



Australian Government
Department of Health



**Literature Review of International Biosimilar Medicines:
Update September – December 2016**

Literature Review of International Biosimilar Medicines: Update October – December 2016

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Introduction

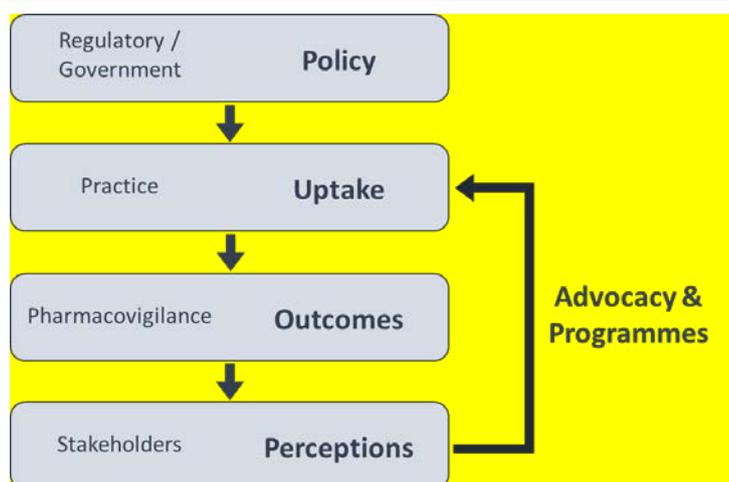
This report provides an update to the comprehensive literature search previously conducted that examined all international and Australian clinical, academic and policy journals and media articles or sources in relation to biosimilar medicines for the purpose of providing evidence which may inform policy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

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

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

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

Figure 1: Stages influencing biosimilar uptake and use



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

which governments, regulators, prescribers, pharmacists and patients are well accustomed. In reflection of this, the following central themes have been identified:

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

Overview of the Published Biosimilar Literature

This report includes literature published 08 September to 01 December 2016.

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 such as the results of a meta-analysis. 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 have been a significant number of manuscripts published that focus upon fundamental and technological issues relating to the production and characterisation of biological agents[1]. Of particular note are a number of manuscripts that describe the physicochemical characterisation of a number of potential biosimilars[2-7]. The regulatory processes required for the registration of biosimilar medicines demand rigorous and extensive characterisation of physicochemical (eg. amino acid sequence, glycosylation pattern) and pharmacological properties (eg. target binding) of potential biosimilar medicines and comparison of these properties with the reference product. 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 and as such manuscripts reporting these findings are of great importance to the development and evaluation of biosimilars.

However, these manuscripts are highly detailed and technical in nature; the specific content of which is outside of the scope of the communication aims of the Initiative. Therefore 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.

Given the general 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.

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 six 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 prespecified acceptance criteria for the relevant pharmacokinetic parameter endpoints. In some instances these phase I pharmacokinetic studies may provide preliminary insight into the pharmacodynamics (PD) or clinical effects of the potential biosimilar medicine, although these studies are not powered for these 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						
BI 695501 Adalimumab (Boehringer Ingelheim)	US and EU Humira 40mg	Randomised, double-blind, single-dose, parallel group study (1:1:1)	Healthy adult male volunteers (n=327; 322PPP)	90% CIs of the geometric mean ratios of AUClast, AUCinf and Cmax were within the prespecified acceptance criteria of 80-125%.	3.4% of subjects (n = 11) had ADAs at baseline; this was equally distributed across treatment groups. At 4 weeks after dosing, 46.7% (n = 50), 56.1% (n = 60), and 37.4% (n = 40) of subjects were confirmed as ADA- positive in the BI 695501, US- and EU- approved Humira groups, respectively. At day 28, median titre values (range) were 2 (1–512), 4 (1–512), and 2 (1–256) for the BI 695501 group, US- and EU-approved Humira groups, respectively.	[8]
MSB11022 Adalimumab (Merck)	US and EU Humira 40mg	Randomised, double-blind, single-dose, parallel group study (1:1:1)	Healthy adult volunteers (n=237; 235M/2F; 236PPP)	90% CIs of the geometric mean ratios of AUClast, AUCinf and Cmax were within the prespecified acceptance criteria of 80-125%. For AUCinf, the lower 90% CI approached the 80% limit for the comparison of MSB11022 and the EU product (80.14– 99.10%)	Up to and including day 15, ADAs were detected in 14.1% (n = 11), 20.5% (n = 16) and 12.7% (n = 10) of subjects for MSB11022, US-RP and EU-RMP, respectively. Up to and including day 71, ADAs were detected in 82.1% (n = 64), 81.3% (n = 65) and 83.5% (n = 66) of subjects for MSB11022, US-RP and EU-RMP, respectively.	[9]

