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Literature Review of International Biosimilar Medicines: Update December 2017 – February 2018

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Sponsor: National Medicines Policy Section
Department of Health
Australian Government

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Version: FINAL

Release Date: 24 APRIL 2018

Introduction

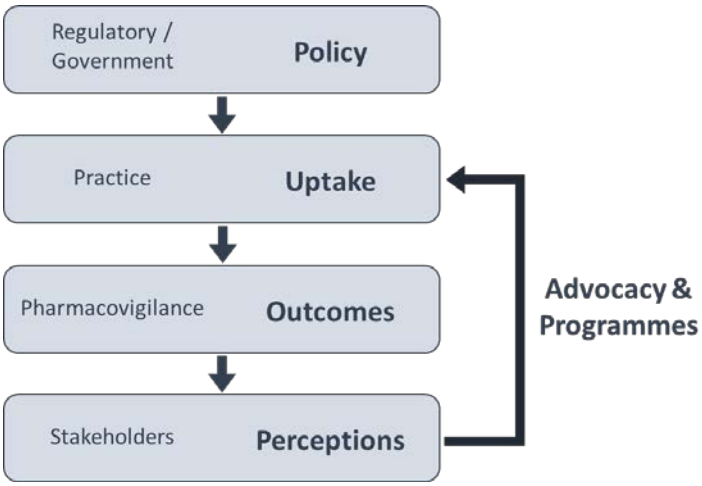
This report provides an update to the comprehensive literature search previously conducted that examined all international and Australian clinical, academic and policy journals and media articles or sources in relation to biosimilar medicines for the purpose of providing evidence which may inform policy 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 December 2017 and 28 February 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
Adalimumab						
M923 (Momenta)	Humira (US and EU)	Randomised, double-blind, three-arm, single-dose study	Healthy participants (n=324, 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 336hrs concentration (AUC_{336}) and maximal plasma concentration (C_{max}) were within the predefined bioequivalence interval of 0.80–1.25	At day 71 the proportion of confirmed ADA responses increased in all study groups to M923 = 78.0%, US Humira = 73.1%, and EU Humira = 75.7% The presence of IgE was confirmed in 13 subjects (2 in the M923 arm, 8 in the US Humira arm, and 3 in the EU Humira arm)	[1]
Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
Insulin lispro						
SAR342434 (Sanofi)	Humalog (Lilly)	Randomised, open-label, 2 × 4-week, two-arm crossover study	Participants with type I diabetes with at least 6 months of continuous subcutaneous insulin infusion treatment	6/25 participants reported 14 infusion set occlusion events whilst receiving SAR342434 as compared to 4/27 participants reporting 9 events whilst receiving Humalog. The event rate (events/participant-month) of any hypoglycemia was similar with SAR342434 (7.15) Humalog (7.98)	No hypersensitivity reactions or allergic reactions	[2]
Rituximab						
RTXM83 (mAbxience Research S.L)	MabThera	Population pharmacokinetic modelling of phase III clinical trial data	Participants with diffuse large B-cell lymphoma (RTXM83=127, MabThera=214; serum concentrations: RTXM83=2703 MabThera=2638)	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	Median values for drug clearance were similar between anti-drug antibody positive and negative subjects in both RTXM83 (10.8 vs 11.3 mL/ min, respectively) and MabThera groups (13.6 vs 11.3 mL/min, respectively)	[3]
Trastuzumab						
CT-P6 (Celltrion)	Herceptin (US)	Single-dose, randomised, double-blind, parallel group study	Healthy adult male volunteers (n=70, randomised 1:1)	90% CI for the ratio of geometric least square means for area-under-the-curve from time zero extrapolated to infinite time (AUC_{inf}), AUC from time 0 to last quantifiable concentration (AUC_{last}) and maximal plasma concentration (C_{max}) were within the prespecified limits of 80- 125% for the comparisons of CT-P6 with US Herceptin	No participants were positive for anti-drug antibodies.	[4]

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 seven reports including proposed biosimilars for etanercept, adalimumab, insulin lispro and trastuzumab.

- Matsuno et al, 2017: Phase III, multicentre, double-blind, randomised, parallel-group study to evaluate the similarities between LBEC0101 and etanercept reference product in terms of efficacy and safety in participants with active rheumatoid arthritis inadequately responding to methotrexate [5]

