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School of Pharmacy and Medical Sciences

Literature Review of International Biosimilar Medicines: Update March – May 2018

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Introduction

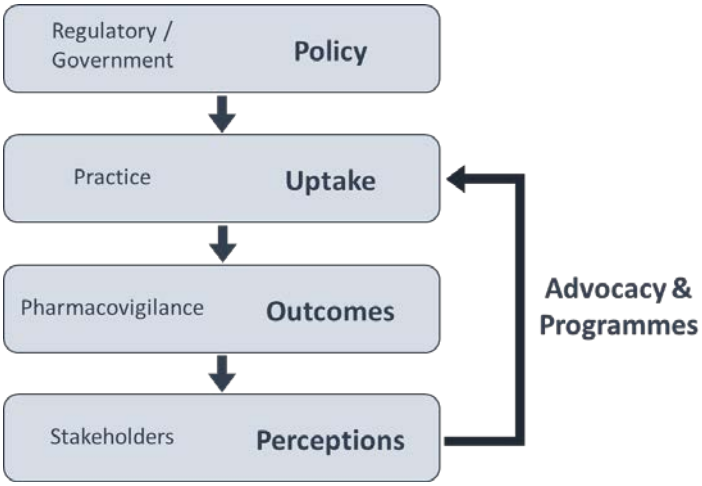
This report provides an update to the comprehensive literature search previously conducted that examined all international and Australian clinical, academic and policy journals and media articles or sources in relation to biosimilar medicines for the purpose of providing evidence which may inform policy 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 polices 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 participants (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 participant 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 participants 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 Participants
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 March 2018 and 31 May 2018.

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 participants depending upon a range of factors such as the potential risks associated with the use of the agent.

During the current update period, four phase I pharmacokinetic studies comparing a potential biosimilar medicine with a reference product were reported. 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).

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
Enoxaparin						
Enoxaparin	Clexane	Single-dose, randomized, double-blind, 2-period,2-sequence crossover study	Healthy adult subjects (n=43)	95% CI of the ratio of geometric least squares means maximum activity (A_{max}) and area under the effect curve from time 0 to the last measured activity (T) ($AUE_{C0–T}$) and from time 0 to infinity ($AUEC_{0–inf}$) of anti-FXa activity were within the predefined bioequivalence interval of 0.80–1.25	Not investigated	[1]

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
Etanercept						
PF-06438179 / GP1111	Remicade (EU and US)	Randomised parallel-group three arm PK study	Healthy adult subjects (n=151, randomised 1:1:1)	90%CI for the ratio between the geometric means of the area-under-the-curve from time zero extrapolated to infinite time (AUC_{inf}), AUC from time 0 to the last measurable concentration (AUC_T) and maximal plasma concentration (C_{max}) were within the predefined bioequivalence interval of 0.80–1.25	Anti-drug antibodies were detected in PF-06438179 / GP1111: 6 of 37 (16.2%) Remicade (EU): 14 of 43 (32.6%) Remicade (US): 11 of 39 (28.2%)	[2]
Peg-filgrastim						
MYL-1401H	Neulasta (EU and US)	Randomized, double-blind, three-way crossover	Healthy volunteers 216 subjects received at least one dose 208 subjects received at least two of the three doses	PK: 90%CI for the ratio between the geometric means of the area-under-the-curve from time zero extrapolated to infinite time (AUC_{inf}), and maximal plasma concentration (C_{max}) were within the predefined bioequivalence interval of 0.80–1.25 PD: 95% CI for the ratios of geometric means for the area under the curve above baseline for absolute neutrophil counts (ANC AUC_{0-t}) and maximum change from baseline for ANC (ANC C_{max}) were within the predefined PD equivalence interval of 0.8500 to 1.1765	After the first treatment period the proportion of subjects with treatment-emergent anti-drug antibodies (excluding ADA positive at baseline) was: MYL-1401H: 14 of 63 (22%) Neulasta (EU): 16 of 68 (24%) Neulasta (US): 21 of 69 (30%)	[3]

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
Trastuzumab						
HD201	Herceptin (EU)	Randomized, blinded, single-dose comparative PK study	Healthy male subjects (n=73, randomised 1:1)	90%CI for the ratio between the geometric means of the area-under-the-curve from time zero extrapolated to infinite time (AUC_{inf}), was within the predefined bioequivalence interval of 0.80–1.25	No subjects were positive for anti-drug antibodies on day 22 or 85	[4]

An additional extension study to a phase I trial of rituximab was also reported and is described below.

- Cohen et al, 2018: An Extension Study of PF-05280586, a Potential Rituximab Biosimilar, versus Rituximab in Subjects with Active Rheumatoid Arthritis [5]

The objectives of this extension study offered to participants with active rheumatoid arthritis who had participated in the randomized, parallel-group, 3-arm, phase I trial were to evaluate overall pharmacokinetics, pharmacodynamics, immunogenicity, safety, and tolerability of PF-05280586 after transition from reference rituximab product to the proposed biosimilar (PF-05280586). Participants were offered up to 3 courses of study treatment (each course consisting of two intravenous infusions of 1,000 mg of study treatment administered on Days 1 and 15, and separated from the next course by 24 weeks ± 8 weeks). Participants that received reference rituximab (EU or US) previously were re-randomized (1:1) to either continue reference rituximab (EU or US) or to switch to the rituximab biosimilar for the first additional treatment cycle. All participants received biosimilar rituximab for cycles two and three. A total of 185 subjects participated in this study of whom, 59 received PF-05280586 in the parent study and remained on PF-05280586, 126 received reference rituximab (EU=66, US=60). There were no notable differences in pharmacokinetics or CD19+ cell depletion between treatment groups or across treatment courses. Of the 146 subjects who were negative for anti-drug antibodies (ADA) at pre-dose, 17 became positive. A total of six participants experienced infusion-related reactions (IRR), all of which occurred in courses one or two. The authors conclude that "…*this study demonstrated tolerability and acceptable safety with or without single transition from licensed rituximab to PF-05280586, and did not demonstrate increased immunogenicity on re-challenge or single transition based on either ADA or IRR reports*"

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 five reports including proposed biosimilars for insulin glargine, adalimumab and filgrastim.

- Blevins et al, 2018: Efficacy and Safety of MYL-1501D Versus Insulin Glargine in Patients With Type 1 Diabetes After 52 Weeks: Results of the Phase 3 INSTRIDE 1 Study [6]

  The aim of this multi-centre, open-label, randomized, parallel-group, phase 3 study in patients with type 1 diabetes was to compare the efficacy and safety of a proposed biosimilar of insulin glargine (MYL-1501D) with the reference product (Lantus). The predefined non-inferiority criteria was defined as the upper limit of the 2-sided 95% CI for the difference in mean change from baseline to endpoint for HbA1c being no greater than 0.4% at week 24. A total of 558 patients were randomized 1:1 to receive either MYL-1501D (n=280) or reference insulin glargine (n=278) in combination with mealtime insulin lispro 3 times a day for the 52-week treatment period. The mean change in HbA1c from baseline to week 24 for the proposed insulin glargine biosimilar was 0.14% (95% CI: 0.033 to 0.244) as compared with 0.11% (95% CI: 0.007 to 0.220) for the reference insulin glargine. The least squares (LS) mean difference in change in HbA1c from baseline to week 24 between the two groups was 0.03% (95% CI: -0.066 to 0.117) which was within the predefined non-inferiority margin. Hypoglycaemia occurred in 154 (55.0%) and 170 (61.2%) patients in the biosimilar and reference groups, respectively. The authors conclude that "*MYL-1501D was associated with similar changes from baseline in HbA1c at week 24, demonstrating the noninferiority of MYL-1501D to reference insulin glargine*" and that "*Overall, MYL-1501D was well tolerated, with no new or significant safety issues as compared with insulin glargine*."

