Literature Review of International Biosimilar Medicines: Update September – November 2017

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Introduction

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

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

- current international 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 patients (Uptake); outcomes resulting from the use of biosimilars outside of the clinical development pathway (Outcomes); and finally the stakeholder perceptions that influence uptake, including the factors that modify these perceptions such as advocacy and associated programmes (Perceptions).

Figure 1: *Stages influencing biosimilar uptake and use*
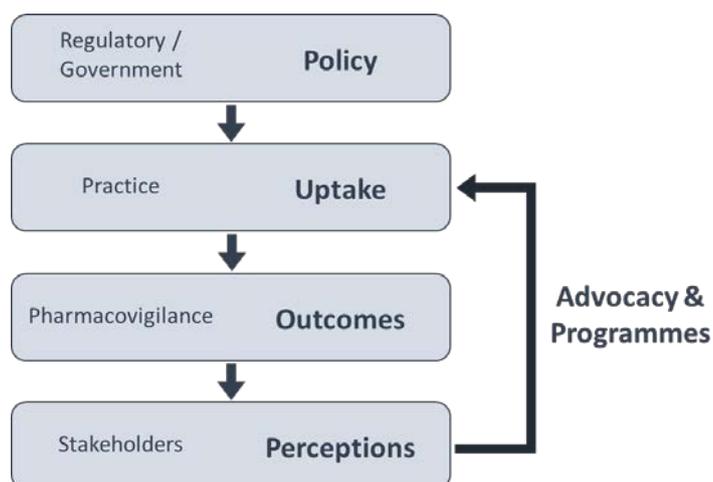
In the context of this review it is critical to appreciate that the fundamental central factor to each of these areas is the potential uncertainty that exists in evidence regarding substitution, switching and extrapolation of indication, which is unique to the consideration of biosimilar medicines. This potential uncertainty originates from the highly complex nature of these medicines and the clinical development pathway of biosimilar medicines that extends from initial laboratory-based characterisation (protein structure, pharmacokinetics, etc.) through to the design and conduct of phase III clinical trials to provide evidence of similarity in clinical safety and efficacy in specific patient populations. The considerations involved in each

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

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

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

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

4. Evaluating and Improving Stakeholder Biosimilar Awareness, Confidence, Attitudes and Acceptance of Biosimilar Medicine

Overview of the Published Biosimilar Literature

This report includes literature published between 1 September 2017 and 30 November 2017.

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

Analysis of these manuscripts identifies the following broad types of contributions:
- Education pieces and literature reviews
- Commentaries and individual opinion pieces
- Preclinical characterisation of potential biosimilar medicines
- Technical/methodological development
- Clinical trials of potential biosimilar medicines
- Investigator-initiated studies and case series

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

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

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

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

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

During the current update period, two 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
Bevacizumab						
ABP15 (Amgen)	US and EU Avastin 1mg/kg	Randomized, single-blind, single-dose, three-arm, parallel- group study (1:1:1)	Healthy male volunteers (n= 202)	90% CI for the ratio of treatment means for area-under-the-curve from time zero extrapolated to infinite time (AUC_{inf}) and maximal plasma concentration (C_{max}) were within the prespecified limits of 80- 125% for the comparisons of ABP15 with US Avastin and ABP15 with EU Avastin, as well as for US and EU Avastin.	No anti-drug antibodies detected at baseline or at end of study	[1]
Infliximab						
SB2 (Samsung Bioepis)	US and EU Remicade 5mg/kg	Pharmacokinetic analysis to investigate the impact of infliximab anti-drug antibodies in healthy subjects receiving a single dose of intravenous infliximab	Healthy volunteers (n=30)	Infliximab clearance was increased in subjects with ant-drug antibodies vs those without (12.89 ± 2.69 vs. 9.90 ± 1.74 ml/h; $p < 0.0005$). Elimination half-time was reduced in those with ADAs (282.4 ± 56.4 vs. 343.3 ± 61.9 h; $p < 0.01$). Serum infliximab measured at 8 weeks correlated closely with infliximab clearance ($R2 = 0.5494$; p\ 0.0001)		[2]

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 potential biosimilars for filgrastim, etanercept, infliximab and adalimumab.

❖ Blackwell et al, 2017: Safety and efficacy of alternating treatment with EP2006, a filgrastim biosimilar, and reference filgrastim: a phase 3, randomised, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy[3]

This phase III randomised, double-blind study conducted in patients with breast cancer receiving (neo)adjuvant myelosuppressive chemotherapy (docetaxel plus doxorubicin plus cyclophosphamide) compares originator filgrastim (Neupogen®, Amgen) with biosimilar filgrastim (Zarxio®/EP2006, Sandoz) and two groups receiving alternate cycles switching between originator and biosimilar filgrastim. Filgrastim was administered from day 2 of each chemotherapy cycle (5 µg/kg/day) until the absolute neutrophil count (ANC) recovered to 10×10^9/L after its nadir or for a maximum of 14 days. Study endpoints included the incidence of febrile neutropenia, incidence of infections, incidence of hospitalisations due to febrile neutropenia, time and depth of ANC nadir, time to ANC recovery, and ANC profile. For analysis, the switching groups were pooled and compared with the group receiving only originator filgrastim. Non-inferiority was defined as containment of the 95% confidence intervals (CIs) for the rate of febrile neutropenia for cycles 2-6 between groups within a margin of −15%. A total of 109 patients were pooled in the switching group and 52 patients were included in the originator only group. The incidence of febrile neutropenia was 0% in the originator only group as compared with 3.4% (n=3) in the pooled switching group (95% CI: −9.65–4.96) which was within the pre-defined noninferiority limit. There were no clinically meaningful differences in other endpoints. On this basis the authors conclude that "*this study showed that there are no clinically meaningful differences regarding efficacy, safety or immunogenicity when switching from reference to biosimilar filgrastim/EP2006, or vice versa, and that switching can be performed without cause for concern*."

❖ Gerdes et al, 2017: Multiple switches between GP2015, an etanercept biosimilar, with originator product do not impact efficacy, safety and immunogenicity in patients with chronic plaque-type psoriasis: 30-week results from the phase 3, confirmatory EGALITY study[4]

This phase III double-blind efficacy and safety study conducted in patients with plaque-type psoriasis aimed to demonstrate equivalent efficacy and comparable safety and immunogenicity of biosimilar etanercept (GP2015) and originator etanercept (Enbrel®) and evaluated the effects of repeated switching between the biosimilar and the originator. Participants were randomized 1:1 to receive biosimilar or originator etanercept twice-weekly until week 12. At week 12, participants achieving a greater than 50% improvement in Psoriasis Area and Severity Index (PASI) scores from baseline (PASI 50) were re-randomized to either continuing group (biosimilar or originator) or to the switching group. Within the switching group participants would initially switch from their prior treatment and then alternate between the biosimilar and the originator, or vice versa, every 6 weeks (switching at weeks 12, 18 and 24). The groups continuing treatment with the biosimilar or originator were pooled and compared with the pooled group of those

assigned to switching. Efficacy was assessed by the proportion of patients demonstrating at least a 50%/75%/90% improvement in PASI score from baseline visit. A total of 196 participants were included in the multiple switching group and 301 participants were included in the continued treatment group. At weeks 12, 18 24 and 30 the mean PASI scores and mean percent change from baseline in PASI score were comparable between the multiple switching group and continued treatment group. No participants were positive for antidrug antibodies between weeks 12 and 30. The authors conclude that "*Similar efficacy was observed between continued treatment and alternating treatment between GP2015 and ETN*" and that "*no clinically relevant differences were noted in safety or immunogenicity between the two groups, indicating no impact of repeated switches between GP2015 and ETN*".

❖ Smolen et al, 2017: Comparing biosimilar SB2 with reference infliximab after 54 weeks of a double-blind trial: clinical, structural and safety results[5]

This manuscript reports on the 54 week safety and efficacy outcomes of a phase III study double-blind, parallel-group, multicentre study in participants with moderate to severe rheumatoid arthritis comparing biosimilar infliximab (SB2) with originator infliximab (Remicade®); extending upon the previously published 30 week study outcomes. This manuscript also reports on the 54 week radiographic outcomes as assessed by the van der Heijde modified total Sharp score (mTSS) with progression of joint damage calculated as the mean difference between the baseline and the measurement at week 54. At week 54, disease activity measures (ACR responses, 28-joint DAS, Clinical Disease Activity Index and Simplified Disease Activity Index) were comparable between the biosimilar and originator groups. The pre-defined equivalence margin of ±15% for the ACR20 rate difference, the primary endpoint at week 30, was also met at week 54. There were no significant differences in the proportion of patients with anti-drug antibodies up to week 54 (P = 0.270). With regards to the radiographic outcomes, the adjusted mean difference of change from baseline in mTSS was 0.01 (95% CI: -0.53 - 0.56). However, it should be noted that "*The study was not powered to detect a significant difference in radiographic progression between the treatment groups, thus drawing a definite conclusion regarding radiographic equivalence is not possible.*" The authors conclude that "*SB2 demonstrated similar efficacy, safety and immunogenicity to its reference INF for up to 54 weeks in patients with moderate to severe RA despite MTX therapy*" and that the radiographic data presented in this manuscript is further evidence of the comparability between SB2 and originator infliximab.