  The objective of this double-blind, randomised, parallel-group phase 3 trial was to compare the efficacy and safety of a potential etanercept biosimilar (LBEC0101, LG Chem, n=187) with reference etanercept (Enbrel, n=187) in participants with active rheumatoid arthritis despite treatment with methotrexate for at least 12 weeks. The primary efficacy endpoint was the change from baseline in the disease activity score in 28 joints based on erythrocyte sedimentation rate (DAS28-ESR) at week 24 with the equivalence margin for similarity predefined as a between group difference in the change from baseline in DAS28-ESR at week 24 of −0.6 to 0.6. The estimated between-group difference in DAS28-ESR at week 24 was −0.15 (95% CI: −0.377 to 0.078) which was within the prespecified equivalence margin. Anti-drug antibodies were detected in three participants in the potential biosimilar group as compared with 18 participants in the reference product group (two of whom were positive at baseline). Serious related adverse events occurred in 7% of participants in both groups. Injection site reactions were less frequent in the potential biosimilar group (10.2%, 19 participants, 77 events) than in the reference product group (34.2%, 64 participants, 438 events). The authors conclude that "*LBEC0101 was shown to be equivalent to ETN-RP* [reference entanercept] *in terms of clinical efficacy. LBEC0101 was well tolerated with a comparable safety profile to ETN-RP*."

- Emery et al, 2017: 52-week results of the phase 3 randomized study comparing SB4 with reference etanercept in patients with active rheumatoid arthritis [6]

  This phase 3, randomized, double-blind, multicentre study, in participants with moderate to severe RA despite treatment with methotrexate aimed to compare the efficacy and safety of a proposed biosimilar of etanercept (SB4) with originator etanercept. The primary endpoint of the study was efficacy at 24 weeks. This manuscript specifically reports on the secondary efficacy endpoints at 52 weeks as assessed according to the American College of Rheumatology (ACR) 20%, 50% and 70% improvement criteria. The ACR20 response rate at week 52 in the per-protocol set was 80.8% for SB4 and 81.5% for originator etanercept (adjusted difference 95% CI: -8.03-6.56%). Amongst participants that have achieved a given ACR response at week 24, a similar proportion of patients in the SB4 and originator groups maintained that response at week 52 (~90% for ACR20, 80% for ACR50 and 80% for ACR70). Radiographic progression from baseline up to week 52 was comparable between the two treatment groups as assessed by the mean change from baseline in the van der Heijde modification of the total Sharp score (mTSS); 0.45 versus 0.74 in the SB4 and originator groups respectively (95% CI difference in mTSS: -0.80 to 0.26). Up to week 52, treatment emergent adverse events were reported in 175 (58.5%) participants in the SB4 group and 179 (60.3%) patients in the originator group. The overall incidence of injection site reactions up to week 52 was 3.7% in the SB4 group (22 reactions reported in 11 participants) and 17.5% (157 reactions reported in 52 participants) in the originator group ($P < 0.001$). The overall incidence of anti-drug antibodies up to week 52 was 1.0% (3/299) in the SB4 group as compared with 13.2% (39/296) in the originator group ($P < 0.001$), noting that there was only a single

additional participant, from the SB4 treatment group, who developed ADA after week 24. The authors conclude that "*SB4 has shown comparable clinical efficacy, including radiographic progression, to ETN* [originator etanercept] *and maintenance of efficacy up to week 52*" and that "*SB4 was well tolerated with a similar 1 year safety profile to ETN*."

Commentary

A reduced incidence of injection site reactions and anti-drug antibodies were observed in the biosimilar group in both etanercept studies reported in this update. It is known that differences in excipients, container closures, aggregates and impurities can influence the risk of anti-drug antibody formation against biopharmaceuticals but this has not been specifically described for the etanercept biosimilars reported here. The basis for these observations is unknown at present.

- Weinblatt et al, 2018: Switching from reference adalimumab to SB5 (adalimumab biosimilar) in patients with rheumatoid arthritis: 52-week phase 3 randomized study results [7]

  The objective of this 52-week transition study was to compare the safety, immunogenicity, and efficacy of continuing treatment with a proposed adalimumab biosimilar (SB5) treatment with switching from originator adalimumab to SB5 and continuing treatment with originator adalimumab. Participants were initially randomized to receive either SB5 or originator adalimumab (1:1). At week 24, participants receiving originator adalimumab were randomized to either continue originator adalimumab (n=129) or to switch to SB5 (n=125). This manuscript reports on efficacy assessment at week 52. The American College of Rheumatology (ACR) responses observed at week 24 were maintained after switching from originator adalimumab to SB5, and the ACR response rates were comparable across treatment groups throughout the study with ACR20 response rates ranging across groups from 73.4% to 78.8% at week 52. Radiographic progression, as assessed by the joint erosion and joint space narrowing scores, was minimal and comparable across treatment groups. Anti-drug antibodies were detected in 16.8% (21/125) of those who switched from originator adalimumab to SB5 as compared with 15.7% (40/254) and 18.3% (23/126) those with continued SB5 and originator adalimumab respectively. After week 24, emergent anti-drug antibodies occurred in 6.3% (5/80) of participants in the switching group as compared with 5.6% (9/160) of participants in the group continuing SB5 group and 12.6% (11/87) in the group continuing originator. The authors conclude that "*Switching from ADA* [originator adalimumab] *to SB5 had no treatment- emergent issues such as increased adverse events, increased immunogenicity, or loss of efficacy*".