- Home et al, 2018: Efficacy and safety of MK-1293 insulin glargine compared with originator insulin glargine (Lantus) in type 1 diabetes: a randomized, open-label clinical trial [7]

  The aim of this phase 3, randomized, active-controlled, open-label, 52-week study was to compare the efficacy and safety of a proposed insulin glargine biosimilar (MK-1293) with reference insulin glargine (Lantus) in participants with type 1 diabetes mellitus (T1DM). The predefined non-inferior criteria was defined as the upper limit of the two-sided 95% confidence interval (CI) for the between-treatment difference in least squares (LS) mean change from baseline to week 24 for HbA1c being no greater than 0.40%. Equivalence was defined as containment of the lower and upper bounds of the two-sided 95% CI of the between-treatment difference between -0.40% and +0.40%. A total of 499 participants received at least one dose of study insulin, of whom 214/241 (89%) in the biosimilar group and 237/258 (92%) in the reference product group completed the initial 24-week treatment period. At week the 24, the model-based treatment difference was 0.04% (95% CI: -0.11 to 0.19) which was within the predefined criteria for non-inferiority and equivalence. The event rate for hypoglycaemia was similar in the biosimilar and reference groups (105.2 vs 101.7 events/person-year, respectively). The frequency of anti-insulin antibodies was similar between the biosimilar and reference group at or before week 24 (70.1% vs 74.0%, respectively) and at week 52 (73.4% vs 75.6%, respectively). The authors conclude that "…*Mk-Gla* [MK-1293] *is a follow-on/biosimilar insulin glargine with clinical properties that are highly similar to those of Sa-Gla* [reference insulin glargine]. *Thus Mk-Gla is expected to be a safe and effective treatment option for people with T1DM*".

- Hollander et al, 2018: Efficacy and safety of MK-1293 insulin glargine compared with originator insulin glargine (Lantus) in type 2 diabetes: a randomized, open-label clinical trial [8]

  The aim of this phase 3, randomized, active-controlled, open-label, 24-week clinical trial was to compare the efficacy and safety of a proposed insulin glargine biosimilar (MK-1293) with reference insulin glargine (Lantus) in participants with type 2 diabetes mellitus (T2DM). The predefined non-inferior criteria was defined as the upper limit of the two-sided 95% confidence interval (CI) for the between-treatment difference in least squares (LS) mean change from baseline to week 24 for HbA1c being no greater than 0.40%. Equivalence was defined as containment of the lower and upper bounds of the two-sided 95% CI of the between-treatment difference between -0.40% and +0.40%. A total of 526 participants received at least one dose of study insulin, of whom 240/263 (91%) in the biosimilar group and 244/263 (93%) in the reference product group completed the 24-week treatment period. At week the 24, the model-based treatment difference was 0.03% (95% CI: -0.12 to 0.18) which was within the predefined criteria for non-inferiority and equivalence. Injection site reactions occurred in 1.9% (5/263) of participants in the biosimilar group as compared with 0.4% (1/263) in the reference group. The incidence of hypoglycaemia was similar between the biosimilar and reference groups (86.3% vs 88.2%, respectively) with four participants in each group experiencing a severe event. The authors conclude that "*…this study demonstrated a high degree of clinical similarity between Mk-Gla* [MK-1293] *and Sa-Gla* [reference insulin glargine] *with regard to glycemic efficacy and safety in participants with T2DM over 24 weeks of treatment*" and that "*Therefore, Mk-Gla is expected to be a safe and effective treatment option for people with T2DM for whom basal insulin therapy is indicated.*"

- Cohen et al, 2018: Similar efficacy, safety and immunogenicity of adalimumab biosimilar BI 695501 and Humira reference product in patients with moderately to severely active rheumatoid arthritis: results from the phase III randomised VOLTAIRE-RA equivalence study [9]

  The aim of this randomised, double-blind, parallel-arm, 58-week trial was to demonstrate equivalent clinical efficacy of a proposed adalimumab biosimilar (BI 695501) with reference adalimumab (Humira, USA source) in patients with moderate to severe rheumatoid arthritis. Patients who were receiving stable methotrexate were randomised 1:1 to receive biosimilar or reference adalimumab. Equivalence was defined as the difference in American College of Rheumatology 20% response criteria (ACR20) at 12 weeks within −12% and 15% (90% CI; per FDA consultation) and at 24 weeks within −15% and 15% (95% CI; per EMA consultation). A total of 645 participants were randomised 1:1 to BI 695501 (n=324) and Humira (n=321). At week 24, 593 patients were re-randomised with 298 continuing BI 695501, 148 continuing reference adalimumab and 147 switching from reference adalimumab to BI 695501. The difference in the proportion of patients achieving an ACR20 response was within the prespecified interval at both week 12 (90% CI −0.9 to 12.7) and week 24 (95% CI −3.4 to 12.5). The frequency of anti-drug antibodies was similar between the biosimilar and reference groups up to week 24 (47.4% vs 53%, respectively). Similar immunogenicity was observed following rerandomization at week 24, including in the group randomised to switch from reference adalimumab to biosimilar. Adverse events requiring drug discontinuation occurred in the reference group only (n=4). The authors conclude that "*VOLTAIRE-RA showed that BI 695501 and*

Humira are highly similar in terms of efficacy, safety and immunogenicity" and that "*The switch from Humira to BI 695501 had no impact on efficacy, safety and immunogenicity*."

- Harbeck, et al: Safety Profile of Biosimilar Filgrastim (Zarzio/Zarxio): A Combined Analysis of Phase III Studies [10]

  This manuscript, sponsored by Sandoz GmbH, reports on the combined analysis of two phase III trials of the filgrastim biosimilar EP2006 in women receiving myelosuppressive breast cancer chemotherapy. The studies combined were a randomized, double-blind comparison of biosimilar and reference filgrastim in women aged ≥18 years receiving (neo)adjuvant treatment with TAC (docetaxel plus doxorubicin plus cyclophosphamide) and a single-arm, open-label study of biosimilar filgrastim in women aged ≥18 years receiving doxorubicin and docetaxel. The primary endpoint was the mean duration of severe (grade 4) neutropenia during the first chemotherapy cycle. A combined total of 277 participants received biosimilar filgrastim. The mean duration of severe neutropenia during the first chemotherapy cycle was 1.04 days (SD ± 1.51). The incidence of adverse events was similar in the combined biosimilar group (98.7%) as compared with the group that received originator filgrastim (96.2%). The most common treatment related adverse event was bone pain which occurred more frequently in the reference group (15%) than in the combined biosimilar group (5.8%). The authors conclude that "*These findings are in line with real-world evidence from the MONITOR-GCSF study, showing that the safety profile of biosimilar filgrastim is similar to historical safety data for reference filgrastim*."

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, four publications were identified that related to this topic which examined the economic impact of the introduction of biosimilars; whilst these papers do not specifically relate to policy, the cost of treatment is a strong determinate informing policy relating to biosimilar access and use.

- Kim et al, 2018: Estimation of cost savings between 2011 and 2014 attributed to infliximab biosimilar in the South Korean healthcare market: real-world evidence using a nationwide database [11]

  This retrospective analysis aimed to estimate the annual cost savings attributed to the introduction of infliximab biosimilar using data obtained from the Korean Health Insurance Review and Assessment Service-National Patients Sample (HIRA-NPS) between 2011 and 2014. The impact of the introduction of the biosimilar was assessed by comparing the period of 2011-2012, prior to the availability of biosimilar, with 2013-2014, following the price discounting on 1 December 2012 with the introduction of the biosimilar. In 2011-2012 the average price of infliximab was $445.5/vial which decreased to $316/vial in 2013 and $311.50 in 2014, equating to an estimated cost saving of $1972.00 /patient in 2013 and $2271.40/patient in 2014. The authors conclude that "*The introduction of infliximab biosimilar reduced direct medical costs for both patients and the payer, which could then be used to increase patient access to biologic medicines*."

- Baji et al, 2018: Cost-effectiveness of biological treatment sequences for fistulising Crohn's disease across Europe [12].