❖ Smolen et al, 2017: Safety, immunogenicity and efficacy after switching from reference infliximab to biosimilar SB2 compared with continuing reference infliximab and SB2 in patients with rheumatoid arthritis: results of a randomised, double-blind, phase III transition study[6]

This manuscript compared outcomes in patients with rheumatoid arthritis who switched from originator infliximab (Remicade ®) to biosimilar infliximab (SB2) with those who maintained treatment with originator or SB2 following 54 weeks of treatment. Following 54 weeks of treatment with originator infliximab eligible participants (those who had not experienced any serious adverse events or intolerance to infliximab) were re-randomised (1:1) to switch to biosimilar infliximab (n=94) or continue originator (n=101) up to week 70. Participants previously treated with biosimilar infliximab continued this treatment (n=201). Efficacy was assessed according to American College of Rheumatology (ACR) response rates (ACR20, ACR50 and ACR70), disease activity score based on a 28-joint count (DAS28 score) and European League Against Rheumatism (EULAR) responses at weeks 62, 70 and 78. ACR response rates and disease activity measure were

comparable at all time points and the proportion of good or moderate EULAR responses at week 78 was comparable across the treatment groups (good: 32.9%–35.6% of patients; moderate: 50.5%–51.8%). Amongst participants that were negative for anti-drug antibodies at week 54, 14.6% of those in the switching from originator infliximab to INF/SB2 developed antidrug antibodies as compared with 14.9% of those who continued treatment with originator infliximab and 14.1% of those that continued treatment with SB2. The authors conclude that SB2 "*maintained comparable efficacy, safety and immunogenicity up to 78 weeks, even after switching from the originator INF*" and that "*SB2, when administered long term or when switched from INF, is comparable with INF*".

❖ Weinblatt et al, 2017: Phase 3 Randomized Study of SB5, an Adalimumab Biosimilar, Versus Reference Adalimumab in Patients With Moderate to Severe Rheumatoid Arthritis[7]

This phase III, randomized, double-blind, parallel-group study, aimed to assess the efficacy, safety, pharmacokinetics and immunogenicity of a potential adalimumab biosimilar (SB5) compared with reference adalimumab (Humira®) in participants with moderate to severe rheumatoid arthritis despite treatment with methotrexate. The primary efficacy endpoint was the American College of Rheumatology 20% (ACR20) response at week 24. A total of 254 patients (93.7%) in the SB5 group and 254 patients (93.0%) in the reference adalimumab group completed 24 weeks of the study. The adjusted difference in ACR20 was 0.1% (95% CI: −7.83% to 8.13%) for the per-protocol set and 0.8% (95% CI: −7.03% to 8.56%) for the full analysis set which were within the predefined equivalence margin of −15% to 15%. Trough adalimumab concentrations were comparable between groups (n=178 per group). The proportion of patients experiencing treatment emergent adverse events requiring treatment discontinuation was lower in the SB5 group than in the originator adalimumab group (0.7% vs 3.7% respectively) and the incidence of anti-drug antibodies up to week 24 was comparable (SB5=33.1% vs originator adalimumab=32.0%). The authors conclude that the "*study showed equivalent efficacy between SB5 and ADL* [reference adalimumab]*, as demonstrated by week 24 ACR20 response rates and other secondary efficacy endpoints*" and that "*SB5 was well tolerated and possessed comparable PK, safety, and immunogenicity profiles to those of ADL* [reference adalimumab]"

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, there was a single publication that examined the financial impact of biosimilars.

❖ McBride et al, 2017: Expanded access to cancer treatments from conversion to neutropenia prophylaxis with biosimilar filgrastim-sndz[8]

Following from their manuscript reported in the previous literature update that investigated the potential cost savings associated with biosimilar filgrastim, the authors developed a model to determine how the identified potential savings could be used to purchase additional supportive and therapeutic cancer care. Funding was provided by Sandoz Inc. The authors adopted the position that "*cost-savings from using biosimilars should be re-allocated on a budget-neutral basis to provide more patients with access to either therapeutic or supportive cancer care*". To explore this the authors created a hypothetical population of 20,000 patients receiving a single cycle of myelotoxic chemotherapy. Patients were converted from originator filgrastim to biosimilar filgrastim, with the treatment duration varying between 5 and 14 days. Based upon the cost savings identified the authors then investigated how many additional patients could receive filgrastim or how many additional patients could be treated with obinutuzumab or pembrolizumab. From this simulated population of 20,000 patients, total savings resulting from switching from originator to biosimilar filgrastim ranged from USD$6,450,000 if only 5 days of filgrastim was administered to USD$18,312,000 if the duration was extended to 14 days. These savings were calculated to enable an additional 1000-2801 patients to be treated with supportive biosimilar filgrastim, 60-169 patients to be treated with obinutuzumab or 21-60 patients to be treated with pembrolizumab. Assuming a filgrastim duration of 5 days, a total of 331 patients would need to be converted from originator filgrastim to biosimilar filgrastim to enable a single additional patient to be treated with obinutuzumab, 940 patients would need to be converted to enable an additional patient to be treated with pembrolizumab whilst only 20 patients would need to be converted to enable an additional patient to receive supportive biosimilar filgrastim. The authors conclude that their results demonstrate that "*The combination of biosimilar savings and expanded access increases the value of cancer care as the same supportive care is provided at lower cost, additional therapeutic care is enabled at no additional cost and more patients will have access to cancer care.*"

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

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

❖ Aladul et al, 2017: Impact of Infliximab and Etanercept Biosimilars on Biological Disease-Modifying Antirheumatic Drugs Utilisation and NHS Budget in the UK[9]

This study examined the impact of the introduction of biosimilars of infliximab and etanercept on overall trends in bDMARD utilisation and the subsequent budget impact in rheumatology specialities. An interrupted time series analysis of secondary care utilisation data was conducted between March 2014 and February 2017 using the DEFINE software, an NHS prescribing database of medicines usage that includes greater than 90% of acute NHS hospitals plus specialist centres within the UK. Utilisation of bDMARDs was expressed as the defined daily dose (DDD) with drug prices expressed as the price per DDD. Over the period examined, adalimumab (Humira®) and etanercept (Enbrel® and Benepali®) accounted for approximately 65% of bDMARDs market. During this time, there was a statistically significant increase in average monthly utilisation of adalimumab (0.48%, 95%CI: 0.22 to 0.75), certolizumab pegol (1.90%, 95%CI: 1.54 to 2.26), golimumab (3.06%, 95%CI: 2.46 to 3.65), abatacept (2.97%, 95%CI: 2.55 to 3.39) and tocilizumab (2.24%, 95%CI: 1.95 to 2.53) whilst etanercept (0.04%, 95%CI: - 0.21 to 0.30) and infliximab 0.03% (95%CI: - 0.25 to 0.18) remained stable.

Following the launch of biosimilars, the utilisation of originator infliximab (Remicade®) and originator etanercept (Enbrel®) decreased gradually whilst utilisation of the biosimilars gradually increased to 58% and 48% of the infliximab and etanercept market, respectively, by February 2017. In the first year of biosimilar infliximab (March 2015–February 2016) originator infliximab (Remicade®) maintained 91% market share. However, there was a statistically significant positive trend for biosimilar infliximab (Inflectra® and Remsima®) utilisation, with Inflectra® demonstrating a greater increasing trend than Remsima® despite only minor price differences between the two biosimilars (£0.28/DDD). In parallel with an increasing trend for the biosimilars there was a significant negative trend for originator infliximab. Similarly, in the first year following the introduction of biosimilar etanercept (March 2016–February 2017) there was a significant increase in the utilisation trend for biosimilar etanercept and a negative trend for originator etanercept. In the first year of biosimilar etanercept availability originator etanercept maintained 80% market share; less than the 91% market share that originator infliximab retained in the equivalent period. The authors suggest that "*This greater uptake of the etanercept biosimilar in the 1st year may reflect the greater experience of rheumatologists with this molecule and increased confidence in bDMARDs biosimilars as a result of previous experience with infliximab*". In the second year of biosimilar infliximab, there was an increase in the utilisation trend for biosimilar infliximab and a negative trend for originator infliximab with the originator market share decreasing to 56% with a greater increasing trend for Remsima® than Inflectra®, which the authors attributed to the greater price differential that emerged between the two (£1.15/DDD). Overall the authors suggest that these utilisation results indicate that, when presented with a range of different bDMARDS from which prescribers can choose, and for some of which biosimilars are available "… *the prescribing decisions were initially based on prescriber/patient preferences among bDMARDs but then based on price when selecting between the brand and biosimilars of the same molecule and between the biosimilars themselves*".