- Derwahl et al, 2018: Efficacy and safety of biosimilar SAR342434 insulin lispro in adults with type 2 diabetes, also using insulin glargine: SORELLA 2 study [8]

  This phase 3, randomised open label study in adult participants with type 2 diabetes aimed to compare the efficacy, safety and immunogenicity of a potential insulin lispro biosimilar (SAR342434, Sanofi, n=253) with originator insulin lispro (Humalog®, n=252) when used as at least thrice daily injections in combination with daily insulin glargine. Participants were required to have been treated with at least thrice daily insulin lispro or insulin aspart in combination with daily insulin glargine for at least 6 months prior to screening. The primary objective was to demonstrate noninferiority of biosimilar insulin lispro compared with reference insulin lispro as defined by change from baseline in glycosylated haemoglobin (HbA_{1c}) to week 26 with a

noninferiority margin of 0.3%. Safety end points included hypoglycaemic events and injection site reactions. The least square mean difference between the potential biosimilar lispro group and reference group was -0.07% (95% CI: -0.215 to 0.067) which was within the predefined noninferiority limit. The percentage of participants experiencing at least one episode of hypoglycaemia was considered to be similar between the two groups (biosimilar lispro = 68.4% vs reference lispro= 74.6%) with severe hypoglycaemia occurring in six participants (nine events total, four in one participant) in the biosimilar lispro group and four participants (four events total) in the reference lispro group. Similar percentages of participants were positive for anti-insulin antibodies (biosimilar lispro = 24.5% vs reference lispro=25.4%) at baseline. Over the course of the study the percentage of participants with treatment-boosted or treatment-induced anti-insulin antibodies was 18.8% (46/245) in the biosimilar lispro group as compared with 14.5% (36/248) in the reference lispro group. Injection site reactions were reported by one participant in the biosimilar group and four participants in reference group. The authors conclude that *"…SAR-Lis and Ly-Lis when used for 6 months in combination with GLA-100* [insulin glargine] *provided effective and similar glucose control in participants with T2DM"* and that "*SAR-Lis* [biosimilar] *and Ly-Lis* [reference] *had similar safety and immunogenicity profiles and no specific safety concerns were observed.*"

- Home et al, 2018: Anti-insulin antibodies and adverse events with biosimilar insulin lispro compared with Humalog insulin lispro in people with diabetes [9]

  This manuscript compares the impact of anti-insulin antibodies (AIA) on safety and glycaemic control with biosimilar insulin lispro as compared with reference insulin lispro using results from two phase III trials, one in participants with type I diabetes (T1DM) and the other in type II diabetes (T2DM). At baseline AIA positive status was similar between the biosimilar and reference groups, but higher in participants with T1DM than in those with T2DM. During the course of the studies, treatment induced AIA occurred in a similar percentage of participants in the biosimilar and reference groups (28.5% vs 27.3% and 18.4% vs 15.1%) and the mean change in glycosylated haemoglobin (HbA_{1c}) from baseline to study end in both studies was similar for the biosimilar and reference groups in both participants with and without treatment-emergent AIA. Maximum individual AIA titres were not associated with the magnitude of change in HbA_{1c}, insulin dose, risk of hypoglycaemia, or hypersensitivity reactions. The authors conclude that "*Insulin lispro SAR342434 and the originator insulin lispro had a similar immunogenicity profile in people with T1DM or T2DM".*

- Pivot et al, 2018: Phase III, randomized, double-blind study comparing the efficacy, safety, and immunogenicity of SB3 (trastuzumab biosimilar) and reference trastuzumab in participants treated with neoadjuvant therapy for human epidermal growth factor receptor 2–positive early breast cancer [10]

  This phase III randomized, double-blind, parallel-group, multicentre study aimed to compare the proposed trastuzumab biosimilar (SB3, n = 437) with reference trastuzumab (Herceptin®, n=438) in the neoadjuvant setting in participants with human epidermal growth factor receptor 2–positive early breast cancer. Participants were randomised (1:1) to receive either SB3 or reference trastuzumab every 3 weeks for eight cycles with eight concurrent cycles of chemotherapy (four cycles of docetaxel followed by four cycles of fluorouracil, epirubicin and cyclophosphamide) following which participants underwent surgery and a subsequent additional 10 cycles of adjuvant SB3 or reference trastuzumab. The primary end point was the rate of pathologic complete response in the primary breast tumour (bpCR), defined as no histologic evidence of residual invasive tumour cells in the breast as assessed by the local pathologist, in the per-protocol set. All