  This study examined optimal sequence of initiation of biological treatments for fistulising Crohn's disease from a cost-effectiveness perspective within nine European countries (Belgium, France, Germany, Hungary, Italy, Spain, Sweden, the Netherlands and the UK). Whilst not the specific aim of the study to examine the budgetary impact of biosimilar treatments, the model did examine biosimilar infliximab as a biologic option, along with originator infliximab, adalimumab and vedolizumab. To examine a real-world scenario, the model assumed a cost reduction from the list price of 30% for both biosimilar and originator infliximab, and 20% for adalimumab; efficacy data was taken from RCT data within the literature. Based on cost-effectiveness, the first-choice biologic treatment was biosimilar infliximab. In the instance of treatment failure, noting that the same treatment could not be used twice in the sequence (including switching of biosimilar to/from originator infliximab), the most cost-effective sequence was biosimilar infliximab – adalimumab – vedolizumab, which was primarily driven by biologic cost. The cost-effectiveness varied significantly between countries; however, this was due to differences in cost rather than health gains.

Commentary

The authors provide no justification for the selected price reductions of 30% for infliximab and 20% for adalimumab; ultimately as cost was the driver for the most cost-effective sequence of available biologics, it is likely to have significantly influenced the conclusions of the study.

- Aladul et al, 2018: The effect of new biosimilars in rheumatology and gastroenterology specialities on UK healthcare budgets: Results of a budget impact analysis [13]

  This study aimed to estimate the budget impact of the introduction of multiple biosimilars of infliximab, etanercept and adalimumab in rheumatology and gastroenterology specialities in the UK. Based upon extrapolation of the utilisation trends and costs derived from the existing biosimilars obtained from the DEFINE Software (an NHS prescribing database of medicines usage), a three-year time horizon budget impact analysis model spanning the years 2018–2020 was created. Modelling included only switching from originator to biosimilar of the same agent and not the potential impact of biosimilars on agent choice. The reference case model assessed the budget impact of the introduction of no new biosimilars into the market, and resulted in a cumulative reduction in expenditure by £48 million in the treatment of rheumatologic diseases (RD) and an increase of £4 million in the treatment of inflammatory bowel diseases (IBD). In comparison, the introduction of biosimilars to infliximab (Flixabi®), etanercept (Erelzi®) and adalimumab (Solymbic®, Amgevita® and Imraldi®) was projected to result in cumulative savings of £187 million and £97 million for RD and IBD respectively; this was largely due to the cost savings from the introduction of adalimumab biosimilars (RD: £176 million, IBD: £91 million) as no existing biosimilar is available.

- Grewal et al, 2018: Cost-savings for biosimilars in the United States: a theoretical framework and budget impact case study application using filgrastim [14]

  Within the context of a broader review (funded by Sandoz), the authors present a case study exemplar examining the potential cost savings across a 5-year time horizon of using biosimilar filgrastim instead of the originator in the United States for the management of neutropenia associated with myelosuppressive chemotherapy of solid tumours. The authors estimated use of filgrastim across the US using a number of different data sources. Using the Surveillance, Epidemiology, and End Results Program Results data the authors estimated that there are 1,617,665 annual prevalent solid tumours cases. From OptumInsight claims data it was estimated that 19.4% of patients with myelosuppressive chemotherapy for solid tumours receive one of the potential agents for the management of neutropenia and that, based upon a RAND analysis of IMS Health data, 15% of these receive filgrastim. Of the total filgrastim use, IMS data indicated that originator filgrastim accounted for 60% with tbo-filgrastim and filgrastim-sndz accounting for 20% each. The model the assumed growth in filgrastim-sndz use which was estimated at 10% annually, coming from originator drug, with tbo-filgrastim remaining constant. Biosimilar filgrastim was estimated to be 22% cheaper than originator. Within this base case scenario, the total 5-year cost savings for the use of filgrastim biosimilar in the United States was estimated at $256 million. If the annual rate of increase in the biosimilar market share increased to 20%, instead of 10%, the total 5-year cost saving was estimated to increase to $313 million and if the biosimilar were 30% cheaper, instead of 22%, the saving increased to $354 million. However, recognising that there is a shifting preference from filgrastim to peg-filgrastim the authors also modelled a shift to peg-filgrastim at an annual rate of 2.3% per year which reduced the estimated cost saving to $170 million.

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

During the current review update period there were two manuscripts published that specifically address the theme of biosimilar uptake.

- Marciano et al, 2018: Pattern of use of biosimilar and originator somatropin in Italy: A population-based multiple databases study during the years 2009-2014 [15]

This manuscript reports a large retrospective, population-based study across six regions in Italy that investigated the use of recombinant growth hormone (rGH) somatropin between 2009 and 2014. A total of 6785 patients received at least one rGH product (originator or biosimilar) during the study period, of these patients 4493 were naïve rGH users. The prevalence of rGH utilisation (originator or biosimilar) increased during the first two observation years (from 0.2 per 1,000 inhabitants in 2009 to 0.3 per 1,000 inhabitants in 2010) and remained stable until the end of the study. The proportion of biosimilar rGH users was low, with the average biosimilar rate of uptake across regions ranging from 6.6% in 2009 to 7.8% in 2014. Two regions observed a decrease in biosimilar uptake during this period (11.6 to 2.1% and 7.7 to 1.9% [2009 to 2014]) whereas others observed an increasing trend (5.0 to 7.5%, 4.7 to 11.6% and 5.2 to 16.9% [2009 to 2014]) which the authors attributed to the fact that "*Each Region can autonomously make specific drug-related policy interventions. In these six Regions, different health policy interventions about biosimilars were implemented at different times during the data collection period applied over time*." The authors did not specifically link any policy interventions in the different regions with these observed changes.

No statistically significant difference (p-value > 0.05) was observed in treatment persistence between biosimilar rGH (Omnitrope®) and originator products. The frequency of switching between different rGH products within 1 year of initiation was low (6.9%).

The authors note that the purchase cost of biosimilar rGH is "*at least 20–30% lower than the reference product*" and conclude that price reduction is not the only factor influencing biosimilar rGH product uptake and that the different rGH products available on the market vary in terms of device design such as "*manual or automatic electronic devices self-injection pens, needle-free devices, with different characteristics in terms of ease of use, lack of pain during injection*". The authors concluded that "*these characteristics may influence the adherence to therapy, especially in younger patients*".

- Di Giuseppe et al, 2018: Uptake of rheumatology biosimilars in the absence of forced switching [16]

This study describes the uptake of infliximab and etanercept biosimilars in Sweden, a country in which forced switching does not occur, and compares the characteristics of patients starting a biosimilar with those initiating the originator product. Patients initiating infliximab or etanercept between 1 April 2016 and 31 December 2016 were identified in the Swedish Rheumatology Quality Register. Between 1 March 2015 and 31 December 2016, a total of 1865 patients initiated infliximab, 522 started originator and 1343 started biosimilar and between 1 April 2016 and 31 December 2016, a total of 2940 patients initiated etanercept, 249 started originator and 2691 the biosimilar. No significant differences in patient characteristics were identified in biological disease modifying antirheumatic drug (bDMARD) naïve patients commencing a biosimilar versus originator. Patients switching to biosimilar etanercept tended to have a shorter duration of treatment with originator than those who continued treatment originator (5 months vs 5.6 months). At

the end of the study period, this corresponded to 22 months post-market entry for biosimilar infliximab and 9 months for biosimilar etanercept, biosimilars accounted for 31% of both infliximab and etanercept treated patients. The authors observed that following biosimilar availability the increase in the number of patients currently receiving any bDMARD increased from 125 new patients per month on average (January 2013 until March 2015) to 165 patients per month (April 2016 through January 2017) whilst for bDMARDs other than infliximab or etanercept this decreased from 103 (January 2013–March 2015) to 68 (April 2016–January 2017). On this basis the authors note that "*Our results suggest that the introduction of biosimilars not only replaced part of the market of their originator products, but also may have contributed to an increase in the overall use of bDMARDs*".

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 13 publications that specifically examine this theme related to erythropoiesis-stimulating agents (ESAs), filgrastim, adalimumab, etanercept and infliximab.

