotherapy were planned. Accofil was used as primary prophylaxis of febrile neutropenia in 40% of cases and as secondary prophylaxis in the remaining 60% of cases. 86.3% of patients continued with Accofil treatment throughout their planned cycles with the most common reason for discontinuation being disease progression. The authors concluded that their results suggest that "*the efficacy and safety of Accofil is comparable to the original filgrastim product (Neupogen)*".

- ❖ Damaj et al. 2017: A Prospective Study of the Use of Biosimilar Filgrastim Zarzio in Clinical Practice in Patients Treated With Chemotherapy for Lymphoid Malignancies[17]

This manuscript reports on a prospective, observational, multicenter study in France to assess use of biosimilar filgrastim (Zarzio) in routine clinical practice in patients undergoing neutropenia-inducing chemotherapy. 1807 cancer patients (Male 61.9%; mean age 64.2 years [range: 23–82]) of which two thirds (64.6%) had NHL. The median duration of Zarzio treatment was 5 days for haematological malignancy and 6 days for NHL. Zarzio was administered for a median of 4 cycles of chemotherapy and treatment stayed consistent for 89.6% of patients throughout these cycles. Overall 28.6% of patients (n=176) stopped Zarzio before the end of study, with the majority due to cessation of chemotherapy. A total of 53 adverse events related to Zarzio were reported during the study, none of which were considered serious. Limitations of the study identified by the authors included selection and recall bias. The authors concluded that "*Use of Zarzio in clinical practice enable a high proportion (90%) of patients with NHL receiving R-CHOP or CHOP-like regimens to maintain the dose intensity necessary for chemotherapy with curative intent*".

Infliximab

- ❖ Shmitz et al, 2017: Therapeutic drug monitoring (TDM) as a tool in the switch from infliximab innovator to biosimilar in rheumatic patients: results of a 12-month observational prospective cohort study [23]

This manuscript reports on the use of therapeutic drug monitoring (TDM) as a tool to monitor switching from originator infliximab to biosimilar infliximab (CT-P13) in 27 rheumatic patients. Patients had received originator infliximab for a median of 143 months (inter-quartile range: 58–161), half (52%) of whom were receiving concomitant immunosuppressants. Blood samples were collected immediately prior to the first infusion of biosimilar infliximab and after the second, fourth, and seventh infusion. There were no statistically significant differences in median infliximab concentrations at any time point ($p = 0.3487$). However, it was noted that infliximab concentrations “*were very constant for some patients, while they varied between the four time points for others*”. No patients developed anti-drug antibodies after switching to biosimilar infliximab.

- ❖ Farkas et al, 2017: Infliximab biosimilar CT-P13 therapy is effective and safe in maintaining remission in Crohn's disease and ulcerative colitis - experiences from a single center [24]

The aim of this prospective observational study conducted between June 2014 and September 2016 was to evaluate the long-term clinical efficacy and safety of CT-P13 in patients with inflammatory bowel disease (Crohn's disease = 57, ulcerative colitis = 57). The primary end points were continuous clinical response, defined as maintained response through week 54 without intermediate relapse, and clinical remission during the 54-week therapeutic period. Secondary end points were clinical and biochemical responses and safety at weeks 14 and 54. Three patients with Crohn's disease and nine with ulcerative colitis had previously received originator infliximab which had resulted in remission in two and six patients respectively. A total of 55 Crohn's disease and 49 ulcerative colitis patients completed the induction therapy with 50 Crohn's disease and 46 ulcerative colitis patients completing the 54-week treatment period. At week 54, the rate of continuous clinical response was 51% in both Crohn's disease and ulcerative colitis with 31 (62%) Crohn's disease patients and 30 (65.2%) ulcerative colitis patients in remission. The authors note that “*Our results showed higher response rates in both CD and UC assessed at week 54 compared to the large randomized controlled trials of IFX, the ACCENT-1 (39%) and the ACT-1 trials (46%)*” and conclude that this prospective study “*confirmed long-term efficacy and safety of CT-P13 therapy in IBD*”