With regards to the budgetary impact of biosimilar availability, in the first year of biosimilar infliximab there was a saving of £2.66 million, equating to a 7.76% reduction in total expenditure on infliximab. Of this saving, £1.37 million was attributed to a reduction in the price of originator infliximab (Remicade®) with the remainder, £1.29 million, due to biosimilar uptake, either new patient initiating treatment with biosimilar infliximab or as established patients switching from originator to biosimilar. In the first year Inflectra® and Remsima® were 42% and 43.6% cheaper than the price of originator infliximab prior to the availability of biosimilars and the originator price decreased by 4.37%. In the second year, Inflectra® and Remsima® were 52% and 59% cheaper respectively than originator infliximab prior to biosimilar availability and 39% and 48% cheaper respectively than originator infliximab at that time. Originator infliximab was 21.17% cheaper. In the second year of biosimilar infliximab savings increased to £12.7 million equating to a 36.8% reduction in infliximab expenditure. Of this, £8.65 million was attributed to increases in the number of new patients initiating biosimilar infliximab or patients switching from originator to biosimilar in combination with price reductions for biosimilar infliximab and £4.08 million attributed to the additional price reductions for originator infliximab. In the first year of biosimilar etanercept there was a saving of £23.4 million, equating to 19.10% of overall expenditure on etanercept, of which £14.5 million was attributed to a 14.85% price reduction in originator etanercept (Enbrel®) and the remainder to new patients initiating biosimilar etanercept or patients switching from originator to biosimilar. Overall, in the context of rheumatology specialities only, it was calculated that the introduction of biosimilar infliximab and biosimilar etanercept resulted in cumulative cost savings over the two year period of a total of £38.8 million when compared with medicine prices prior to the availability of biosimilars for these agents.

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 17 publications that specifically examine this theme related to erythropoietin, filgrastim, infliximab and etanercept.

Erythropoiesis Stimulating Agents (ESAs)

❖ Casadevall et al, 2017: Evaluation of the safety and immunogenicity of subcutaneous HX575 epoetin alfa in the treatment of anemia associated with chronic kidney disease in predialysis and dialysis patients[10]

This manuscript reports an open-label, single-arm, multicentre study conducted in 7 European countries (Germany, Italy, Poland, Romania, Russia, Turkey, and Ukraine) investigating the safety and immunogenicity of the epoetin-alpha biosimilar Binocrit® (HX575) in patients with chronic kidney disease (CKD). Patients aged at least 18 years and had CKD-induced anaemia [Hb less than 11.0 g/dL] with or without dialysis and requiring erythropoiesis-stimulating agent (ESA) treatment were included. Patients were treated with sub-cutaneous Binocrit® at least once weekly. ESA-naïve patients began treatment on a starting dose of 25 IU/kg body weight 3 times weekly or 75 IU/kg body weight once per week from week 1 to week 5. 1,202 patients were screened of which 416 (mean 52.3 years; 52.4% female; 60.1% ESA naive) received at least 1 dose of Binocrit®. Mean duration of treatment with Binocrit® was 43.4 (15.8) weeks and 45.3 (13.7) weeks in the ESA-naïve and maintenance groups, respectively. The Binocrit® dose was stable for both groups once maintenance phase was achieved. In ESA-naïve patients, the mean (SD) increase in Hb from baseline was 1.61 (1.60) g/dL at the end of the study. In ESA-maintenance patients, the mean (SD) change in Hb from baseline was 0.22 (1.22) g/dL. The percentage of patients within the Hb target range was 76.5% (95% CI: 69.3%, 82.7%) at baseline and 70.1% (95% CI: 62.0%, 77.5%) at the end-of-study visit. Binding, non-neutralizing antibodies were detected with highly sensitive assays in 1.7% of patients with anemia receiving SC Binocrit®, however the authors reported that this had "*no evidence of a clinically-relevant impact*". The authors concluded that "*HX575 administered SC at least once a week was effective in managing anemia in CKD patients, regardless of whether they had previously been treated with ESA*" and that "*SC administration of HX575 is a suitable treatment option for CKD patients with anemia*".

❖ London et al, 2017: Long-term treatment with biosimilar epoetin-alpha (HX575) in hemodialysis patients with renal anemia: real-world effectiveness and safety in the MONITOR-CKD5 study[11]

This manuscript reports the MONITOR-CKD5 study which is the largest prospective observational study of intravenously administered epoetin-alpha biosimilar Binocrit® (HX575) in the haemodialysis setting. Patients who received at least one dose of Binocrit® were followed for up to 24 months to evaluate effectiveness and safety outcomes. 2,023 patients were enrolled (median age 68 years [range: 20-93]; 59.3% male) from Western European (74.7%) and Eastern European (25.3%) countries. 1,000 patients (49.4%) completed all follow-up visits, with 1,023 patients (50.6%) ending the study prematurely. The mean Hb levels (SD) observed during Binocrit® treatment increased from 11.09 (± 1.41) IU/kg/week at enrolment to 11.25 (± 1.19) g/dL at month 24. The highest mean Hb levels were recorded at month 4 (11.29±1.18 g/dL). The absolute mean change in Hb relative to baseline at months 2 − 24 varied from 0.06 (recorded at months 18 and 20) to 0.18 (month 4). During the 24 month reporting period 148 AEs were observed in 108

patients, of which 12 events occurring in 11 patients (0.5%) were reported as serious and determined to be Binocrit® related. No patients were reported to have developed non-neutralizing or neutralizing anti-epoetin antibodies or pure red cell aplasia. The authors summarised that "*Patients treated for up to 24 months with HX575 showed Hb outcomes equivalent to reference epoetin-α [alpha] under dosing patterns similar to the reference medicine*" and concluded that "*No unknown safety signals, including immunogenicity, were detected*".

Filgrastim

❖ Zecchini et al, 2017: A single-center, retrospective analysis to compare the efficacy and safety of filgrastim-sndz to filgrastim for prophylaxis of chemotherapy-induced neutropenia and for neutrophil recovery following autologous stem cell transplantation[12]

This manuscript reports on a 1-year retrospective chart review of adult patients who received either originator filgrastim or biosimilar filgrastim (Zarxio, Sandoz) for prophylaxis of chemotherapy-induced myelosuppression or neutrophil recovery after autologous stem cell transplantation (ASCT). Data was collected for the first 100 consecutive patients that received originator filgrastim between September 1, 2015 through February 29, 2016, and the first 100 consecutive patients who received biosimilar filgrastim between March 1, 2016 and August 31, 2016. When comparing the originator filgrastim group with the biosimilar group, no differences in the duration of treatment (originator = 7.96 versus biosimilar = 8.5 days, P = 0.36), white blood count (originator = 8.99 versus biosimilar = 8.04, P = 0.28) or absolute neutrophil count (ANC) (originator=7.62 versus biosimilar = 6.91 × 109/L, P = 0.36) at the time of discontinuation of filgrastim. The authors conclude that "*our retrospective data showed that clinical efficacy and safety of filgrastim and filgrastim-sndz [biosimilar filgrastim] are similar for prevention of chemotherapy-induced neutropenia and for neutrophil recovery following ASCT*".

❖ Yoshimura et al, 2017: Evaluation of a biosimilar granulocyte colony-stimulating factor (filgrastim XM02) for peripheral blood stem cell mobilization and transplantation: a single center experience in Japan[13]

The study aimed to compare the outcomes of biosimilar filgrastim (XM02) for the mobilisation of peripheral blood stem cells for autologous stem cell transplantation with those of a historic control group receiving originator filgrastim or lenograstim. A total of 14 patients received biosimilar filgrastim between July 2014 and October 2015. The historic control group comprised 34 patients who received originator filgrastim and 23 patients that received lenograstim between 2006 and 2013. There were no significant differences between treatments with regards to the success of cell mobilisation (eg. number of CD34+ cells harvested, scores for granulocyte/macrophage colony forming units) or transplantation outcomes (eg. time to engraftment). The authors conclude that "*In comparison with the originator G-CSFs, biosimilar FBNK [XM02] shows the same efficacy and safety for facilitating bone marrow recovery in Japanese patients with ML [lymphoma] and MM [multiple myeloma] who undergo stem cell transplantation*".