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
Etanercept						
GP2015 Etanercept (Hexal) Pre-Filled Syringe	EU Enbrel 50mg	Randomised, double-blind, single-dose, crossover study	Healthy adult male volunteers (n=54; 54PPP)	90% CIs of the geometric mean ratios of AUClast, AUCinf and Cmax were within the prespecified acceptance criteria of 80-125%.	All samples from the pre-dose (Day 1) time-point in each study period were ADA negative. Three subjects had a confirmed positive non-neutralising ADA response at the follow up visit (Day 29, Period 2) with a low titre close to the detection limit (treatment sequence GP2015/Enbrel).	[10]
GP2015 Etanercept (Hexal) Autoinjector	GP2015 Etanercept (Hexal) Pre-Filled Syringe	Randomised, open-label, single-dose, crossover study	Healthy adult male volunteers (n=51; 48PPP)	90% CIs of the geometric mean ratios of AUClast, AUCinf and Cmax were within the prespecified acceptance criteria of 80-125%.	No ADAs were detected during the treatment periods nor at the follow-up visit.	
Filgrastim						
Pegfilgrastim (Apotex)	Neulasta 6mg	Randomised, assessor-blinded, single-dose, crossover study	Healthy adult volunteers (n=66; 49M/17F; 56PPP)	90% CIs of the geometric mean ratios of AUClast, AUCinf and Cmax were within the prespecified acceptance criteria of 80-125%. 95% CIs of the geometric mean ratios of each of the PD endpoint parameters (ANC, AUEct, and Emax) were fully contained within the prespecified acceptance criteria of 80-125%.	No samples at the 0 and 672 hr timepoints (n=190) were identified as ADA positive.	[11]

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
Human Growth Hormone						
r-hGH (Cristália Produtos Químicos Farmacêuticos)	Genotropin Pfizer 12.8IU	Randomised, open-label, single-dose, crossover study	Healthy adult volunteers (n =38; 19M/19F; 34PPP)	<p><u>Pharmacokinetics</u> 90% CIs of the geometric mean ratios of AUClast, AUCinf and Cmax were within the prespecified acceptance criteria of 80-125%.</p> <p><u>Pharmacodynamics</u> 90% CIs of the geometric mean ratios of each of the PD end-point parameters (AUEct and Emax for IGF-1 and IGFBP-3) were fully contained within range of 80-125%.</p>	Not assessed.	[12]

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
Rituxumab						
PF-05280586 Rituximab (Pfizer)	US (Rituxan) and EU (MabThera) Rituximab 1000mg	Randomised, double-blind, two-dose, parallel- group study (1:1:1)	Patients with active rheumatoid arthritis on a background of methotrexate and inadequate response to anti-TFN therapy (n=220; 50M/170F; 198PPP)	90% CI of ratios for C _{max} , AUCT, AUC _{0-∞} and AUC ₂ -90% CIs of the geometric mean ratios of AUC _{last} , AUC _{inf} and C _{max} were within the prespecified acceptance criteria of 80-125%. No observed differences among groups in the CD19+ B cell count versus time profile and the parameters determined (B cell AUC _{last} , C _{min} , T _{min} and τ).	No observed differences among treatment groups in the incidence of ADAs, time of ADA emergence or ADA titres. No samples were positive for neutralising antibodies. Thirteen patients tested positive for ADAs at baseline (n=4, n=6 and n=3 receiving PF-05280586, rituximab-EU and rituximab-US, respectively). Of these, eight (n=4, n=3 and n=1, respectively) tested negative in all subsequent post-dose samples. The remaining 5 patients tested positive for ADAs at at least one post-dose time-point. A total of 26 patients tested positive for ADAs at at least one post-dose time point (n=7, n=10 and n=9 receiving PF-05280586, rituximab-EU and rituximab-US, respectively). Of these, 22 patients did not have detectable levels of ADAs until Day 85 or later (n=6, n=7 and n=9, respectively).	[13]

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 three reports describing the clinical outcomes obtained in phase III clinical trials of potential biosimilar medicines.