Erythropoiesis-stimulating agents (ESAs)

- Motola et al, 2018: Comparative risk/benefit profile of biosimilar and originator erythropoiesis-stimulating agents (ESAs): data from an Italian observational study in nephrology [17]

This manuscript reports a multi-centre retrospective observational study comparing drug utilization, efficacy and safety of biosimilar erythropoiesis-stimulating agents (ESAs) vs originator in patients with chronic kidney disease in daily clinical practice. Patients were treated with epoetin alfa, beta, and darbepoetin as originator and epoetin zeta as biosimilar. A total of 104 patients from nine participating regional centres across Italy were followed between September 2014 and July 2016. The average age was 72.9 ([range: 36-92]; 63% male) and 74.9 years [range: 48-95]; 60% male) for originator and biosimilar groups, respectively. For each enrolled patient, glomerular filtration rate (GFR), haemoglobin level (g/dL), type of epoetin used (name, route of administration, dose, and frequency of administration), concomitant drugs, and ADRs were recorded during the first visit and after 3, 6, and 12 months of follow-up. The authors reported that "*patients of the biosimilar group were in slightly worse health conditions as for their differences in the initial glomerular filtration rate and comorbidities*" but the only statistically significant difference between the baseline characteristics of the study groups was the presence of hypertension (63.2% in originator group vs 87.2% in biosimilar group, $p = 0.005$). Of the 104 patients, 57 patients (55%) were initiated on originator ESA and 47 (45%) were initiated on the biosimilar. Baseline haemoglobin levels were similar between the biosimilar and originator groups, 9.4 (± 0.85) g/dL and 9.3 (± 1.23) g/dL respectively. After 3 months, 48 patients remained in the originator group as compared to 44 in the biosimilar group. The increase in haemoglobin at this time was significantly greater in the biosimilar compared to the originator group (absolute increase 1.6 vs 1.0 g/dL, $p < 0.001$). At 12 months, data was only available for 19 patients in the biosimilar group and 16 in the originator group. The absolute mean increase in haemoglobin was 2.0 g/dl in the biosimilar group as compared with 1.0 g/dl in the originator

group (p < 0.001). The authors conclude that "*Our results have shown that originator and biosimilar ESAs are at least equally effective and safe for the treatment of anaemia due to CKD*" and that "*…the most important challenge should be the increase in confidence of authorities, clinicians, and patients in efficacy and safety of biosimilars that will lead to an increased use of biosimilar in clinical practice*."

Commentary

The inclusion of darbepoetin in this study complicates the interpretation as the outcomes associated with the use of biosimilar erythropoietin is being compared against a group that contains not only originator erythropoietin but also darbepoetin, which whilst being closely related to erythropoietin is a different agent.

Filgrastim

- Schwartzberg et al, 2018: Clinical Outcomes of Treatment with Filgrastim Versus a Filgrastim Biosimilar and Febrile Neutropenia-Associated Costs Among Patients with Nonmyeloid Cancer Undergoing Chemotherapy [18]

  This retrospective cohort study from health care administrative claims data aimed to compare the incidence of febrile neutropenia and potential serious adverse event in patients receiving originator filgrastim with those receiving biosimilar filgrastim (filgrastim-sndz). Patients were identified from the Optum Research Database between September 2014 to 31 July 2016 if they had a diagnosis of nonmyeloid malignancy and at least one claim for chemotherapy in the 30 days prior to a claim for originator or biosimilar filgrastim. Filgrastim use considered prophylactic if administered within 5 days of chemotherapy. Specific details regarding chemotherapy are not provided. Efficacy outcomes included neutropenia plus fever, neutropenia plus infection and neutropenia plus infection plus fever, as documented by relevant International Classification of Diseases codes. Equivalence between originator and biosimilar filgrastim considered if the 90% confidence interval for the between group difference in incidence were between -6% and +6%. A total of 3542 patients were included of whom 172 received biosimilar filgrastim and 3370 received originator. The difference in incidence between biosimilar and originator groups was 0.47 (90%CI:-0.86 to 2.87) for neutropenia plus fever, 0.57 (90%CI: 1.57 to 4.41) for neutropenia plus infection and 0.3 (90% not calculated due to 0 incidence in biosimilar group) for neutropenia plus infection plus fever, all of which were within the equivalence criteria. The authors conclude that "*In this real-world study of patients with nonmyeloid cancers undergoing chemotherapy, the incidence of FN* [febrile neutropenia] *was statistically equivalent between individuals treated with filgrastim-sndz* [biosimilar filgrastim] *versus filgrastim-ref* [originator filgrastim] *during their first chemotherapy cycle*."

Adalimumab

- Cohen et al, 2018: Successful administration of BI 695501, an adalimumab biosimilar, using an autoinjector (AI): results from a Phase II open-label clinical study (VOLTAIRE®-RL) [19]

The aim of this 7-week, open-label, single-arm, interventional clinical trial in participants with rheumatoid arthritis was to assess the real-life patient handling of a proposed adalimumab biosimilar (BI 695501) when administered via an autoinjector (AI). Following participant training, the primary end point was the percentage of successful self-injections as reported in the questionnaires completed by participants and trial site personnel among the three planned self-injections. A total of 77 participants were included. Of the 218 injections made by these participants, 216 (99.1%) were considered successful by both study site personnel and the participant. Both unsuccessful injections were a result of the participant being unable to press the injection button and were attributed to user error, not device failure. The authors conclude that "*After training by site personnel, almost all patients with moderately to severely active RA without prior experience of self-injections with AIs were able to successfully self-administer BI 695501 SC using an AI*."

Etanercept

- Tweehuysen et al, 2018: Open-Label Non-Mandatory Transitioning From Originator Etanercept to Biosimilar SB4: 6-Month Results From a Controlled Cohort Study [20]

The aim of this study, sponsored by Biogen, was to evaluate the impact of non-mandatory switch from originator etanercept to biosimilar etanercept (SB4) on drug survival and effectiveness in a cohort of patients with inflammatory rheumatic disease. A total of 642 patients treated with originator etanercept were approached, by letter, to consider switching to the etanercept biosimilar. The authors state that they developed "*a structured communication strategy for transitioning to a biosimilar including proper patient information and healthcare providers' education"* but details are not provided in the manuscript. At the time of their next prescription refill patients were asked if they would switch to the biosimilar. Those that did not switch at that time were contacted by their rheumatologist to discuss switching and if they continued to decline remained on treatment with originator etanercept. Of those approached, 635 (99%) agreed to switch to biosimilar etanercept of whom 625 patients were included in the study. These patients were then compared against a historical control group of patients treated with originator etanercept at the institution in 2014. The primary outcome was the adjusted hazard ratio (HR) for discontinuation in the switching cohort as compared with the historical cohort. Patients who discontinued treatment as a result of achieving remission were not coded as an event and were censored at the time of discontinuation. A multivariate Cox regression analysis was used to adjust the HR of discontinuation for differences in potential baseline confounders including etanercept treatment duration, etanercept dose interval, concomitant therapy and demographics factors. Most characteristics were considered similar between the switching and historical cohorts except the switching group had a longer etanercept treatment duration (3 [p25-p75: 2-6] versus 2 [p25-p75: 1-4] years, $P < 0.001$) and a longer etanercept dose interval (7 [p25-p75: 7-14] versus 7 [p25-p75: 7-10] days, $P < 0.001$). The disease activity measure DAS28-CRP was lower in the switching group (1.9 [p25-p75: 1.5- 2.6] versus 2.1 [p25-p75: 1.6-2.9], $P < 0.001$).