❖ Gascón et al, 2017: MONITOR-GCSF DLBCL subanalysis: treatment patterns/outcomes with biosimilar filgrastim for chemotherapy-induced/febrile neutropenia prophylaxis[14]

In this manuscript the authors describe a subanalysis of the previously reported MONITOR-GCSF study, of the outcomes of biosimilar filgrastim focussing specifically on patients with diffuse large B-cell lymphoma. The aim of this analysis was to describe the incidence of chemotherapy induced febrile neutropenia, febrile neutropenia, antibiotic prophylaxis and changes to other G-CSF products. A total of 239 patients were included, of whom 87 (35.5%) experienced one or more episode of chemotherapy induce neutropenia (any grade) and 24 (9.8%) experienced at least one episode of febrile neutropenia. Results for antibiotic prophylaxis were not provided. A total of four (1.7%) patients were reported as having changed to another G-CSF product but details were not provided. The authors conclude that "*This analysis reports the effectiveness and safety of Sandoz biosimilar filgrastim in real-life practice in patients with DLBCL*" and that "*This supports the use of filgrastim in patients with NHL in a real-world setting*".

❖ Puertolas et al, 2017: Effectiveness of biosimilar filgrastim vs. original granulocyte colony-stimulating factors in febrile neutropenia prevention in breast cancer patients[15]

This retrospective drug utilization study aimed to compare the effectiveness of biosimilar filgrastim with lenograstim and pegfilgrastim for prophylaxis of febrile neutropenia patients with breast cancer receiving docetaxel/doxorubicin/cyclophosphamide (TAC) as adjuvant/neoadjuvant treatment. A total of 98 patients (97 females) were identified between January 2012 and December 2014 equating to 518 chemotherapy cycles. Biosimilar filgrastim was administered in 303 cycles, pegfilgrastim in 180 cycles and lenograstim in 35 cycles. The majority of patients (83.7%) received the same agent for each of their chemotherapy cycles for their total course of therapy, with 14.3% of patients changed from pegfilgrastim or lenograstim to biosimilar filgrastim as a result of "*institutional's recommendation to more cost-effective option*". A total of 17 patients who experienced 18 episodes of febrile neutropenia were identified. There were no statistically significant differences in the incidence of febrile neutropenia (3.7% pegfilgrastim/lenograstim vs. 3.3% biosimilar filgrastim, p = 0.79) or neutropenia-related hospitalizations (3.3 vs. 3.6%, p = 0.19). The cost of treatment with biosimilar filgrastim was nine and three times lower than pegfilgrastim and lenograstim respectively.

❖ Douglas et al, 2017: A Comparison of Brand and Biosimilar Granulocyte-Colony Stimulating Factors for Prophylaxis of Chemotherapy-Induced Febrile Neutropenia[16]

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 Humana Research Database between October 2015 and September 2016 if they received originator or biosimilar filgrastim within 6 days following exposure to chemotherapy and with at least 14 days between subsequent exposure to chemotherapy. Specific details regarding chemotherapy are not provided. Efficacy outcomes included hospitalisation for febrile neutropenia, defined as hospitalisation for both neutropenia and infection, as documented by relevant International Classification of Diseases codes, or as a composite of a hospitalisation for either neutropenia or infection. Safety was assessed according to a composite comprising spleen rupture, acute respiratory syndrome, serious allergic reactions, capillary leak syndrome, thrombocytopenia, leukocytosis, cutaneous vasculitis, bone ache and muscle ache. Non-inferiority was

defined as an incidence difference of less than 1% with the 90% confidence interval including zero. A total of 189 patients were identified, of whom 88 received originator filgrastim and 101 received biosimilar. Of these, 3 patients (3.4%) receiving originator filgrastim and 4 patients (4%) receiving biosimilar were hospitalised with infection or neutropenia codes whilst 1 patient (1.1%) receiving originator filgrastim and 2 patients (2%) receiving biosimilar filgrastim were hospitalised with both neutropenia and infection. Non-inferiority was demonstrated for hospitalisation for febrile neutropenia (difference in incidence = −0.8%, 90%: −3.8% - 2.1%, P = 0.64) and for the composite of neutropenia or infection (difference in incidence = −0.6%, 90%CI = -5.1% - 4.0%, P = 0.84). With regards to the safety outcome, adverse events were recorded for 3 patients (3.4%) receiving originator filgrastim and 6 patients (5.9%) receiving biosimilar filgrastim corresponding to a difference of 2.5% and as such non-inferiority was not demonstrated, however there was no significant difference in the safety outcome (90%CI: −7.5% - 2.5%, P=0.42).

Commentary

As acknowledged by the authors, the use of administrative claims data is subject to significant limitations with regards to the assessment of the specific efficacy and safety outcomes. Interpretation of the results of this study is also restricted by the limited information presented describing the patient groups, particularly with regards to chemotherapy regimens. The authors also acknowledge the limitation associated with the small number of patients with the outcomes of interest and the use of a safety outcome based upon a composite including a diverse range of adverse effects.

Infliximab

❖ Gonczi et al, 2017: Long-term Efficacy, Safety, and Immunogenicity of Biosimilar Infliximab After One Year in a Prospective Nationwide Cohort[17]

This manuscript reports on a multicenter nationwide prospective observational study conducted at 12 centers in Hungary aimed to evaluate the efficacy, safety, and immunogenicity of treatment with biosimilar infliximab (CT-P13) for up to 54 weeks in patients with inflammatory bowel disease. Eligible patients were either anti-TNFalpha naïve or had previously responded to an anti-TNFalpha agent but had ceased infliximab for nonmedical reasons at least 12 months prior. Clinical response, remission, biochemical response, immunogenicity, and safety were evaluated at weeks 14, 30, and 54. A total of 353 consecutive patients (Crohn's disease = 209, ulcerative colitis = 144) were included, of whom 77 had previously received anti-TNFalpha treatment (infliximab only = 56, infliximab and adalimumab = 3, adalimumab only = 18). Of the 353 patients included, 229 patients completed the week 54 follow-up whilst treatment was ceased in 37 patients due to adverse events, in 11 owing to primary nonresponse and in 27 due to loss of response. Over the time points assessed clinical remission rates in patients with Crohn's disease varied between 48% and 53% and between 43% and 56% in patients with ulcerative colitis. The mean C-reactive protein level decreased significantly in patients with both Crohn's disease and ulcerative colitis by week 14 and was maintained throughout the follow-up (P < 0.001). There were statistically significant differences in rates of remission between anti-TNFalpha naïve and previously treated patients but these differences occurred only at selected time points and these differed between those with Crohn's disease and ulcerative colitis. Similarly, infliximab trough concentrations were statistically significantly lower in previously anti–TNF-

exposed patients with ulcerative colitis at selected time points but not in patients with Crohn's disease. Cumulative anti-drug antibody positivity rates were significantly higher in anti–TNF-exposed patients (P < .0001) at all time points. On the basis of these results the authors consider that "*clinical remission and response rates were maintained throughout 54 weeks and were in line with the previously published data on the originator product or CT-P13 biosimilar*".

Commentary

The anti-TNFalpha exposed group contained patients that had received infliximab, adalimumab or both which complicates the comparison with the anti-TNFalpha naïve group. Analysis of results excluding those previously exposed only to adalimumab and not infliximab, are not presented.

❖ Richmond et al., 2017: Biosimilar infliximab use in paediatric IBD[18]

This prospective study, sponsored by Napp Pharmaceuticals (the distributor of Remsima in the UK), reports on the outcomes associated with the initiation of biosimilar infliximab (Remsima) in 40 paediatric patients with inflammatory bowel disease (Crohn's disease = 29, ulcerative colitis/unclassified = 11) from Glasgow and Edinburgh. The median age at diagnosis was 12.7 years (inter-quartile range: 10-14) with biosimilar infliximab initiated at 13.7 years (inter-quartile range: 13-16). The majority of patients (95%; 38/40) were on immunosuppressive therapy; 71% (27/38) on azathioprine/mercaptopurine and 29% (11/38) on methotrexate and at initiation, 43% (17/40) were also receiving oral prednisolone. At initiation, 8/29 patients with Crohn's disease were considered to be in remission. Data were collected at treatment initiation, following the three induction doses and at approximately 12 weeks post initiation. Disease activity was assessed according to the weighted Paediatric Crohn's Disease Activity Index (wPCDAI) and the Paediatric Ulcerative Colitis Activity Index (PUCAI). Biomarkers included calprotectin and C reactive protein (CRP). At 12 weeks, data were available for a maximum of 27 patients. Reasons for loss to follow-up are not provided. Relative to baseline values, at 12 weeks post initiation, biosimilar infliximab resulted in statistically significant reductions in calprotectin (840 vs 250, p=0.008) and CRP (5.5 vs 1, p=0.0004) and the wPCDAI (2.75 vs 5 (p=0.002). A total of 14 of 21 patients with Crohn's disease were in remission at the end of the study. The PUCAI did not reach statistical significance (45 vs 23.8, p=0.4). Two patients were positive for anti-drug antibodies, of whom one had received originator infliximab 6 years prior to initiating biosimilar infliximab and had previously developed "*a mild sensitivity*" to originator infliximab. The authors note that the use of biosimilar infliximab in these patients was estimated to save £47800 GBP. The authors conclude that "*These baseline data have now enabled us to confidently switch patients from originator to biosimilar, adopting the same prospective methodology to monitor effectiveness, safety and cost.*"