- ❖ Smits et al, 2017: Long-Term Clinical Outcomes After Switching from Remicade® to Biosimilar CT-P13 in Inflammatory Bowel Disease [25]

This single-centre, prospective observational cohort study describes the outcomes associated with an elective switch from originator infliximab to biosimilar infliximab (CT-P13) in 83 patients with inflammatory bowel disease (Crohn's disease = 57, ulcerative colitis = 24, unclassified = 2). Prior to switching, 53 patients (64%) were in remission and the median duration of treatment of originator infliximab was 25 months (range 1–168). Five patients were positive for anti-drug antibodies prior to switching. A total of 68 patients completed one-year follow-up. At week 52 following switching, 61 patients (73%) were considered to be in remission and there was no change in the median disease activity measures (Harvey–Bradshaw Index and Simple Clinical Colitis Activity Index) or inflammatory markers (CRP, fecal calprotectin). Two patients developed anti-drug antibodies following the switch. There was no significant difference in median

infliximab trough concentrations at baseline as compared with week 52 post-switch (3.6ng/mL versus 3.7 ng/mL respectively, $p = 0.559$). Six patients (7%) discontinued CT-P13 due to adverse events. The authors conclude that *“no significant impact on clinical outcomes that included disease activity, safety, drug survival, and pharmacokinetics”* and that *“These outcomes support feasibility for switching to CT-P13”*.

- ❖ Vergara-Dangond et al, 2017: Effectiveness and Safety of Switching from Innovator Infliximab to Biosimilar CT-P13 in Inflammatory Rheumatic Diseases: A Real-World Case Study[26]

This small, retrospective study reports on patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) and had responded to originator infliximab and were either switched to biosimilar infliximab (CT-P13, $n = 7$) or continued on originator ($n = 6$). The median duration of infliximab treatment prior to switching or continuation was 76 and 75 cycles respectively. Prior to switching or continuation 2/7 and 4/6 patients were considered to be in remission. Clinical outcomes were compared between groups after a further four treatment cycles. In the group that switched to biosimilar infliximab, remission was maintained in the two patients in remission at baseline and an additional three patients achieved remission following the switch. The remaining two patients were considered to have maintained a response to treatment. In those continuing originator infliximab, remission was maintained in the four patients already in remission, one additional patient achieved remission and response was maintained in one patient. The authors conclude that *“Switching from the RP (originator infliximab) to CT-P13 did not affect the safety or effectiveness of treatment”*.

THEME 4: Evaluating and Improving Stakeholder Biosimilar Awareness, Confidence, Attitudes and Acceptance of Biosimilar Medicines

Four original research articles were published during the review update period addressing the topic of biosimilar perception amongst healthcare professionals.

- ❖ Chapman et al, 2017: Knowledge, attitude and practice of healthcare professionals towards infliximab and insulin glargine biosimilars: result of a UK web-based survey [27]

This study aimed to investigate healthcare professionals' knowledge and attitudes towards biosimilar infliximab and biosimilar insulin glargine, the factors that influence their prescribing of these agents using a web-based survey and to compare these results with the utilisation of these biosimilars in hospitals within the UK. The survey was conducted between August 2016 and January 2017. Data on infliximab and insulin glargine utilisation was obtained from the NHS prescribing database of medicines usage (known as DEFINE). A total of 234 responses were received, 64% of whom were medical consultants or registrars (n=150) with a specialty in dermatology, gastroenterology, rheumatology or diabetology. The remaining respondents were nurses (n=58) or pharmacists (n=11). The authors state that it was *"not possible to calculate the response rate as the total number of members of the professional associations and societies are confidential"*. When asked to select from a list of options regarding the statement *"Which statement best describes what you understand a biosimilar to be?"*, 72% indicated that biosimilars are *"A similar copy of a biological medicine"*, 18% selected that they are *"A generic biological medicine"*, whilst 3% indicated that they were counterfeit medicines and 1% believed them to be new biological medicines. Responses were not analysed in respondent sub-groups. When asked to rate *"How important are the following factors when considering prescribing a biosimilar?"* on a Likert scale from *"Not at all important"* to *"Extremely important"* over 50% of respondents indicated that *"Important to save costs for the NHS"* was *"Extremely important"*. Responses were more evenly distributed across all ratings for questions such as *"Important to increase the overall use of biologics"* and *"Important to stimulate competition on the biological medicine market"*. The majority of gastroenterologists indicated that they had *"No concerns"* or *"Minor concerns"* about the safety (95%) and efficacy (90%). Similarly, rheumatologists had had *"No concerns"* or *"Minor concerns"* about safety (92%) and efficacy (88%) when *"Starting new patients"* but had *"Major concerns"* about safety (53%) and efficacy (55%) when asked about *"Switching patients"*. Respondents were not provided the opportunity to explain the reasons for their ratings.