The crude persistence rate at 6 months in the switching group was 90% (95%CI: 88% to 93%) as compared with 92% (95%CI: 90% to 94%) in the historical cohort and the adjusted hazard ratio for discontinuation in the switching group as compared with the historical cohort was 1.57 (95%CI: 1.05 to 2.36). The authors note that "*It is likely that in 2016 (at the time of the transition cohort) treatment was more strongly adherent to the "treat-to-target" principle than in 2014 (at the time of the historical cohort)*" and as such these finding might have been impacted by changes in practice that have occurred in the intervening time between the historical control cohort and the switching cohort. When analysing the reasons for treatment discontinuation, lack of effect (43% in the switching group versus 61% in the historical control) and adverse events (47% in the switching group versus 28% in the historical control) were most common. The switching cohort reported a greater number of adverse events per patient than the historical cohort (1.5 [p25-p75: 1-3] versus 1 [p25-p75: 1-1] respectively, P = 0.01) and that "*…more AEs* [adverse events] *were categorized as subjective health complaints (46 of 55 (84%) versus 6 of 15 (40%), P < 0.001)*". The authors consider that "*Although it is challenging to demonstrate, we presume that the higher rate of subjective health complaints in the transitioning cohort is nocebo-related*". Of those that discontinued biosimilar etanercept, 17 restarted originator etanercept, 32 changed to an alternative bDMARD and 11 ceased treatment with any bDMARD. Of those that ceased biosimilar etanercept due to adverse events, 46% (13/28) resumed treatment with originator etanercept as compared with 15% (4/26%) that ceased due to lack of effect. Outcomes are not provided for these patients.

The authors conclude that "*…non-mandatory transitioning from ENB [originator etanercept] to SB4 [biosimilar etanercept] using a specifically designed communication strategy showed a slightly lower persistence rate and smaller decreases in disease activity compared with a historical cohort, but these differences were considered as not being clinically relevant*".

Infliximab

- Ratnakumaran et al, 2018: Efficacy and tolerability of initiating, or switching to, infliximab biosimilar CT-P13 in inflammatory bowel disease (IBD): a large single-centre experience [21]

This observational study aimed to assess whether it was effective and safe to switch patients with inflammatory bowel disease from originator infliximab to biosimilar infliximab (CT-P13) and to assess whether biosimilar infliximab was as effective and safe as originator infliximab in patients newly commenced on infliximab therapy.

Prior to the switch date in February 2016, a total of 210 patients were receiving maintenance originator infliximab therapy and were considered to have responded or were in remission. Of these, 191 (91.0%) patients consented to switch to biosimilar infliximab and 19 (9.0%) continued treatment with the originator. Of those who switched, the mean duration of infliximab treatment prior to switching was 55 months. At 12 months post-switch 58.1% (n=111/191) of patients remained in remission as compared with 47.4% (n=9/19) of those that continued treatment with originator infliximab (p = 0.37) and 24.6% (n=47/191) who switched were considered to be secondary non-responders as compared with 42.1% (n=8/19) of those who continued with originator (p =0.10). No patients who continued originator infliximab

experienced an adverse event as compared with nine of those that switched including four patients that developed dermatitis and three that developed infusion reactions.

A total of 69 patients were newly initiated on biosimilar infliximab. These patients were compared against a historical cohort of 53 patients initiated on originator infliximab in the 12 months prior to the implementation of biosimilar infliximab. As compared with the historical cohort, the biosimilar infliximab group included a greater proportion of patients with ulcerative colitis (50.7% vs. 24.5%, p = 0.003) and had a higher mean CRP (20.2 vs. 10.6, p = 0.008) but a lower median partial Mayo score (5 vs. 11, p = 0.007). Remission occurred in 42.0% (n=29/63) patients who commenced biosimilar infliximab as compared with 26.4% (n=14/53) patients receiving originator infliximab (p = 0.07) whilst a response occurred in 21.7% (n=15/69) and 26.4% (n=14/53) patients respectively (p=0.91). Secondary loss of response occurred in 21.7% (n=15/69) of those receiving biosimilar infliximab as compared with 22.6% (n=12/53) of those receiving originator. Adverse events occurred in six patients in both groups (p=.95).

The authors conclude that "*These data highlight that there is no difference in remission, response, loss of response or adverse events when initiating or switching to CT-P13 compared with initiating or continuing infliximab originator for IBD.*"

- Chanchlani et al, 2018: Use of infliximab biosimilar versus originator in a paediatric United Kingdom inflammatory bowel disease induction cohort [22]

This study aimed to compare the short term effectiveness, safety, and cost of biosimilar infliximab with originator infliximab in biologic naïve paediatric patients with inflammatory bowel disease. Data was obtained from a total of 27 sites, including 19 of 25 specialist UK paediatric IBD sites. Patients were included if they commenced treatment after February 2015. A total of 175 patients were started on originator infliximab and 82 on biosimilar infliximab. At baseline, median Paediatric Crohn's Disease Activity Index (PCDAI) was considered to be similar between the two originator and biosimilar groups (36 vs 28 respectively, p=0.08). At 3-months, the median PCDAI score was 5 in the originator group as compared with 0 in the biosimilar group (p = 0.35). During induction, three patients in the originator group experienced adverse events. At 3-months there were no differences in adverse events. Assuming an average weight of 40 kilograms per patient and approximately nine infusions in the first year, it was estimated that a cost saving of approximately £875,000 was associated with the use of biosimilar infliximab over a one-year period. The authors conclude that "*IFX-B* [biosimilar infliximab] *is likely as effective as IFX-O* [originator infliximab] *in treating IBD in comparable pediatric populations"* and that *"Sites should adopt infliximab biosimilar for new starts due to cost reduction with no difference in other parameters*."

- Binkhorst et al, 2018: Switching to a infliximab biosimilar: short-term results of clinical monitoring in patients with inflammatory bowel disease [23]

This manuscript describes the outcomes from 197 patients with inflammatory bowel disease that switched from originator to biosimilar infliximab. After two infusion of biosimilar infliximab there was no difference in median CRP as compared with baseline (P = 0.55, n = 102) and median fecal calprotectin levels were within the normal range. There were no significant differences identified in serum trough concentration of between baseline and after switching (P = 0.08, n = 98). A total of 20 patients discontinued treatment. Loss of response was reported in 11 patients (details not provided), of whom seven received dose intensification

whilst four were switched back to originator infliximab. It is reported that "A*fter this switch, disease-related complaints disappeared in these patients*". A total of 11 patients experienced adverse events including one infusion reaction. The authors conclude that "*Our study indicates that switching from Remicade* [originator infliximab] *to the biosimilar infliximab is safe in clinical practice*" and that "*No clinically relevant differences were observed between the two treatments in disease activity, adverse reactions, and serum infliximab concentrations*."

- Strik et al, 2018: Serum concentrations after switching from originator infliximab to the biosimilar CT-P13 in patients with quiescent inflammatory bowel disease (SECURE): an open-label, multicentre, phase 4 non-inferiority trial [24]

  This prospective, open-label, interventional, non-inferiority, multi-centre study investigated the impact of switching from originator infliximab to biosimilar infliximab (CT-P13) on serum infliximab concentrations in patients with inflammatory bowel disease who had received continuous treatment with originator infliximab for at least 30 weeks. Infliximab concentrations were measured prior to the switch and at 8 and 16 weeks post-switching. At week 16, the geometric mean ratio of serum infliximab concentrations compared to baseline was 110·1% (90%CI: 96·0–126·3) in patients with ulcerative colitis and 107·6% (90%CI: 97·4–118·8) in those with Crohn's disease which were higher than the lower bound of the predefined non-inferiority limit of 85%.