❖ Guerrero Puente et al, 2017: Evolution after switching to biosimilar infliximab in inflammatory bowel disease patients in clinical remission[19]

This retrospective observational study describes the outcomes associated with switching from originator infliximab (Remicade®) to biosimilar infliximab (CT-P13) in patients with inflammatory bowel disease. Patients were required to have been in remission for at least 3 months and to have received a minimum 6 months treatment with originator infliximab. Study outcomes included the incidence of relapse, adverse

effects and changes in infliximab trough concentrations or antidrug antibodies. A total of 36 patients (ulcerative colitis = 13, Crohn's disease = 23) were included in the study. Following the switch from originator to biosimilar infliximab, the mean duration of follow-up was 8.4 months (±3.5). A total of five patients (13.9%) experienced a loss of response during follow-up (ulcerative colitis = 2, Crohn's disease = 3) with a mean time to relapse of 2.4 months (±1.9). Following relapse, three patients received a high dose of infliximab and two received alternative treatments. All five patients returned to remission. There were no differences in pre-switching infliximab concentrations when compared with those at 8 and 16 weeks post-switch (p = 0.94). Antidrug antibodies were detected in a single patient prior to switching but were not detected post-switch. The authors conclude that "…*switching to biosimilar infliximab in a real-life cohort of patients with IBD in clinical remission does not seem to have a significant impact on short-term clinical outcomes*" and that "*The factors associated with relapse were similar to those expected during follow-up in patients who continued with the reference product*".

❖ Tweehuysen et al., 2017: Subjective Complaints as Main Reason for Biosimilar Discontinuation after Open Label Transitioning from Originator to Biosimilar Infliximab[20]

The aim of this prospective study was to evaluate the impact of switching from originator infliximab to biosimilar infliximab (CT-P13) with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. The primary outcome was change in disease activity, DAS28 and BASDAI, at month 6 (± 2 months) relative to baseline. Infliximab trough concentrations were assessed prior to the switch and at 6 months. A total of 222 patients were invited to switch from originator infliximab to biosimilar infliximab, of whom 192 patients (88%) agreed to do so and 19 patients declined but agreed to participate in the study as a control group. Due to the low number of patients opting to continue originator infliximab, the authors did not conduct any further analysis of this group. Within the group of patients switching to biosimilar infliximab the median treatment duration with originator infliximab prior to switching was 7 years (p25-75: 4-9). At baseline 14 patients were positive for antidrug antibodies. At six months following the switch, disease activity in patients with rheumatoid arthritis and psoriatic arthritis was considered to have remained stable (difference in DAS28 = 0.0, 95%CI: -0.1-0.2) whilst BADSAI increased in patients with ankylosing spondylitis (difference= 0.5, 95%CI:0.1-0.9). Infliximab trough levels were not significantly different between baseline and 6 months post-switch (2.0 µg/ml [range 0–25] versus 1.9 µg/ml [range 0–22, p = 0.45]). Over the course of the 6 month period, antidrug antibodies became undetectable in seven of those positive at baseline whilst two patients who were negative at baseline became positive such that a total of nine patients were positive for antidrug antibodies at six months post-switch.

At six months post-switch, 47 patients (24%) had discontinued biosimilar infliximab due to a "*perceived lack of effect*" (n=26), adverse events (n=11) or a combination of these (n=10). Of these, 37 patients resumed treatment with originator infliximab, seven changed to an alternative biologic DMARD whilst three did not receive another biologic DMARD. Within this group of patients, DAS28 and BASDAI increased by 0.8 (95% CI: 0.3 - 1.3) and 1.8 (95% CI: 0.4-3.2) respectively which was attributed to increases in tender joint counts and patient's global disease activity but not swollen joint counts and CRP. On this basis the authors believe that discontinuation "*was mainly driven by an increase in subjective tender joint count and patients' global disease activity and/or subjective AEs rather than objective signs and symptoms*". Patients who were receiving intensified treatment with originator infliximab through shortening of the interval between infusions were more likely to discontinue biosimilar infliximab (hazard rate = 0.77, 95%CI: 0.62-0.95). The

authors note that "*the discontinuation rate of 24% in the transition group is much higher than expected based on existing data on long-term REM* [originator infliximab] *treatment*" but consider that "*In our view, the reason for the substantial discontinuation rate in open label studies is the awareness of both patients and physicians of the transition to the biosimilar*", the so-called nocebo effect. The authors suggest that the observation that intensified treatment was a predictor of discontinuation of biosimilar infliximab may be explained by the fact that "*patients who are treated with a shorter infusion interval feel more dependent on REM* [originator infliximab] *and are consequently more prone to the nocebo effect*". The authors also note that "*in our hospitals groups of patients received their infliximab infusions together in one room for years*" which may contribute to the observed discontinuation rate as "*When a patient restarted REM* [originator infliximab] *treatment because of complaints, the other patients observed this, potentially leading to the group think effect that CT-P13 is inferior and the desire to restart REM*[originator infliximab]". The authors acknowledge that beliefs and attitudes of patients and clinicians toward biosimilar medicines were not assessed in this study.

❖ Eberl et al., 2017: Switching maintenance infliximab therapy to biosimilar infliximab in inflammatory bowel disease patients[21]

The aim of this prospective cohort study conducted at Helsinki University Hospital was to evaluate the impact of switching from originator infliximab to biosimilar infliximab (Remsima) on trough infliximab concentrations, anti-drug antibody formation and disease activity in 62 patients with inflammatory bowel disease (Crohn's disease = 32, ulcerative colitis/unclassified = 30) after three infusions of the biosimilar. There was no statistically significant change in median infliximab trough concentrations following the switch as compared with baseline (5.5 mg/L, IQR: 3.15–7.8 mg/l versus 5.5 mg/L, IQR: 3.85–8.65 mg/L respectively, p=0.05). When analysed by disease, median trough concentrations decreased from 5.2 mg/L (IQR: 3.8–8.65 mg/L) at baseline to 4.25 mg/L (IQR: 2.6–6.45 mg/L, p = 0.019) at baseline in the ulcerative colitis/unclassified group but not within the Crohn's disease group (p=0.68). Prior to switching, no patients were positive for antidrug antibodies but were detected in two patients post switching. There were no statistically significant changes in disease activity following switching in either patient group (UC, p=0.89, CD, p=0.07) or in feacal calprotectin concentrations (p=0.78). The authors note that due to absence of a control group continuing treatment with originator infliximab "*it remains unresolved whether the change in median TL* [trough concentration] *in UC patients is due to switching to the biosimilar IFX* [infliximab] *or due to other patient dependent or pharmacological factors*" and that the result "*should be interpreted with caution because of the rather low patient number in the UC subgroup*". Although a statistical difference in infliximab concentrations was identified "*no changes in disease clinical activity occurred and a constantly low FC* [faecal calprotectin] *concentration in these patients suggested a stable remission after switching*". Overall, the authors consider that "*Our findings are in line with results from recently published studies*".

❖ Scherlinger et al, 2017: Switching from originator infliximab to biosimilar CT-P13 in real-life: the weight of patient acceptance[22]

The aims of this study, conducted in patients with rheumatoid arthritis, ankylosing spondyloarthritis and psoriatic arthritis were to assess the retention rates following switching from originator infliximab to biosimilar infliximab and to compare this with a group initiating treatment with biosimilar infliximab and a retrospective control group treated with originator infliximab. Patients were switched to biosimilar

infliximab and prospectively followed between November 2015 and October 2016. In order to be eligible for switching, patients must have been receiving stable infliximab treatment for at least 6 months and "*there* (sic) *disease was controlled according to physician opinion*". Patients were provided with information about biosimilars and informed that "*upon simple request switching back to the originator would be possible*". A total of 89 patients were switched to biosimilar infliximab. A total of 82 historic controls treated during 2013 and 29 infliximab naïve patients initiated on biosimilar infliximab were included. After a median follow-up of 33 weeks (range 6-50), the retention rate for those switching to biosimilar infliximab was 72% (64/89). The infliximab naïve group was followed for a median of 30 weeks and the historic originator infliximab control group was followed for one year. The discontinuation rate in the switched group (28%, 25/89) was significantly higher (p=0.0002) than in the infliximab naïve group (10%, 3/29) and the historic control group (12%, 10/82). Of the 25 patients in the switched group that discontinued treatment with the biosimilar, 11 patients (44%) "*without objective clinical activity*" (as assessed by relevant disease activity measures) requested to return to treatment with originator infliximab. However, when retention rates were restricted to those who discontinued "*due to objective clinical activity worsening*" there were no statistically significant differences (p=0.453). The authors state that "*On a total of a hundred patients who were proposed to switch, 89 accepted among which 13 failed because of objective clinical activity which is the expected rate of failure in patients treated with TNF blockers*". The authors suggest that their observation that a significant proportion of patients requested to switch back to originator infliximab despite no objective evidence of increased disease activity "*…is a major concern for clinicians, health authorities and pharmaceutical companies, indicating that information on biosimilars will be a key point to promote the acceptance of switching a biodrug for a non-medical reason…*".