With regards to biosimilar utilisation, gastroenterologists had the greatest utilisation of biosimilar infliximab, increasing from 14% in 2015 to 62% in 2016, followed by rheumatologists increasing from 6% to 39%. Biosimilar insulin glargine utilisation increased 0.5% in 2015 to 9% in 2016. *"Guidance from NICE or other reputable national body"* and *"Robust pharmacovigilance studies on biosimilars"* were most highly rated amongst options to increase biosimilar use.

- ❖ Aladul et al, 2017: Patients' Understanding and Attitudes Towards Infliximab and Etanercept Biosimilars: Result of a UK Web-Based Survey [28]

This study aimed to investigate the knowledge and attitudes of patients with ankylosing spondylitis and rheumatoid arthritis towards infliximab and etanercept. A self-administered web survey of members of the National Rheumatoid Arthritis Society and the National Ankylosing Spondylitis Society in the UK was

conducted between March and June 2017. A total of 182 were received. The majority of respondents (73%) were currently receiving treatment with etanercept. A significantly higher percentage of participants (41%) were receiving the etanercept biosimilar (Benepali) as compared with 24% on infliximab biosimilars (Remsima and Inflectra). The results indicate that current treatment status with a biosimilar or originator product influenced the responses received. Most participants currently receiving treatment with a biosimilar (72%) believed that biosimilars were as safe and effective as the originator. In contrast, 45% of participants currently receiving an originator product believed that biosimilars were less safe and 60% believed them to be less effective. Of those currently receiving a biosimilar, 74% were “comfortable and open” to switching to other biosimilars compared with only 28% of participants receiving an originator product ($p < 0.001$). Consistent with this, respondents currently receiving a biosimilar expressed greater confidence in their doctor’s decision to initiate and/or to switch to a biosimilar than participants currently receiving an originator product. When asked an open response question “Aside from the cost, what would be your main question(s) if your healthcare professional wanted to switch you from branded etanercept to biosimilar etanercept?”, participants currently receiving a biosimilar more commonly wanted to know about side effects and safety, whereas participants receiving originator biologics more commonly wanted more evidence from trials. Similar proportions in both groups wanted to ask about the reasons for switching and if they could switch back (originator $n=16$ (13%) versus biosimilar $n=10$ (17%). The authors conclude that the results indicate that “More communication and reassurance of the patient by healthcare professional teams and further involvement in the decision making concerning biosimilars is required to increase biosimilars acceptance”.

- ❖ O’Callaghan et al, 2017: Assessing awareness and attitudes of healthcare professionals on the use of biosimilar medicines: A survey of physicians and pharmacists in Ireland [29]

This study aimed to assess the awareness of, and attitudes toward biosimilars of medical specialists, General Practitioners and community pharmacists in Ireland. Pharmacists received the questionnaire by post in August 2015 (supported by funding from AbbVie Limited). Medical specialists and general practitioners were invited to respond to an online questionnaire between April and May 2016. A total of 143 responses were received from community pharmacists (response rate=72%), 253 general practitioners (response rate = 9%) and 102 medical specialists (response rate uncertain). The majority of medical specialists (85%) and pharmacists (77%) who responded indicated that they were either “Very familiar (complete understanding)” or “Familiar (basic understanding)” with the term biosimilar in contrast with 60% of general practitioners who indicated that they had either “Heard of the term – can’t define it” or “Never heard of the term”. The difference between general practitioners and the two other groups was statistically significant. However, when asked “Would you consider biosimilars to be the same as generic medicines?” 21% of the 410 respondents to this question indicated that they believed a biosimilar was the same as a generic medicine. Respondents that had previously indicated that they had “Never heard of the term” were excluded from this analysis. There were no statistically significant differences between the groups in the response to this question. Further, 47% of total respondents indicated that they “Agree strongly” or “Agree” that biological medicines with the same international non-proprietary name have an “Identical structure”, with 50% of pharmacists agreeing with this statement as compared with 31% of medical specialists (value not provided for general practitioners).