bpCRs were reviewed by the study pathologist board. Equivalence was defined as containment of the 95% CI of the ratio in the bpCR rate between arms within the range of 0.785 to 1.546 or if the 95% CI of the difference in the bpCR rate between treatments was contained within the predefined margin of ±13%. The proportion of participants achieving bpCR was 51.7% (208/402) in the SB3 group as compared with 42.0% (167/398 participants) in the reference trastuzumab group. The adjusted rate difference was 10.70% (95% CI: 4.13% to 17.26%) with the lower margin contained within but the upper margin was outside the predefined equivalence criteria whilst the adjusted ratio of bpCR was within the predefined equivalence margins (1.259, 95% CI: 1.085 to 1.460). With regards to the numerically higher bpCR observed within the SB3 group, the authors note that "*Participant demographic and baseline disease characteristics were well balanced between arms; therefore, the difference observed in bpCR rates is difficult to explain*" but suggest that in the development of SB3 it has been observed that "*Among numerous lots of TRZ* [reference trastuzumab] *that have been analyzed for physicochemical and biologic properties for > 5 years, certain lots showed a marked downward drift in the level of glycosylation, FcγRIIIa binding activities, and antibody-dependent cell-mediated cytotoxicity activities*" and that "*Because some of these lots were used as a reference drug in this clinical study, it cannot be excluded that the shifts of these quality attributes in the reference drug did not have an impact on the presented results*". During the neoadjuvant period, treatment emergent adverse events were reported by a similar proportion of participants in both groups (96.6% of SB3 participants vs. 95.2% of reference trastuzumab participants). The most common adverse events were neutropenia, alopecia, nausea, and leukopenia. Up to cycle 9, anti-drug antibodies were detected in three participants (0.7%) in the SB3 group only. The authors conclude that "*Equivalence for efficacy was demonstrated between SB3 and TRZ* [reference trastuzumab] *on the basis of the ratio of bpCR rates. Safety and immunogenicity were comparable"*.

- Pivot et al, 2018: A phase III study comparing SB3 (a proposed trastuzumab biosimilar) and trastuzumab reference product in HER2-positive early breast cancer treated with neoadjuvant-adjuvant treatment: Final safety, immunogenicity and survival results [11]

  Following on from the above manuscript this paper reports on the secondary study endpoints of event-free survival, defined as disease recurrence or progression or death due to any cause, and overall survival following the complete 1 year of neoadjuvant-adjuvant therapy with a proposed trastuzumab biosimilar (SB3) as compared with originator trastuzumab. With a data cut-off of 30 days post completion of adjuvant therapy, at 12 months the event free survival and overall survival rates for SB3 and originator trastuzumab were comparable (event free survival: SB3 = 93.7% vs originator = 93.4%, overall survival: SB3 = 99.8% vs originator = 98.8%). The corresponding event free survival hazard ratio (SB3/originator) was 0.94 (95% CI: 0.59 to 1.51). The incidence of treatment-emergent adverse events was also comparable between groups (SB3 = 97.5% vs originator = 96.1%). Anti-drug antibodies were detected in 3 participants in each group. The authors conclude that "*Using the totality of evidence approach, the final safety, immunogenicity and survival results of this study further support the biosimilarity established between SB3 and TRZ* [originator trastuzumab]".

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.

- Husereau et al, 2018: Policy options for infliximab biosimilars in inflammatory bowel disease given emerging evidence for switching [12]

The stated goal of this manuscript was to "*call attention to the evidence-based policy options available for providing access to biosimilars through switching in cases where direct evidence is lacking*". Through the detailed introduction the authors outline five policy options for biosimilar pricing and reimbursement including:

1. Watch and wait until more evidence emerges before funding switches
2. Use product listing agreements to manage uncertainty
3. Provide access for one-time informed substitution with biosimilar infliximab in any patient
4. Provide access to either treatment using tiered or co-payments to incentivise use of less costly products
5. Mandate producers to provide evidence of interchangeability

In this context the authors used the patient clinical characteristics described in the NOR-SWITCH study to calculate a value-based price in the scenario of a one-time switch to biosimilar infliximab following 6-months of originator infliximab therapy in patients with Crohn's disease (CD). The authors employed a Markov model that accounts for dose escalation and disease progression and assumed that patients were switched at a fixed point in time. The authors based this calculation on the result from NOR-SWITCH whereby "*In CD, for example, the risk difference for switching to biosimilar product was -14.3% (95% CI - 29.3 to 0.7)*" and assumed a price of $987.56 per vial for originator infliximab and $525 per vial for the biosimilar. On this basis the 10-year costs associated with originator infliximab is $168,210 as compared with $120,753 for biosimilar but, because of the assumed risk difference for switching to the biosimilar, the saving of $47,457 was associated with a 0.27 loss of quality adjusted life years (QALYs). In performing this calculation, the authors assume a risk difference exists between originator and biosimilar infliximab in the management of Crohn's disease, however the authors note that "*…NOR-SWITCH was not statistically powered or intended to demonstrate non-inferiority for individual diseases*".