- Kolar et al, 2018: Pregnancy outcomes in women with inflammatory bowel disease treated with biosimilar infliximab [25]

  The authors report on the outcomes of 20 female patients with inflammatory bowel disease that either became pregnant whilst receiving treatment with biosimilar infliximab or in whom treatment was initiated during pregnancy. Of these patients, there were 19 live births and one spontaneous abortion. Of the live births, 18 were at term and one pre-term. One congenital defect was detected. The authors conclude that "*… out study found no new safety concerns regarding use of biosimilar IFX (CT-P13) during pregnancy in terms of birth outcomes, however, further evaluation of a larger cohort of patients is warranted.*"

- Aarebrot et al, 2018: Phosphorylation of intracellular signalling molecules in peripheral blood cells from patients with psoriasis on originator or biosimilar infliximab [26]

  As a component of a larger study this study investigated the impact of switching patients with psoriasis from originator infliximab to the biosimilar infliximab (CT-P13) on the activity of a range of intracellular signalling molecules thought to be important in psoriasis. The study included 25 patients with a history of severe psoriasis but who were now considered to be maintained in remission with regular administration of infliximab. Of these, 13 patients were switched to biosimilar infliximab and 12 continued with originator. Blood samples were collected at inclusion and at 3 and 12 months post-switching from which specific blood cells were isolated and the pattern of phosphorylation of five intracellular signalling molecules, a marker of activity, was assessed. When comparing the phosphorylation pattern of these signalling molecules between those who continued originator infliximab and those who switched to biosimilar there were no significant differences in the phosphorylation patterns at either 3 or 12 months with exception of a modest, but statistically significant increase in one molecule (pSTAT3) in one blood cell type at 3 months in those who

switched. This statistical difference was not observed at 12 months. On the basis of these results the authors conclude that "*Switching from infliximab to CT-P13 did not worsen clinical parameters or increase intracellular phosphorylation of NF-jB, ERK, p38 or STAT3.*"

Commentary

This study utilised complex methods to investigate the impact of switching from originator to biosimilar infliximab on very detailed cellular pathways that are thought to be related to psoriasis and how infliximab might work in this condition. During the development of biosimilar medicines, detailed experiments are conducted to compare the effect of a proposed biosimilar and the originator on intracellular signalling molecules prior to any human studies occurring. This manuscript conducts a similar type of experiment but with the use of blood cells obtained from patients that switched from originator to biosimilar in a real-life setting. The authors note that this study provides real-life evidence that "*Switching from originator to biosimilar infliximab does not seem to influence intracellular signalling activity of PBMCs* [the blood cells studied]" which complements the existing clinical evidence, such as disease activity measures, related to switching from originator to biosimilar infliximab.

- Fiorino et al, 2018: Full Interchangeability in Regard to Immunogenicity Between the Infliximab Reference Biologic and Biosimilars CT-P13 and SB2 in Inflammatory Bowel Disease [27]

  This study investigated the cross-reactivity of anti-drug antibodies obtained from patients with inflammatory bowel disease treated with originator and/or biosimilar infliximab (CTP-13) against originator and biosimilar infliximab (CT-P13 and SB2). Anti-drug antibodies were obtained from 34 patients, of whom 13 were treated with originator infliximab only, 9 were treated with CT-P13 only and 12 had received both originator and CT-P13. In laboratory testing the antidrug antibodies obtained from these patients were considered to have "*identically cross-reacted*" with originator infliximab, CT-P13 and SB2. On the basis of these results the authors conclude that "*This study demonstrates for the first time identical reactivity of ATI* [anti-drug antibodies] *with the reference RMC* [originator infliximab] *and the 2 approved biosimilar molecules in patients with IBD*" and that "*…we conclude that CT-P13 and SB2 biosimilars could be interchangeable and that switching between biosimilars and their reference product will not lead to differences in ATI* [anti-drug antibody] *production.*"

- Høivik et al, 2018: Switching from originator to biosimilar infliximab – real world data of a prospective 18 months followup of a single-centre IBD population [28]

  In this manuscript the authors report on the outcomes associated with switching from originator to biosimilar infliximab (CT-P13) in 143 adult patients with inflammatory bowel disease. The primary endpoints were the proportion of patients remaining on biosimilar infliximab at 18 months after switching and the immunogenicity during the 18 months post-switching. Of the 143 patients that switched, 130 patients remained on biosimilar infliximab through the 18 month period, twelve patients discontinued and one was lost to follow-up. Of those that discontinued, two developed anti-drug antibodies (ADAs), two lost response but were ADA negative, four experienced adverse effects, four were in remission and one requested to stop. When compared with the time of the switch, there was no statistically significant change in the proportion of patients in clinical remission at 18 months. The authors conclude that "*…the present*

study provides valuable evidence for the safety and effectiveness of switching from originator to biosimilar IFX over a prolonged follow-up period of 18 months and demonstrates that switching was well tolerated and did not affect the long term clinical outcome."

- Schimmelpennink et al, 2018: Efficacy and safety of infliximab biosimilar Inflectra® in severe sarcoidosis [29]

This retrospective cohort study describes the outcomes of the use of biosimilar infliximab (CT-P13) in 29 patients with sarcoidosis. All patients had failed or were intolerant of at least two systemic treatments which included corticosteroids, methotrexate, azathioprine and hydroxychloroquine. In patients where respiratory function was the predominant indication for treatment, respiratory function significantly improved (p = 0.026) after 26 weeks of treatment as indicated by a change in forced vital capacity (% predicted) increasing from 74.3% (± 17.6) at baseline to 82.4% (± 24.1). Following the induction phase, eight patients (28%) achieved a total resolution of inflammatory activity on PET-scan. The authors conclude that "*…the response rate and safety profile of Inflectra®* [biosimilar infliximab] *seems comparable to that of Remicade®*[originator infliximab]".

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

There was a single original research articles published during the review update period addressing the topic of biosimilar perception amongst patients with psoriasis.

- Ighani et al, 2018: An Evaluation of Psoriasis Patient Perceptions and Understanding of Biosimilars: A Canadian Survey Comparing Biologic and Nonbiologic Users [30]

In this letter, the authors describe the outcomes of an online survey conducted between July and September 2016 by the Canadian Association of Psoriasis Patients which aimed to assess the perception and understanding of biosimilars in adult patients with moderate to severe psoriasis. Prior to completing the survey respondents were informed that "*After the patent on a biologic drug has expired, a manufacturer may seek approval for a drug that is similar but not identical to the original drug. SEBs are not considered generics and not considered to be interchangeable by Health Canada*" and that "*Because they are made from living organisms, biologics "tend to be significantly more variable and structurally complex than chemically synthesized drugs." Therefore, unlike "generic" copies of a "chemical" drug, biosimilars are not exact replicas of the original biologic medicine but "highly similar"*." A total of 343 responses were received, of whom 218 were biologic users and 125 non-users, with biologic users more likely than non-users to indicate that they were somewhat or very familiar with biosimilars (P = 0.012) on a five-point Likert scale ranging from not at all familiar to very familiar. When asked "*How concerning would it be for you if the government or private insurance plan made the determination which biologic (biologic treatment or subsequent entry biologic) to prescribe or reimburse on initiation of treatment?"* 69.4% of respondents *(n = 238/343)* were somewhat or very concerned whilst 22.7% were not sure and 7.9% were not concerned. Similarly when asked "*How concerning would it be for you if the government or private insurance plan made the determination of which biologic (biologic treatment or SEB) to dispense to you during your treatment,*

including maintenance therapy (making you switch medicines without telling you)? (single response permitted)" 75% of respondents were somewhat or very concerned, 17% were not sure and 8% were not concerned. "*Safety*" and "*efficacy*" were considered to be the most important factors regarding regulation. The authors state that "*Based on these findings, it may be helpful for patients to be informed about the differences between originator biologics and biosimilars, particularly for nonbiologic users who are considering using a biologic agent to manage their psoriasis for the first time or patients who may be seeking a more cost effective alternative for biologic treatment.*"

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27. Fiorino, G, Ruiz-Arguello, MB, Maguregui, A, et al. Full Interchangeability in Regard to Immunogenicity Between the Infliximab Reference Biologic and Biosimilars CT-P13 and SB2 in Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*, 2018; **24**(3): 601-606.

28. Hoivik, ML, Buer, LCT, Cvancarova, M, et al. Switching from originator to biosimilar infliximab - real world data of a prospective 18 months follow-up of a single-centre IBD population. *Scandinavian Journal of Gastroenterology*, 2018: 1-8.

29. Schimmelpennink, MC, Vorselaars, ADM, van Beek, FT, et al. Efficacy and safety of infliximab biosimilar Inflectra in severe sarcoidosis. *Respiratory Medicine*, 2018; **138**(Supplement): S7-S13.