Medical specialists who indicated that they were aware of biosimilars specialty (n = 73) were also asked about their prescribing behaviour. Of these, 59% indicated that they prescribed biosimilars to patients, 40% had not and 1% were uncertain. Of those who had prescribed a biosimilar (n=43), 67% indicated that they would be “*Likely or extremely likely*” to most likely to “*prescribe a biosimilar to a patient on treatment initiation*” whilst 28% indicated that they would be “*Likely or extremely likely*” to “*switch from an originator medicine to a biosimilar when a patient is clinically stable*” and 19% indicated that they would be “*Likely or extremely likely*” to “*switch to a biosimilar when a patient has had a poor clinical response to the originator medicine*”. When asked about substitution, defined in the survey as “*a pharmacist dispensing a biosimilar in place of an originator medicine (or vice versa) without consulting the prescriber*” 5% and 3% responded “*Yes*” to the question “*Do you think substitution of a biological medicine by a pharmacist could be appropriate*” either on treatment initiation or during a patient’s treatment course respectively. In contrast, 49% and 61% of respondents indicated “*No- this should be the prescriber decision*” at treatment initiation and during a patient’s treatment, respectively. If substitution by a pharmacist were to occur, either on treatment initiation or during the course of treatment, 84% and 90% respondents respectively indicated that they believed it to be “*very important or critical*” for the prescriber to be notified.

When pharmacists were asked about substitution of biological medicines in Ireland 59% correctly indicated that it was not permitted however 30% responded that they did not know and 10% believed that it was permitted. Pharmacists were also asked how comfortable they would be with regards to substitution, were it permitted, with 58% of respondents indicating that they would only be comfortable to do so with the agreement of the prescriber, 14% would be comfortable substituting and 27% were not comfortable.

The authors conclude that the observation that “*21% of those surveyed responded that a biosimilar was the same as a generic medicine*” indicating “*a lack of awareness among some respondents on the differences between generic and biosimilar medicines*” and that “*Healthcare professionals may also benefit from targeted educational initiatives to reduce the information gap on biosimilar medicines*”.

❖ Barsell et al, 2017: A Survey Assessment of US Dermatologists' Perception of Biosimilars [30]

An online survey of dermatologists within the US with regard to their perceptions of biosimilar medicines was conducted between January and April 2015. The survey was a modified version of that utilized by the Alliance for Safe Biologic Medicines. A total of 97 dermatologists responded (response rate not provided), of whom 69% worked in private practice and 22% in academic medical centres. The vast majority (84%) of respondents prescribe biological medicines in their practice. Overall, 62% responded that they had a basic understanding of biosimilars, 27% believe they have a “*complete understanding*” and 11% having not heard of biosimilars. However, when asked “*How would you describe a biosimilar?*” only 37% selected “*Product that is highly similar to a US-licensed reference biologic product*” whilst 26% selected “*Generic of a known biologic*”, including 21% of those who believe they have a “*complete understanding*” of biosimilars and 27% selected “*Same biologic with equal bioequivalence*”. When asked “*If a biologic has the same name as a biologic, what does this suggest to you?*”, 37% selected “*They are structurally identical*” whilst 29% selected “*Patients can safely receive either with same result*”. However, when asked about the potential disadvantages of biosimilars, safety (66%), efficacy (71%), immunogenicity (63%), the potential for “*patients to be switched from a biologic to a biosimilar without their knowledge*” (68%) and “*the FDA ability to regulate good clinical practices in manufacturing biosimilars*” (61%) were most commonly reported. The majority of respondents (88%) believed that “*in the future, substitutions from biologics to biosimilars will be*