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

During the current review update period there were no manuscripts published that specifically address the theme of biosimilar uptake.

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 9 publications that specifically examine this theme related to filgrastim and infliximab.

Filgrastim

- Bhamidipati et al, 2017: Results of a prospective randomized, open-label, noninferiority study of tbo-filgrastim (Granix) versus filgrastim (Neupogen) in combination with plerixafor for autologous stem cell mobilization in patients with multiple myeloma and non-Hodgkin lymphoma [13]

  This prospective, randomized open-label single-institution noninferiority study aimed to compare the efficacy and safety of biosimilar filgrastim (tbo-filgrastim) with originator filgrastim when used in combination with plerixafor for the mobilization of hematopoietic progenitor cells for autologous transplantation in patients with multiple myeloma or non-Hodgkin lymphoma. Teva Pharmaceutical Industries provided the tbo-filgrastim and funded the trial through an unrestricted grant. A total of 100 patients were randomized to the tbo-filgrastim (n = 49) or originator filgrastim (n = 51). The primary endpoint was the number of CD34+ cells per kilogram of body weight collected on day 5, the first day of apheresis. The mean number of CD34+ cells/kg collected on day 5 was 11.6 ± 6.7 cells/kg (range, 1.4 to 37.6 cells/kg) in the tbo-filgrastim arm as compared with 10.0 ± 6.8 cells/kg (range, 1.2 to 29.1 cells/ kg) in the originator filgrastim arm (t = −1.15; P = 0.873). A non–statistically significant trend toward increased mobilization in the tbo-filgrastim arm was identified in the multivariate analysis after controlling for age, diagnosis, and volume of blood processed (β = 1.76; P = 0.214). The authors conclude that "*Based on the results of the randomized trial presented herein and the growing body of literature on tbo-filgrastim, we conclude that tbo-filgrastim is bioequivalent to filgrastim in stem cell mobilization for auto-HSCT*".

- Sevinc et al, 2018: Biosimilar filgrastim vs filgrastim: A multicentre nationwide observational bioequivalence study in participants with chemotherapy-induced neutropenia [14]

  This multicentre, observational study conducted at 14 centres in Turkey compared the effectiveness of biosimilar filgrastim (Leucostim®) with originator filgrastim in participants with chemotherapy-induced neutropenia. A total of 337 participants were included of whom 61.6% received biosimilar filgrastim and 38.1% originator. Neutropenia resolved within ≤4 days of filgrastim therapy in 60.1%, 56.7%, and 52.6% of the participants receiving biosimilar filgrastim (30 MIU), originator filgrastim (30 MIU) and originator filgrastim (48 MIU), respectively with no significant difference between the three arms (p=0.468). Time to absolute neutrophil recovery was comparable between the three groups (p=0.332). The authors conclude that "*The results of this observational study indicate that original filgrastim and biosimilar filgrastim have comparable efficacy in treating neutropenia in participants receiving cancer chemotherapy*".

- Tamura et al, 2018: Clinical safety and efficacy of "filgrastim biosimilar 2" in Japanese participants in a post-marketing surveillance study [15]

  This manuscript reports on the outcomes of a 2-year post marketing surveillance of biosimilar filgrastim (F-BS2) in Japan. A total of 653 participants were registered from 67 institutions, and 643 case report forms

were collected of which sixteen were excluded due to registration errors resulting in evaluation of 627 participants. Of these, biosimilar filgrastim was used in 616 participants for neutropenia associated with cancer chemotherapy, six for autologous hematopoietic stem cells mobilization, and five the enhancement of engraftment of hematopoietic stem cell transplants. Among the 576 cancer participants who developed Grade 2-4 neutropenia after chemotherapy, recovery to Grade 1/0 was reported in 553 participants (96%) following treatment with biosimilar filgrastim. A total of 43 adverse drug reactions were reported in 33 participants (5.26%) of which back pain was most common (20 participants, 3.19%), followed by pyrexia (1.28%) and bone pain (0.96%). The authors conclude that "*this study showed that filgrastim biosimilar 2 has a similar safety profile and comparable effects to the original G-CSF product in the real world clinical setting*"

Infliximab

- Glintborg et al, 2018: Drug concentrations and anti-drug antibodies during treatment with biosimilar infliximab (CT-P13) in routine care [16]