30. Ighani, A, Wang, JY, Manolson, MF. An Evaluation of Psoriasis Patient Perceptions and Understanding of Biosimilars: A Canadian Survey Comparing Biologic and Nonbiologic Users. *Journal of Cutaneous Medicine and Surgery.*, 2018; **01**.

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. This list includes several network meta-analyses, the results of which are consistent with the individual studies previously reported.

1. Aapro, M., et al., Development and 10-year history of a biosimilar: the example of Binocrit. Therapeutic Advances in Medical Oncology, 2018. 10: p. 1758835918768419.
2. Aapro, M., et al., Epoetin Biosimilars in the Treatment of Chemotherapy-Induced Anemia: 10 Years' Experience Gained. BioDrugs, 2018. 32(2): p. 129-135.
3. Abraham, J., Trastuzumab-dkst approval adds to the biosimilar cancer drug market. Journal of Community and Supportive Oncology, 2018. 16(2): p. e63-e65.
4. Abraham, J., Bevacizumab-awwb becomes first biosimilar approved for cancer treatment. Journal of Community and Supportive Oncology, 2018. 16(2): p. e60-e62.
5. Amato, L., et al., Comparative efficacy and safety in ESA biosimilars vs. originators in adults with chronic kidney disease: a systematic review and meta-analysis. Journal of Nephrology, 2018. 31(3): p. 321-332.
6. Arguelles Arias, F., J. Hinojosa Del Val, and I. Vera Mendoza, Update of the SEPD position statement on the use of biosimilars for inflammatory bowel disease. Revista Espanola de Enfermedades Digestivas, 2018. 110(6): p. 407.
7. Bae, S.C. and Y.H. Lee, Comparative efficacy and safety of biosimilar adalimumab and originator adalimumab in combination with methotrexate in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials. Clinical Rheumatology, 2018. 37(5): p. 1199-1205.
8. Bae, S.C. and Y.H. Lee, Comparative efficacy and safety of biosimilar-infliximab and originator-infliximab in combination with methotrexate in patients with active rheumatoid arthritis: a meta-analysis of randomized controlled trials. International Journal of Rheumatic Diseases, 2018. 19: p. 19.
9. Barker, J., Biosimilars. Journal of the European Academy of Dermatology & Venereology, 2018. 10: p. 10.
10. Blackwell, K., et al., The Global Need for a Trastuzumab Biosimilar for Patients With HER2-Positive Breast Cancer. Clinical Breast Cancer, 2018. 18(2): p. 95-113.
11. Bridges, S.L., et al., The Science Behind Biosimilars: Entering a New Era of Biologic Therapy. Arthritis and Rheumatology, 2018. 70(3): p. 334-344.
12. Carrascosa, J.M., et al., Biosimilar Drugs for Psoriasis: Principles, Present, and Near Future. Dermatology And Therapy, 2018. 16: p. 16.
13. Carroll, D., et al., Biosimilar infliximab introduction into the gastroenterology care pathway in a large acute Irish teaching hospital: A story behind the evidence. GaBI Journal, 2018. 7(1): p. 14-21.
14. Cazap, E., et al., Global Acceptance of Biosimilars: Importance of Regulatory Consistency, Education, and Trust. Oncologist., 2018.

15. Chance, K., FDA Expectations for Demonstrating Interchangeability. Therapeutic Innovation and Regulatory Science, 2018. 52(3): p. 369-373.

16. Cohen, H.P., et al., Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes. Drugs, 2018. 78(4): p. 463-478.

17. Cornes, P. and M. Aapro, The impact of biosimilars in supportive care in cancer. European Oncology and Haematology, 2018. 14(1): p. 20-32.

18. Danese, S. and G. Fiorino, Anti-TNF biosimilars in inflammatory bowel disease: searching the proper patient's profile? Current Medicinal Chemistry, 2018. 13: p. 13.

19. Davies, R. and K.L. Hyrich, Biologics registers in rheumatoid arthritis. Medicine (United Kingdom), 2018. 46(4): p. 243-246.

20. Declerck, P., et al., Monoclonal Antibody Biosimilars in Oncology: Critical Appraisal of Available Data on Switching. Clinical Therapeutics, 2018. 40(5): p. 798-809.e2.

21. Dellanna, F., et al., HX575: Established biosimilarity in the treatment of renal anemia and 10 years of clinical experience. Drug Design, Development and Therapy, 2018. 12: p. 9-14.

22. El Zorkany, B., et al., Biosimilars in rheumatology: recommendations for regulation and use in Middle Eastern countries. Clinical Rheumatology, 2018. 37(5): p. 1143-1152.

23. Esteva, F.J., et al., Efficacy and safety of the trastuzumab biosimilar candidate CT-P6. Future Oncology, 2018. 27: p. 27.

24. Eustace, G.J. and G.Y. Melmed, Therapy for Crohn's Disease: a Review of Recent Developments. Current Gastroenterology Reports, 2018. 20 (5) (no pagination)(19).

25. Feldman, S.R., J. Bagel, and S. Namak, Biosimilars for Immune-Mediated Chronic Diseases in Primary Care: What a Practicing Physician Needs to Know. American Journal of the Medical Sciences, 2018. 355(5): p. 411-417.

26. Fernandes, G.S., et al., The use of biosimilar medicines in oncology - position statement of the brazilian society of clinical oncology (SBOC). Brazilian Journal of Medical and Biological Research, 2018. 51 (3) (no pagination)(e7214).

27. Fitton, J., A. Giollo, and M.H. Buch, GP2015 as a promising therapy for rheumatoid arthritis. Expert Opinion on Biological Therapy, 2018. 18(4): p. 477-481.

28. Frank, R.G., Friction in the path to use of biosimilar drugs. New England Journal of Medicine, 2018. 378(9): p. 791-793.

29. Gamez-Belmonte, R., et al., Biosimilars: Concepts and controversies. Pharmacological Research., 2018.

30. Gisbert, J.P. and M. Chaparro, Switching from an originator anti-TNF to a biosimilar in patients with inflammatory bowel disease: Can it be recommended? A systematic review. Gastroenterologia y Hepatologia., 2018.

31. Goldsmith, D., et al., Epoetin Biosimilars in the Treatment of Renal Anemia: What Have We Learned from a Decade of European Experience? Clinical Drug Investigation, 2018. 38(6): p. 481-490.

32. Goll, G.L., E.A. Haavardsholm, and T.K. Kvien, The confidence of rheumatologists about switching to biosimilars for their patients. Joint Bone Spine., 2018.

33. Greenwald, M., J. Tesser, and K.L. Sewell, Biosimilars Have Arrived: Rituximab. Arthritis, 2018. 2018: p. 3762864.

34. Hajba, L., et al., On the glycosylation aspects of biosimilarity. Drug Discovery Today, 2018. 23(3): p. 616-625.

35. Ilias, A., et al., Biosimilars in ulcerative colitis: When and for who? Best Practice and Research: Clinical Gastroenterology., 2018.

36. Ingrasciotta, Y., et al., Safety of Biologics, Including Biosimilars: Perspectives on Current Status and Future Direction. Drug Safety, 2018: p. 1-10.

37. Janjigian, Y.Y., et al., Talking to patients about biosimilars. Future Oncology, 2018. 01: p. 01.

38. Kang, H.N. and I. Knezevic, Regulatory evaluation of biosimilars throughout their product life-cycle. Bulletin of the World Health Organization, 2018. 96(4): p. 281-285.

39. Karas, L., et al., Limited distribution networks stifle competition in the generic and biosimilar drug industries. American Journal of Managed Care, 2018. 24(4): p. e122-e127.

40. Kiss, S., H.F. Fine, and J. Krawitz, Coming of age: Biosimilars. Ophthalmic Surgery Lasers and Imaging Retina, 2018. 49(3): p. 162-165.

41. Kurti, Z., L. Gonczi, and P.L. Lakatos, Progress with infliximab biosimilars for inflammatory bowel disease. Expert Opinion on Biological Therapy, 2018: p. 1-8.