❖ Argüelles-Arias et al, 2017: Switching from reference infliximab to CT-P13 in patients with inflammatory bowel disease: 12 months results[23]

This manuscript reports on a prospective single-center observational study in patients with moderate to severe Crohn's disease (CD, n=67) and ulcerative colitis (UC, n=31) who were switched from originator infliximab (Remicade) to biosimilar infliximab (CT-P13) and followed up for up to 12 months. Prior to switching the median duration of treatment with originator infliximab was 297 weeks (interquartile range:158-432) for patients with Crohn's disease and 203 weeks (interquartile range: 42-294) for patients with ulcerative colitis. Prior to switching, 84% (56/67) patients with Crohn's disease and 81% (25/31) patients with ulcerative colitis were considered to be in remission. At 12 months post-switching to biosimilar infliximab 63% (42/67) of patients with Crohn's disease and 64% (18/28) of patients with ulcerative colitis were in remission. Of those in remission prior to switching, 70% (37/53) of patients with Crohn's disease and 81% (17/21) of patients with ulcerative colitis remained in remission at 12 months. The authors state that "*Results indicate that CT-P13 treatment is effective and safe for up to 1 year in patients switched from infliximab RP* [originator infliximab]".

❖ Avouac et al, 2017: Systematic switch from innovator infliximab to biosimilar infliximab in inflammatory chronic diseases in daily clinical practice: The experience of Cochin University Hospital, Paris, France[24]

This prospective observational study aimed to investigate effectiveness of systematic switching treatment from originator infliximab to biosimilar infliximab at a single institution in France. Participants were eligible for inclusion if they had received a minimum of three infusions of originator infliximab prior to switching

and agreed to switching. A total of 260 were included with a diverse range of indications for infliximab (axial spondyloarthritis = 131, rheumatoid arthritis = 31, psoriatic arthritis = 14, juvenile arthritis = 3, undifferentiated arthritis = 3, Crohn's disease = 41, ulcerative colitis = 23, uveitis = 8, Takayasu's arteritis = 4 and Behcet's disease = 2). The primary outcome of the study was the retention rate of biosimilar infliximab in the overall population at the time of the third infusion following switching. A total of 221/260 participants received a third infusion of biosimilar infliximab, resulting in a retention rate of 85%. Of those that discontinued, 47/59 (80%) discontinued due to a lack of efficacy with the remainder due to a range of reasons including loss to follow-up (n=6), pregnancy (n=1) and transient elevated liver enzymes (n=1). Forty-seven participants switched back to originator infliximab and were followed up for 32.3 ± 5.4 weeks. Within patients with rheumatoid arthritis (n=5) that switched back to originator infliximab there was no change in disease activity as assessed by DAS28. However, within patients with axial spondyloarthritis there was an improvement in BASDAI (2.98 ±2.13 vs. 4.21 ± 2.07, P= 0.012) and the ASDAS (2.02 ± 1.17 vs. 2.42 ± 0.92, P = 0.041). In both groups there were no changes in CRP (P= 0.592) or infliximab trough concentrations (P=0.342). The authors consider that the discontinuation of biosimilar infliximab "*mainly concerned patients with axSpA* [axial spondyloarthritis] *due to a subjective significant increase in patient reported outcome measures, including BASDAI or ASDAS scores, which is possibly explained by suggestion or attribution effects rather than pharmacological differences*" and that "*This is sustained by the stability of infliximab through levels and other objective measures (e.g., CRP and swollen joints) over time*".

❖ Kaniewska et al, 2017: The efficacy and safety of the biosimilar product (Inflectra®) compared to the reference drug (Remicade®) in rescue therapy in adult patients with ulcerative colitis[25]

The aim of this retrospective study aimed to compare the efficacy and safety of the biosimilar infliximab (Inflectra®) with originator infliximab (Remicade®) as rescue therapy in adults with acute severe ulcerative colitis and to assess the recurrence rate during a 6-month observation period. Disease activity was assessed at qualification for treatment, at conclusion of rescue treatment, and after 6 and 12 months of observation. Efficacy was assessed according to the proportion of patients attaining clinical remission (defined as obtaining a Mayo score of ≤ 2 with no component exceeding one at the end of treatment) and clinical response (defined as a 3 point reduction in Mayo score with ≥ 1 point reduction in rectal bleeding and bleeding ≤1 at the end of treatment), mucosal healing and endoscopic remission. A total of 83 patients were identified, of whom 55 patients had received originator infliximab and 28 had received the biosimilar. No significant differences between the originator and biosimilar groups were identified in the proportion of patients attaining clinical remission (42% vs. 32%, p > 0.05), clinical response (81% vs. 77%, p > 0.05), mucosal healing (15% vs. 13%, p > 0.05) or endoscopic remission (13.8% vs. 13.2%, p > 0.05). Allergic reactions occurred in three patients treated with biosimilar infliximab and one treated with originator, all of who had previously received originator infliximab. At 6 months, an exacerbation had occurred in 75% of those who received originator infliximab versus 64% of those who received biosimilar infliximab (p = 0.64). The authors conclude that "*Based on the data presented, we can confirm the efficacy and safety of short-term UC therapy with the biosimilar compared to the reference drug, not only in induction but also during a 6-month observation*".

Infliximab and Etanercept

❖ Egeberg et al, 2017: Safety, efficacy, and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis[26]

This manuscript reports findings from the DERMBIO registry which contains mandatory reported data on all Danish patients with moderate-to-severe plaque psoriasis who have received biologics since 2007. The broad objective of this study was to examine safety, efficacy, and time to discontinuation (referred to as drug survival) of range of biologics (adalimumab, etanercept, infliximab, secukinumab, and ustekinumab) and specifically for infliximab and etanercept to compare originators with biosimilars. Biosimilar versions of infliximab and etanercept have been available in Denmark since March 2015 (Remsima®) and March 2016 (Benepali®), respectively. The DERMBIO dataset records biologic drug usage as a treatment series/sequences of continuous treatment with the same biologic drug. Treatment sequences were merged together if the same drug was used in two consecutive series and the discontinuation was within a suitable window period. Due to strict adherence to prescribing guidelines enforced at the national level, whereby switching is only permitted in stable patients, switching from other compounds directly to a biosimilar (e.g. from adalimumab to biosimilar infliximab) was unlikely in this dataset. In analyses of etanercept and infliximab, series were joined if patients were switched between Enbrel® and Benepali®, and Remicade® and Remsima®. The total number of treatment series were reported for Remicade® (114), Remsima® (34), Enbrel® (147), and Benepali® (44). The median treatment duration prior to switching was 2089 for Enbrel® and 1589 days for Remicade®. No significant differences in drug survival between Remsima compared with Remicade (HR = 1.64, 95%CI: 0.69-3.89, p=0.264) or Benepali (HR = 0.46, 95%CI: 0.11-1.98, p=0.297) compared with Enbrel (HR = 0.46, 95%CI: 0.11-1.98, p=0.297) were reported. The authors concluded that "*switching from originator to biosimilar infliximab or etanercept had no significant impact on drug survival*" in patients with psoriasis.

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

There was a single original research article published during the review update period addressing the topic of biosimilar perception amongst patients and healthcare professionals.

❖ van Overbeeke et al, 2017: Perception of Originator Biologics and Biosimilars: A Survey Among Belgian Rheumatoid Arthritis Patients and Rheumatologists[27]

Using anonymous web-based surveys, conducted between January and March 2016, this study aimed to investigate the knowledge and perception of rheumatologists and patients with rheumatoid arthritis in Belgium.