  In this letter, the authors report on the serum drug concentrations and anti-drug antibodies (ADAs) in participants with arthritis who switched from originator infliximab to biosimilar infliximab (CT-P13) or initiated biosimilar infliximab without previous infliximab treatment. Trough infliximab concentrations were dichotomised as either low (< 1mg/L) or high (≥ 1mg/L). ADA status was recorded as either positive or negative. A total of 373 participants who switched from originator to biosimilar infliximab and 173 infliximab naïve participants with at least one blood sample were included. The median duration of treatment with originator infliximab prior to switching was 7.0 years. Median follow-up was 539 days in the switching group and 300 days in the naïve group. Amongst the previously infliximab naïve group, infliximab concentrations were high in 76% (96/126) of participants and 13% (17/126) were positive for ADAs. Of those who switched, 330 participants had two or more blood samples and within this group the infliximab concentration status was unchanged in 81% (n=269). ADAs developed in 4% (13/330) and disappeared in 9% (30/330). The risk of withdrawal for those who switched ADA status from negative to positive was similar to that of participants that were continuously negative (HR = 1.2, 95% CI: 0.3 to 5.1, p = 0.8). The authors conclude that "*this study of real-life participants showed that in participants who had received originator IFX for a median of 7 years, and who were switched from originator to biosimilar IFX* [infliximab]*, few changes in sIFX level* [serum infliximab concentration] *and ADAs were observed, and they were not statistically significantly associated with CT-P13 withdrawal"*.

- Boone et al, 2018: The nocebo effect challenges the non-medical infliximab switch in practice [17]

  This manuscript describes the 1-year outcomes of a "*pragmatic study*" of switching participants from originator infliximab to biosimilar infliximab "*on the basis of shared decision-making under effectiveness and safety monitoring*". A total of 146 participants were invited to participate between July 2016 and April 2017. Of these, 125 (85.6%) agreed to switch to biosimilar infliximab. The majority of participants were receiving infliximab for inflammatory bowel disease (Crohn's disease = 73, ulcerative colitis = 28). The remaining participants included nine with rheumatoid arthritis, five with psoriatic arthritis and ten with ankylosing spondylitis. The mean duration of originator infliximab treatment prior to switching ranged from 2.9 (±1.2 SD) years in participants with psoriatic arthritis to 4.6 (±0.5 SD) years in participants with ankylosing

spondylitis. In participants with inflammatory bowel disease, disease activity was assessed according to the participant's assessment of disease activity on a scale ranging from 0 (worse) – 10 (good). Rheumatoid arthritis and psoriatic arthritis were assessed according to the Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) whilst ankylosing spondylitis was assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Faecal calprotectin and C-reactive protein (CRP) were analysed in participants with inflammatory bowel disease and CRP and erythrocyte sedimentation rate (ESR) were assessed in rheumatology participants. Serum trough infliximab concentrations and neutralizing antibodies were measured. A nocebo effect was defined as "*unexplained, unfavorable therapeutic effect subsequent to a non-medical switch from originator infliximab to biosimilar infliximab with regaining of the beneficial effects after reinitiating the originator*" as determined by the participant's physician. At 9 months post-switching, 61 (86.3%) of participants with Crohn's disease and 21 (78.6%) of participants with ulcerative colitis remained on biosimilar infliximab with a median number of four infusions. Four participants with Crohn's disease and three with ulcerative colitis ceased infliximab biosimilar therapy on the basis of ineffectiveness evidenced by the clinical presentation and laboratory findings with all participants being switched to a non-infliximab treatment. Eight rheumatoid arthritis, five participants with psoriatic arthritis, and eight ankylosing spondylitis participants were considered to have continued to respond after a median number of three, four, and four biosimilar infliximab infusions, respectively. A total of 16 participants were designated as "*nocebo participants*", all of whom were successfully treated with at least two additional infusions of originator infliximab. Within the conclusion the authors state that "*Although our study is not controlled for measuring the nocebo-response effect of shared decision-making, we hypothetically propose that participant empowerment may decrease nocebo-response rate, whilst effectiveness and safety are maintained.*"

- Codreanu et al, 2018: Assessment of effectiveness and safety of biosimilar infliximab (CT-P13) in a real-life setting for treatment of participants with active rheumatoid arthritis or ankylosing spondylitis [18]