made by pharmacists or health insurance companies under some circumstances without consulting the physician” but the majority of respondents believed that it was either “very important” (76%) or “somewhat important” (18%) that they have control over this. When asked about the major advantages of biosimilars 71% indicated low price to patients, 65% indicated low price to payers and 68% indicated the potential for easier access to treatment for patients. Dermatologists reported that their understanding of biosimilars most commonly arose from self-study (35%) scientific publications (25%) and conferences or seminars (17%). The authors conclude that “our study highlights the need for more educational initiatives concerning biosimilars”.

- ❖ Christianson et al, 2017: Use of various gonadotropin and biosimilar formulations for in vitro fertilization cycles: results of a worldwide Web-based survey [31]

This study reports the findings of a web-based survey investigating trends in gonadotropin therapy worldwide. A 19-item survey focussed on various aspects of preference of urinary versus recombinant gonadotropin formulations and included 4 questions relating to attitudes and experiences of gonadotropin biosimilars. A total of 314 IVF centres from 73 countries responded to the survey representing 218,300 IVF cycles annually, of which almost half (44%) of all IVF cycles were completed in Europe and one quarter (25%) from Asia. The analysis presented was based on the total number of IVF cycles reported rather than by IVF centres. Thus, the relative proportion of responses reflects the total proportion of IVF cycles completed rather than the proportion of IVF centres.

Results of the survey indicated that respondents responsible for 74% of IVF cycles were aware of new biosimilar gonadotropin products entering the market. Respondents responsible for 26% of all IVF cycles reported having experience with these new biosimilar products, of which 80.3% indicated that they were similar in efficacy to previously used gonadotropins in a similar patient group. Respondents responsible for 92% of IVF cycles indicated that additional information would be beneficial. The authors conclude that *“Education centered on the biosimilar mechanism of action, efficacy, dosing, and side effect profile is needed for IVF practitioners worldwide.”*

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APPENDIX 1

The following list contains manuscripts that were published during the review period that are of an educational or review nature. These manuscripts did not contribute new information to literature on biosimilar medicines. Some manuscripts provide a broad, relatively superficial, overview of biosimilar medicines. Other manuscripts provide an in-depth review of specific biosimilar medicines, reporting only on previously published data, but not contributing new information.

1. Danese, S. and L. Peyrin-Biroulet, *IBD: To switch or not to switch: that is the biosimilar question*. Nature Reviews Gastroenterology & Hepatology, 2017. **14**(9): p. 508-509.
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14. Gils, A., et al., *Biopharmaceuticals: Reference Products and Biosimilars to Treat Inflammatory Diseases*. Therapeutic Drug Monitoring, 2017. **39**(4): p. 308-315.
15. Strand, V., et al., *Immunogenicity of Biologics in Chronic Inflammatory Diseases: A Systematic Review*. BioDrugs, 2017. **31**(4): p. 299-316.
16. Stevenson, J.G., et al., *Biosimilars: Practical Considerations for Pharmacists*. Annals of Pharmacotherapy, 2017. **51**(7): p. 590-602.
17. Boccia, R., et al., *Can biosimilars help achieve the goals of US health care reform?* Cancer Management and Research, 2017. **9**: p. 197-205.
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29. Yoo, D.H., *CT-P13 in the treatment of rheumatoid arthritis*. *Expert Review of Clinical Immunology*, 2017. **13**(7): p. 653-666.
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38. Blauvelt, A., et al., *Biosimilars for psoriasis: clinical studies to determine similarity*. *British Journal of Dermatology*, 2017. **177**(1): p. 23-33.
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APPENDIX 2

The following list contains manuscripts that were published during the review period that are of a technical nature and relate to topics such as the physicochemical and pharmacological characterisation of potential biosimilar medicines.

1. Bisio, A., et al., Structural Characterization of the Low-Molecular-Weight Heparin Dalteparin by Combining Different Analytical Strategies. *Molecules*, 2017. 22(7): p. 24.
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