A total of 121 patients responded to the survey, of whom 79% had heard of biologics and 49% had heard of biosimilars. Of those who had heard of biosimilars, when asked "*What does the term 'biosimilar medicine' (biosimilar) mean to you?*" 77% selected the option "*A biologic similar to an existent (originator) biologic*" from options that included "*Not sure*", "*A biologic*" and "*A biologic identical to an existent (originator) biologic*". When participants were asked the questions "*When my physician prescribes me an originator I wonder if …*" and "*When my physician prescribes me a biosimilar I wonder if …*", participants were more likely to select the option "*This medicine is safe*" when considering biosimilars compared with originators (p<0.05). However, there were no statistically significant difference between response for biosimilar and originator with regards to the percentage of participants selecting any of the other options such as "*There are side effects*" or "*This medicine has a proven efficacy in RA*". With regards to the impact of price, participants were presented with the scenarios of "*When the price of the originator has decreased, but is higher than the biosimilar, which one do you prefer to be treated with?*" and "*When the prices of an originator and a biosimilar are equal, which one do you prefer to be treated with?*". In both scenarios, approximately 60% of respondents indicated that "*I have no preference, and I trust my physician in prescribing me the best suitable medicine*" with less than 10% of participants selecting the biosimilar and the remainder indicating preference for the originator.

A total of 41 rheumatologists responded to the survey, equating to 18% of rheumatologists in Belgium at that time. Three respondents had prescribed a biosimilar. The vast majority of respondents (95%) indicated that a biosimilar is "*A biological similar to an original*" but when asked "*Which of the following elements can, according to you, differ between an originator and a biosimilar?*" (multiple responses possible) 63% of respondents indicated "*Safety*", 61% indicated "*Quality*", 61% indicated "*Efficacy*" and 93% indicated "*Price*". Subsequently, in response to the question "*For which patients would you prescribe a biosimilar?*" (six options, multiple responses possible) approximately 60% of respondents indicated "*Only in biologic-naïve patients*", 40% indicated "*Patients with indications for which the biosimilar is registered*", less than 10% indicated "*I would not prescribe this*" and no participants selected "*Stable patients treated with the original*". With regards to the impact of price, when asked "*When the price of the originator has decreased, but is higher than the biosimilar, which one do you prefer to prescribe?*" responses were approximately evenly distributed between the options of the "*Originator*", the "*Biosimilar*" and "*No preference*" with slight preference toward the originator. However, when the price of the biosimilar and originator were the same, greater than 70% of respondents chose the "*Originator*" and no respondents selected preference for the biosimilar.

Commentary

The authors acknowledge that participant responses may have been influenced by the wording of the survey questions. Authors of this paper include an employee of Pfizer.

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6. Smolen, J.S., et al., Safety, immunogenicity and efficacy after switching from reference infliximab to biosimilar SB2 compared with continuing reference infliximab and SB2 in patients with rheumatoid arthritis: results of a randomised, double-blind, phase III transition study. Annals of the Rheumatic Diseases, 2017. 17: p. 17.

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8. McBride, A., et al., Expanded access to cancer treatments from conversion to neutropenia prophylaxis with biosimilar filgrastim-sndz. Future Oncology, 2017. 13(25): p. 2285-2295.

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10. Casadevall, N., et al., Evaluation of the safety and immunogenicity of subcutaneous HX575 epoetin alfa in the treatment of anemia associated with chronic kidney disease in predialysis and dialysis patients. Clin Nephrol, 2017. 88(10): p. 190-197.

11. London, G., et al., Long-term treatment with biosimilar epoetin-alpha (HX575) in hemodialysis patients with renal anemia: real-world effectiveness and safety in the MONITOR-CKD5 study. Clinical Nephrology, 2017. 23: p. 23.

12. Zecchini, J., et al., A single-center, retrospective analysis to compare the efficacy and safety of filgrastim-sndz to filgrastim for prophylaxis of chemotherapy-induced neutropenia and for neutrophil recovery following autologous stem cell transplantation. Supportive Care in Cancer, 2017: p. 1-4.

13. Yoshimura, H., et al., Evaluation of a biosimilar granulocyte colony-stimulating factor (filgrastim XM02) for peripheral blood stem cell mobilization and transplantation: a single center experience in Japan. Journal of Blood Medicine, 2017. 8: p. 5-12.

14. Gascon, P., et al., MONITOR-GCSF DLBCL subanalysis: treatment patterns/outcomes with biosimilar filgrastim for chemotherapy-induced/febrile neutropenia prophylaxis. European Journal of Haematology, 2017. 24: p. 24.

15. Puertolas, I., et al., Effectiveness of biosimilar filgrastim vs. original granulocyte colony-stimulating factors in febrile neutropenia prevention in breast cancer patients. European Journal of Clinical Pharmacology, 2017. 19: p. 19.

16. Douglas, A.G., et al., A Comparison of Brand and Biosimilar Granulocyte-Colony Stimulating Factors for Prophylaxis of Chemotherapy-Induced Febrile Neutropenia. J Manag Care Spec Pharm, 2017. 23(12): p. 1221-1226.

17. Gonczi, L., et al., Long-term Efficacy, Safety, and Immunogenicity of Biosimilar Infliximab After One Year in a Prospective Nationwide Cohort. Inflammatory Bowel Diseases, 2017. 23(11): p. 1908-1915.

18. Richmond, L., et al., Biosimilar infliximab use in paediatric IBD. Archives of Disease in Childhood, 2017. 07: p. 07.

19. Guerrero Puente, L., et al., Evolution after switching to biosimilar infliximab in inflammatory bowel disease patients in clinical remission. Gastroenterologia y Hepatologia, 2017. 40(9): p. 595-604.

20. Tweehuysen, L., et al., Subjective Complaints as Main Reason for Biosimilar Discontinuation after Open Label Transitioning from Originator to Biosimilar Infliximab. Arthritis & Rheumatology, 2017. 18: p. 18.

21. Eberl, A., et al., Switching maintenance infliximab therapy to biosimilar infliximab in inflammatory bowel disease patients. Scandinavian Journal of Gastroenterology, 2017. 52(12): p. 1348-1353.

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27. van Overbeeke, E., et al., Perception of Originator Biologics and Biosimilars: A Survey Among Belgian Rheumatoid Arthritis Patients and Rheumatologists. Biodrugs, 2017. 31(5): p. 447-459.

APPENDIX 1

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

1. Bellinvia, S., et al., A review article on biosimilar infliximab SB2 in the treatment of rheumatoid arthritis. Immunotherapy, 2017. 9(14): p. 1133-1142.

2. Blair, H.A., GP2013: A Rituximab Biosimilar. BioDrugs, 2017. 31(5): p. 465-468.

3. Blandizzi, C., M. Galeazzi, and G. Valesini, Transitioning from first- to second-generation biosimilars: An appraisal of regulatory and post-marketing challenges. Pharmacological Research., 2017.

4. Chaplin, S., Biosimilars in the EU: a new guide for health professionals. Prescriber, 2017. 28(10): p. 27-31.

5. Chopra, R. and G. Lopes, Improving Access to Cancer Treatments: The Role of Biosimilars. Journal of Global Oncology, 2017. 3(5): p. 596-610.

6. Coiffier, B., Pharmacokinetics, efficacy and safety of the rituximab biosimilar CT-P10. Expert Review of Clinical Pharmacology, 2017. 10(9): p. 923-933.

7. Conti, R.M., Biosimilars: Reimbursement Issues in Your Oncology Practice. Journal of oncology practice/American Society of Clinical Oncology, 2017. 13(9_suppl): p. 12s-14s.

8. Correale, J., Follow-on products for treatment of multiple sclerosis in Latin America: An update. Journal of the Neurological Sciences, 2017. 381: p. 153-159.

9. Cozijnsen, M.A., J.N. Samsom, and L. de Ridder, Anti-Tumour Necrosis Factor Therapy for Paediatric Crohn's Disease: Improved Benefits Through Treatment Optimisation, Deeper Understanding of Its Risks, and Reduced Costs due to Biosimilar Availability. Pediatric Drugs, 2017: p. 1-10.

10. Danese, S. and L. Peyrin-Biroulet, To switch or not to switch: That is the biosimilar question. Nature Reviews Gastroenterology and Hepatology, 2017. 14(9): p. 508-509.

11. Davies, M., et al., Introduction of biosimilar insulins in Europe. Diabetic Medicine, 2017. 34(10): p. 1340-1353.

12. Deeks, E.D., GP2015: An Etanercept Biosimilar. BioDrugs, 2017: p. 1-4.

13. Dougherty, M.K., I. Zineh, and L. Christl, Perspectives on the Current State of the Biosimilar Regulatory Pathway in the United States. Clinical Pharmacology and Therapeutics., 2017.

14. Dranitsaris, G., et al., Drug tendering: Drug supply and shortage implications for the uptake of biosimilars. ClinicoEconomics and Outcomes Research, 2017. 9: p. 573-584.

15. Farkas, K. and T. Molnar, A review on biosimilar infliximab, CT-P13, in the treatment of inflammatory bowel disease. Immunotherapy, 2017. 10: p. 10.

16. Fleischmann, R., Therapy: Biosimilars in rheumatology-why, how and when in 2017. Nature Reviews Rheumatology, 2017. 13(12): p. 701-703.