  This multicentre, non-interventional, observational study aimed to assess the effectiveness and safety of biosimilar infliximab (CT-P13) in adults with active rheumatoid arthritis (RA) or ankylosing spondylitis (AS). A total of 151 participants with severe active RA (n = 81) or AS (n = 70) were included of whom 67% of RA participants and 80% of AS participants had not been treated previously with an anti-TNF alpha agent. Disease activity was assessed using the Disease Activity Score 28 with C-reactive protein (DAS28-CRP) for participants with RA or the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for participants with AS at baseline, week 12 and week 24. The primary endpoint was the percentage of participants at week 24 with a response to biosimilar infliximab, good and moderate response as per EULAR criteria for participants with RA and an improvement of at least 50% in the BASDAI score or an absolute change of two units (on a 0–10 scale) relative to baseline for participants with AS. A total of 129 participants had efficacy assessments at baseline and week 24. Those who discontinued treatment or had missing data were considered to be non-responders. A total of 19 participants withdrew from the study, seven due to adverse events, five due to therapeutic failure, two were non-compliant, two withdrew consent and one participant was withdrawn due to an ambiguous tuberculosis result. At week 24, mean DAS28-CRP scores had improved from the 5.8 ± 1.0 at baseline of 3.2 ± 1.4 (P = 0.0001) in participants with RA, whilst in participants with AS the mean BASDAI scores had improved from 6.8 ± 1.7 at baseline to 2.6 ± 1.8 at week 24 (P = 0.0001). The response rate at week 24 in the overall population was 75.5%, ranging from 71.6% in participants with RA to 80% in those with AS. The authors conclude that "…*the results presented in the current study corroborate previous research*

findings from CTP13 RCTs of up to 2 years' duration and suggest that biosimilar CT-P13 is an effective and safe alternative to originator infliximab in a real-world setting in participants with active RA or AS" and that "*CT-P13 has the potential to provide equivalent disease control and tolerability as reference infliximab in a greater number of participants with RA and AS, in a more cost-effective manner*."

- Kang et al, 2018: Long-term outcomes after switching to CT-P13 in pediatric onset inflammatory bowel disease: A single-center prospective observational study [19]

  This prospective observational study conducted in the Department of Pediatrics, Samsung Medical Center, Republic of Korea, aimed to investigate the outcomes in paediatric participants with inflammatory bowel disease at 1-year of switching from originator infliximab to biosimilar infliximab (CT-P13) as compared with continuing originator infliximab. The primary endpoint of the study was the proportion of participants continuously receiving infliximab and the proportion achieving persistent remission at 1 year as assessed by the clinical disease activity scores (Pediatric Crohn's Disease Activity Index, the Harvey-Bradshaw Index, the Pediatric Ulcerative Colitis Activity Index and the Simple Clinical Colitis Activity Index). A total of 36 participants were recruited to the originator maintenance group and 38 to the switching group. The mean ages at baseline were 17.3 years (SD = 3.4 years) and 17.5 years (4.0 years) in the maintenance group and switching groups, respectively (P = 0.785). There were no statistically significant differences in the age of disease onset, time from diagnosis to initiation of originator infliximab or proportion of participants in clinical remission between the two groups (33 participants per group) but dose intensification prior to baseline tended to be more common in the switching group (25% in the maintenance group as compared with 50% in the switching group, P = 0.048). Treatment with concomitant azathioprine was similar between the two groups; 72.2% in the maintenance group as compared with 71.1% in the switching group (P = 1.000). Three participants in each group had anti-drug antibodies ≥10 AU/mL at baseline. At 1-year follow-up, 86.1% (31/36) in the maintenance group and 92.1% (35/38) participants in the switching group had continuously received infliximab (P = 0.649). There was no difference in the proportion of participants with persistent remission between the two groups; 8/36 (77.8%) participants in the maintenance group as compared with 30/38 (78.9%) participants in the switching group (P = 1.000). There were no statistically significant differences between disease activity measures between the maintenance and switching group. Anti-drug antibodies resolved in one participant in the maintenance group and two in the switching group whilst new anti-drug antibodies were detected in two participants in the maintenance group and one in the switching group. The authors conclude that "*….the current 1-year study found that switching from maintenance infliximab RP to CT-P13 did not result in any significant differences in efficacy, pharmacokinetics, or immunogenicity in pediatric-onset IBD participants, and there were no unexpected safety issues*".

- Ricceri et al, 2018: Clinical experience with infliximab biosimilar in psoriasis [20]

  In this letter, the authors report on their clinical experience associated with switching 22 participants with psoriasis from originator infliximab to biosimilar infliximab. Prior to switching, participants had a median of 5 years duration of originator infliximab therapy. Following a mean duration of 10 months of biosimilar infliximab the rates of clinical remission, defined as PASI and/or Ritchie index not increasing by greater than 10%, were 86% for participants with psoriasis and 77% for participants with psoriatic arthritis. The authors conclude that "*In our experience, switching from the originator (INX)* [originator infliximab] *to INB* [biosimilar infliximab] *in participants with psoriasis seems to be safe*" and that "*…the effectiveness of INB appeared*

similar to INX, specifically for cutaneous symptoms over a median of 10 months in participants who switched from INX to INB" whilst noting that "*Regarding the efficacy on articular symptoms according to our experience, we registered a mild decrease in efficacy (data not reported in the literature)"*.