42. Lamb, Y.N., SB3 (Ontruzant®): A Trastuzumab Biosimilar. BioDrugs, 2018: p. 1-4.

43. Lyman, G.H., et al., American society of clinical oncology statement: Biosimilars in oncology. Journal of Clinical Oncology, 2018. 36(12): p. 1260-1265.

44. Lyman, G.H., et al., Rationale, opportunities, and reality of biosimilar medications. New England Journal of Medicine, 2018. 378(21): p. 2036-2044.

45. Melosky, B., et al., Bevacizumab biosimilars: scientific justification for extrapolation of indications. Future Oncology, 2018. 25: p. 25.

46. Mengato, D. and A. Messori, Adalimumab biosimilar in rheumatoid arthritis: a total-evidence assessment to evaluate equivalence with the originator based on network meta-analysis. Clinical & Experimental Rheumatology, 2018. 20: p. 20.

47. Mielke, J., et al., An update on the clinical evidence that supports biosimilar approvals in Europe. British Journal of Clinical Pharmacology., 2018.

48. Moots, R.J., et al., Efficacy and Safety Outcomes for Originator TNF Inhibitors and Biosimilars in Rheumatoid Arthritis and Psoriasis Trials: A Systematic Literature Review. Biodrugs, 2018. 22: p. 22.

49. Paplomata, E. and R. Nahta, ABP 980: Promising trastuzumab biosimilar for HER2-positive breast cancer. Expert Opinion on Biological Therapy, 2018. 18(3): p. 335-341.

50. Pelechas, E., P.V. Voulgari, and A.A. Drosos, ABP 501 for the treatment of rheumatoid arthritis. Expert Opinion on Biological Therapy, 2018. 18(3): p. 317-322.

51. Rawla, P., T. Sunkara, and J.P. Raj, Role of biologics and biosimilars in inflammatory bowel disease: Current trends and future perspectives. Journal of Inflammation Research, 2018. 11: p. 215-226.

52. Reinivuori, T., P. Kurki, and P. Chamberlain, Immunogenicity Assessment of Biosimilars. Pharmaceutical Medicine, 2018. 32(2): p. 103-121.

53. Rocco, P., S. Selletti, and P. Minghetti, Biosimilar switching and related medical liability. Journal of Forensic and Legal Medicine, 2018. 55: p. 93-94.

54. Schaeverbeke, T., et al., Biosimilars: An opportunity. Position statement of the French Rheumatology Society (SFR) and Inflammatory Rheumatic Disease Club (CRI). Joint Bone Spine., 2018.

55. Scott, F.I. and G.R. Lichtenstein, Biosimilars in the Treatment of Inflammatory Bowel Disease: Supporting Evidence in 2017. Current Treatment Options in Gastroenterology, 2018. 16(1): p. 147-164.

56. Tieu, C., et al., Efficacy and safety of biosimilar insulins compared to their reference products: A systematic review. PLoS ONE, 2018. 13 (4) (no pagination)(e0195012).

57. Trifiro, G., I. Marciano, and Y. Ingrasciotta, Interchangeability of biosimilar and biological reference product: updated regulatory positions and pre- and post-marketing evidence. Expert Opinion on Biological Therapy, 2018. 18(3): p. 309-315.

58. Wang, R., A. Dasgupta, and M.M. Ward, Comparative efficacy of tumor necrosis factor-alpha inhibitors in ankylosing spondylitis: A systematic review and Bayesian network metaanalysis. Journal of Rheumatology, 2018. 45(4): p. 481-490.

59. Yamada, T., et al., Biosimilar vs originator insulins: Systematic review and meta-analysis. Diabetes, Obesity & Metabolism, 2018. 14: p. 14.

60. Yamauchi, P., et al., Biosimilars: What the dermatologist should know. Journal of the European Academy of Dermatology and Venereology., 2018.

61. Zhao, S., E. Mysler, and R.J. Moots, Etanercept for the treatment of rheumatoid arthritis. Immunotherapy, 2018. 10(6): p. 433-445.

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. Cowper, B., et al., Comprehensive glycan analysis of twelve recombinant human erythropoietin preparations from manufacturers in China and Japan. Journal of Pharmaceutical and Biomedical Analysis, 2018. 153: p. 214-220.
2. Gupta, R. and M.P. Ponnusamy, Analysis of sulfates on low molecular weight heparin using mass spectrometry: structural characterization of enoxaparin. Expert Review of Proteomics, 2018: p. 1-11.
3. Jeong, Y.R., et al., Comprehensive Physicochemical and Biological Characterization of the Proposed Biosimilar Darbepoetin Alfa, LBDE, and Its Originator Darbepoetin Alfa, NESP®. BioDrugs, 2018. 32(2): p. 153-168.
4. Kim, J., et al., Evaluation of the physicochemical and biological stability of reconstituted and diluted SB2 (infliximab). European Journal of Hospital Pharmacy Science & Practice, 2018. 25(3): p. 157-164.
5. Lepelaars, L.R.A., et al., Comparing safety information of biosimilars with their originators: a cross-sectional analysis of European risk management plans. British Journal of Clinical Pharmacology, 2018. 84(4): p. 738-763.
6. Luchese, M.D., et al., A new CHO (Chinese hamster ovary)-derived cell line expressing anti-TNFalpha monoclonal antibody with biosimilar potential. Immunologic Research, 2018. 31: p. 31.
7. Mielke, J., H. Schmidli, and B. Jones, Incorporating historical information in biosimilar trials: Challenges and a hybrid Bayesian-frequentist approach. Biometrical Journal, 2018. 60(3): p. 564-582.
8. Montacir, O., et al., Bioengineering of rFVIIa Biopharmaceutical and Structure Characterization for Biosimilarity Assessment. Bioengineering, 2018. 5(1): p. 19.
9. Montacir, O., et al., Physicochemical Characterization, Glycosylation Pattern and Biosimilarity Assessment of the Fusion Protein Etanercept. Protein Journal, 2018. 37(2): p. 164-179.
10. Peraza, M.A., et al., Nonclinical assessments of the potential biosimilar PF-06439535 and bevacizumab. Regulatory Toxicology & Pharmacology, 2018. 95: p. 236-243.
11. Schoergenhofer, C., et al., Single, very low rituximab doses in healthy volunteers - a pilot and a randomized trial: implications for dosing and biosimilarity testing. Scientific Reports, 2018. 8(1): p. 124.
12. Seo, N., et al., Analytical and functional similarity of Amgen biosimilar ABP 215 to bevacizumab. mAbs, 2018. 10(4): p. 678-691.
13. Todoroki, K., et al., Current Mass Spectrometric Tools for the Bioanalyses of Therapeutic Monoclonal Antibodies and Antibody-Drug Conjugates. Analytical Sciences, 2018. 34(4): p. 397-406.
14. Vandekerckhove, K., et al., Rational Selection, Criticality Assessment, and Tiering of Quality Attributes and Test Methods for Analytical Similarity Evaluation of Biosimilars. AAPS Journal, 2018. 20 (4) (no pagination)(68).

15. Weiss, R.E., et al., Bayesian methods for analysis of biosimilar phase III trials. Statistics in Medicine., 2018.

16. Xiao, Z., et al., A comprehensive approach for evaluating charge heterogeneity in biosimilars. European Journal of Pharmaceutical Sciences, 2018. 115: p. 19-24.

17. Zeng, D., et al., Improving the power to establish clinical similarity in a Phase 3 efficacy trial by incorporating prior evidence of analytical and pharmacokinetic similarity. Journal of Biopharmaceutical Statistics, 2018. 28(2): p. 320-332.

18. Zhao, Y., Y. Chang, and S. Chow, On sample size requirement for analytical similarity assessment. Journal of Biopharmaceutical Statistics, 2018: p. 1-17.

19. Zhu, P., S.K.B. Sy, and A. Skerjanec, Application of Pharmacometric Analysis in the Design of Clinical Pharmacology Studies for Biosimilar Development. AAPS Journal, 2018. 20 (2) (no pagination)(40).