17. Ghosh, P.K., Similar Biologics: Global Opportunities and Issues. Journal of Pharmacy & Pharmaceutical Sciences, 2017. 19(4): p. 552-596.

18. Gran-Ruaz, S., A. Mani, and S. O'Quinn, An overview of biosimilars and non-biologic complex drugs in Europe, the United States, and Canada and their relevance to multiple sclerosis. Multiple Sclerosis, 2017. 23(14): p. 1824-1829.

19. Harvey, R.D., Science of Biosimilars. Journal of oncology practice/American Society of Clinical Oncology, 2017. 13(9_suppl): p. 17s-23s.

20. Heinemann, L. and A.W. Carter, Will Biosimilar Insulins Be Cheaper? Diabetes Technology & Therapeutics, 2017. 19(9): p. 513-515.

21. Jongsma, M.M.E., A. Vulto, and L. de Ridder, The use of biosimilars in paediatric inflammatory bowel disease. Current Opinion in Pediatrics, 2017. 29(5): p. 560-565.

22. Jurczak, W., et al., Research on Biosimilars: pivotal trials and principles. The Lancet Haematology, 2017. 4(9): p. e409-e410.

23. Kirchhoff, C.F., et al., Biosimilars: Key regulatory considerations and similarity assessment tools. Biotechnology and Bioengineering, 2017. 114(12): p. 2696-2705.

24. Klein, A.V., et al., Biosimilars: State of Clinical and Regulatory Science. Journal of Pharmacy & Pharmaceutical Sciences, 2017. 20(1): p. 332-348.

25. Knezevic, I. and E. Griffiths, WHO standards for biotherapeutics, including biosimilars: an example of the evaluation of complex biological products. Annals of the New York Academy of Sciences, 2017. 1407(1): p. 5-16.

26. Korkmaz, S. and F. Altuntas, What is the role of biosimilar G-CSF agents in hematopoietic stem cell mobilization at present? Transfusion and Apheresis Science., 2017.

27. Krendyukov, A., et al., Clinical equivalence with G-CSF biosimilars: methodologic approach in a (neo)adjuvant setting in non-metastatic breast cancer. Supportive Care in Cancer, 2017: p. 1-8.

28. Kuribayashi, R. and K. Sawanobori, Current Japanese Regulatory Systems for Generics and Biosimilars. Journal of Pharmaceutical Sciences, 2017. 04: p. 04.

29. Ledon, N. and A. Lage, Biosimilars and the real world. MEDICC Review, 2017. 19(4): p. 9-14.

30. Linial, M., N. Rappoport, and D. Ofer, Overlooked short toxin-like proteins: A shortcut to drug design. Toxins, 2017. 9 (11) (no pagination)(350).

31. Lyman, G.H., Emerging Opportunities and Challenges of Biosimilars in Oncology Practice. Journal of oncology practice/American Society of Clinical Oncology, 2017. 13(9_suppl): p. 7s-9s.

32. Mellstedt, H., European Perspective on Biosimilars. Journal of oncology practice/American Society of Clinical Oncology, 2017. 13(9_suppl): p. 15s-16s.

33. Moore, C., Biosimilar monoclonal antibodies (mAbs) in oncology. British Journal of Nursing, 2017. 26(16): p. S26-S32.

34. Park, S.H., S. Aniwan, and E.V. Loftus, Advances in the use of biologics and other novel drugs for managing inflammatory bowel disease. Current Opinion in Pharmacology, 2017. 37: p. 65-71.

35. Patel, D., et al., The rise of biosimilars: How they got here and where they are going. Metabolism: Clinical and Experimental, 2017. 75: p. 45-53.

36. Radin, M., et al., Infliximab Biosimilars in the Treatment of Inflammatory Bowel Diseases: A Systematic Review. Biodrugs, 2017. 31(1): p. 37-49.

37. Rezk, M.F. and B. Pieper, Treatment Outcomes with Biosimilars: Be Aware of the Nocebo Effect. Rheumatology & Therapy, 2017. 4(2): p. 209-218.

38. Rifkin, R.M. and S.R. Peck, Biosimilars: Implications for Clinical Practice. Journal of oncology practice/American Society of Clinical Oncology, 2017. 13(9_suppl): p. 24s-31s.

39. Rosen, L.S., I.A. Jacobs, and R.L. Burkes, Bevacizumab in Colorectal Cancer: Current Role in Treatment and the Potential of Biosimilars. Targeted Oncology, 2017. 12(5): p. 599-610.

40. Scavone, C., et al., Strengths, weaknesses and future challenges of biosimilars' development. An opinion on how to improve the knowledge and use of biosimilars in clinical practice. Pharmacological Research, 2017. 126: p. 138-142.

41. Schioppo, T. and F. Ingegnoli, Current perspective on rituximab in rheumatic diseases. Drug Design, Development and Therapy, 2017. 11: p. 2891-2904.

42. Simoens, S., et al., Assessing the Value of Biosimilars: A Review of the Role of Budget Impact Analysis. PharmacoEconomics, 2017. 35(10): p. 1047-1062.

43. Toussirot, E. and H. Marotte, Switching from originator biological agents to biosimilars: What is the evidence and what are the issues? RMD Open, 2017. 3 (2) (no pagination)(e000492).

44. Trifiro, G., et al., Biosimilars in Italy: What do real-world data reveal? GaBI Journal, 2017. 6(3): p. 114-119.

45. Triplitt, C., D. Hinnen, and V. Valentine, How similar are biosimilars? What do clinicians need to know about biosimilar and follow-on insulins? Clinical Diabetes, 2017. 35(4): p. 209-216.

46. Tsai, W.C., Update on Biosimilars in Asia. Current Rheumatology Reports, 2017. 19(8): p. 47.

47. Yale, K., et al., Understanding state regulation of biosimilars and effect on prescribers. Journal of Drugs in Dermatology, 2017. 16(10): p. 995-1000.

48. Yu, Y.B., et al., Improving Biopharmaceutical Safety through Verification-Based Quality Control. Trends in Biotechnology, 2017. 35(12): p. 1140-1155.

49. Zucker, M., A review of reusable auto-injectors for biological & biosimilar drugs. ONdrugDelivery, 2017. 2017(79): p. 64-68.

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. Afonso, J., et al., Therapeutic drug monitoring of CT-P13: a comparison of four different immunoassays. Therapeutic Advances in Gastroenterology, 2017. 10(9): p. 661-671.

2. Cilia, M., et al., Quality Issues Identified During the Evaluation of Biosimilars by the European Medicines Agency's Committee for Medicinal Products for Human Use. AAPS PharmSciTech, 2017: p. 1-23.

3. Devanarayan, V., et al., Recommendations for Systematic Statistical Computation of Immunogenicity Cut Points. AAPS Journal, 2017. 19(5): p. 1487-1498.

4. Endrenyi, L., Biosimilar Clinical Development - Scientific Considerations and New Methodologies, by Boca Raton. Journal of Biopharmaceutical Statistics, 2017: p. 1-3.

5. Hassiki, R., et al., Biochemical and biological quality control of two recombinant human erythropoietin biosimilar products. Current Pharmaceutical Analysis, 2017. 13(6): p. 566-573.

6. Mastrangeli, R., et al., In-vivo biological activity and glycosylation analysis of a biosimilar recombinant human follicle-stimulating hormone product (Bemfola) compared with its reference medicinal product (GONAL-f). PLoS ONE, 2017. 12 (9) (no pagination)(e0184139).

7. Pisupati, K., et al., Biosimilarity under stress: A forced degradation study of Remicade and RemsimaTM. mAbs, 2017. 9(7): p. 1197-1209.

8. Prior, S., et al., International standards for monoclonal antibodies to support pre- and post-marketing product consistency: Evaluation of a candidate international standard for the bioactivities of rituximab. mAbs, 2017: p. 1-14.

9. Ryding, J., M. Stahl, and M. Ullmann, Demonstrating biosimilar and originator antidrug antibody binding comparability in antidrug antibody assays: A practical approach. Bioanalysis, 2017. 9(18): p. 1395-1406.

10. Shatat, S.M., et al., Coupling of on-column trypsin digestion-peptide mapping and principal component analysis for stability and biosimilarity assessment of recombinant human growth hormone. Journal of Chromatography B: Analytical Technologies in the Biomedical & Life Sciences, 2017. 1072: p. 105-115.

11. Uozumi, R. and C. Hamada, Adaptive Seamless Design for Establishing Pharmacokinetic and Efficacy Equivalence in Developing Biosimilars. Therapeutic Innovation and Regulatory Science, 2017. 51(6): p. 761-769.

12. Wan, M.T., et al., How similar are the treatment responses to biosimilars in patients with psoriasis? A systematic review of statistical margins in comparative clinical trials. Journal of the American Academy of Dermatology, 2017. 77(3): p. 569-572.