- Cantini et al, 2017: Rapid loss of efficacy of biosimilar infliximab in three participants with Behçet's disease after switching from infliximab originator [21]

  This manuscript reports on three participants with Behçet's disease (BD) with severe uveitis and neurological involvement in stable clinical remission and who were considered to have relapsed after switching from reference infliximab to biosimilar infliximab. As of October 2015, there were 26 patients with uveoretinitis and/or neuro-Behçet managed at the Rheumatology Department of Prato with originator infliximab and considered to be in stable remission. The authors note that because "*…a local health authority issued a rule stating that patients who did not reside in Prato should receive the current intravenous treatment in the hospitals of the area where they lived…*" three patients were switched from originator infliximab to biosimilar infliximab in their local hospital. For these three patients the authors report that relapse was considered to have occurred following the first, second or third infusions of biosimilar infliximab. In all three patients biosimilar infliximab was ceased and treatment was changed to adalimumab. All patients were reported to have responded to this treatment. The authors conclude that "… *the rapid disease relapse observed in our 3 patients with BD soon after switching from re-IFX* [originator infliximab] *to bio-IFX* [biosimilar infliximab] *further reinforces the claims that suggest caution concerning the automatic substitution of one treatment with the other. The loss of efficacy of bio-IFX may be related to the development of ADAs, and in order to verify this hypothesis, further investigations need to be conducted*.

Commentary

The authors selectively report on the outcomes of three of 26 patients in their clinic. No details are provided regarding the clinical outcomes of the remaining 23 patients. There is a risk of reporting bias in publications of this nature. Varying details regarding the indicators of relapse are provided and for at least one of the three patients reported to have relapsed it is possible that the issues highlighted by Boone et al [17] (reviewed above) contribute to this presentation.

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

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

- Jiménez-Pichardo et al, 2017: Degree of prescriber's knowledge about variability in biological drugs "innovators" in manufacturing process [22]

  The aim of this survey was to investigate awareness of prescribers about potential manufacturing changes in originator biological medicines. A total of 35 responses were received; 20 from the posting on the Rheumatology Andalusian Society's website and eight physicians working at the Jerez de la Frontera Hospital, Spain, of whom 30 were rheumatologists, four were gastroenterologists and a single dermatologist. Only 37% of respondents were aware of changes in manufacturing process for biological medicines. When asked "*Did you know that changes in biological 'innovator' drugs during the manufacturing process force the manufacturer to determine the comparability with any previous product*" 29% selected the option "*I knew this need to establish comparability among the biotechnological 'innovator' drugs, although I related only with the biotechnological biosimilars*". The authors conclude that "*To realise that even years after the commercialization of biotechnological innovator medicines, they have undergone changes during their manufacturing processes without any efficacy or safety difficulties, might increase confidence for biosimilars, thus facilitating and accepting the exchange between biotechnological innovators and biosimilars.*"

- Olivera et al, 2018: Physicians' perspective on the clinical meaningfulness of inflammatory bowel disease trial results: An International Organization for the Study of Inflammatory Bowel Disease (IOIBD) survey [23]

  The aim of this online survey of members of the International Organization for the Study of Inflammatory Bowel Diseases was to better understand physicians' perspectives on the clinical meaningfulness of trial results across a broad range of topics which included biosimilar medicines. A total of 46 responses were received (response rate = 52%). Participants were asked to consider "*In bioequivalence studies that compare a biosimilar and the originator biologic in IBD; what difference would you consider appropriate*:". With regards to pharmacokinetic parameters 46% of respondents selected the option ±5% and 28% selected ±10% from a range that spanned from ±2.5% to ±15%. Similarly, when asked about efficacy 41% and 26% opted for ±5% and ±10% respectively. However, when asked about safety and immunogenicity 39% and ~45% opted for the lower values of ±2.5% and ±5%, respectively.

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5. Matsuno, H., et al., Phase III, multicentre, double-blind, randomised, parallel-group study to evaluate the similarities between LBEC0101 and etanercept reference product in terms of efficacy and safety in patients with active rheumatoid arthritis inadequately responding to methotrexate. Ann Rheum Dis, 2017. 19: p. 19.
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7. Weinblatt, M.E., et al., Switching From Reference Adalimumab to SB5 (Adalimumab Biosimilar) in Patients With Rheumatoid Arthritis: 52-Week Phase 3 Randomized Study Results. Arthritis Rheumatol, 2018.
8. Derwahl, K.M., et al., Efficacy and Safety of Biosimilar SAR342434 Insulin Lispro in Adults with Type 2 Diabetes, Also Using Insulin Glargine: SORELLA 2 Study. Diabetes Technol Ther, 2018. 20(1): p. 49-58.
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23. Olivera, P., et al., Physicians' perspective on the clinical meaningfulness of inflammatory bowel disease trial results: an International Organization for the Study of Inflammatory Bowel Disease (IOIBD) survey. Aliment Pharmacol Ther, 2018. 47(6): p. 773-783.

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.

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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.

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