- ❖ Rugo et al, 2016: Effect of a Proposed Trastuzumab Biosimilar Compared With Trastuzumab on Overall Response Rate in Patients With ERBB2 (HER2)-Positive Metastatic Breast Cancer: A Randomized Clinical Trial[14]

This phase III study investigated a potential trastuzumab biosimilar in combination therapy with a taxane in patients without prior treatment for ERBB2-positive metastatic breast cancer. The primary outcome was week 24 overall response rate (ORR) defined as complete or partial response with equivalence boundaries set at 0.81 to 1.24 with a 90% CI for ORR ratio and -15% to 15% with a 95% CI for ORR difference. Secondary outcome measures included time to tumour progression, progression-free and overall survival at week 48, and adverse events. The 24 week ORR was 69.6% (95%CI: 63.62–75.51%) for the proposed biosimilar vs 64.0% (95%CI: 57.81–70.26%) for the reference product and as such the ORR ratio (1.09; 90%CI: 0.974–1.211) and ORR difference (5.53; 95%CI: -3.08–14.04) were within the equivalence boundaries. At week 48, there was no statistically significant difference with the proposed biosimilar vs trastuzumab for time to tumour progression (41.3% vs 43.0%; 95%CI: -11.1– 6.9%), progression-free survival (44.3% vs 44.7%; 95%CI: -9.4–8.7%), or overall survival (89.1% vs 85.1%; 95% CI: -2.1–10.3%). In the proposed biosimilar and reference product groups, 239 (98.6%) and 233 (94.7%) had at least 1 adverse event, the most common including neutropenia (57.5% vs 53.3%), peripheral neuropathy (23.1% vs 24.8%), and diarrhoea (20.6% vs 20.7%). With regards to anti-drug antibodies, the overall rate was 2.4% (6 of 245 patients) in the proposed biosimilar group and 2.8% (7 of 246 patients) in the reference product group. Antibody titres were considered to be low (proposed biosimilar: mean 3.2, median 2.5; reference product: mean 2.0, median 2.3). Overall the authors conclude that the immunogenicity profile was low and similar between the biosimilar and reference product, that *“among women with ERBB2-positive metastatic breast cancer receiving taxanes, the use of a proposed trastuzumab biosimilar compared with trastuzumab resulted in an equivalent overall response rate at 24 weeks”* and that *“further study is needed to assess safety and long-term clinical outcome”*.

Commentary

This report is notable in that it represents the first phase III clinical trial of a biosimilar monoclonal antibody for the treatment of cancer. The nature of the outcome in this clinical context is significantly different to that of the previous biosimilars used in oncology, such as filgrastim for supportive care, or biosimilars in other therapeutic areas such as those in auto-immune conditions.

In this context, the editorial published in association with this manuscript [15] poses the question *“Would you use the trastuzumab biosimilar for your mother if she had ERBB2-positive breast cancer?”* and concludes that the answer *“should be yes”* but with the caveat of the importance of ongoing pharmacovigilance.

- ❖ Griffiths et al, 2016: The EGALITY study: A confirmatory, randomised, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, versus the originator product in patients with moderate to severe chronic plaque-type psoriasis[16]

The EGALITY study is a phase III multicentre, randomised, double blind study investigating the efficacy, safety and immunogenicity of the potential etanercept biosimilar GP2015 in comparison with the originator Enbrel in patients with moderate-to-severe chronic plaque-type psoriasis. Patients with a Psoriasis Area and Severity Index (PASI) score ≥ 10 , an Investigator's Global Assessment modified 2011 (IGA mod 2011) score ≥ 3 (based on a scale of 0–4) and $\geq 10\%$ affected body surface area were included. Eligible patients had clinically stable psoriasis diagnosed ≥ 6 months before baseline and had previously received phototherapy or systemic psoriasis therapy. Patients were randomized 1:1 to self-administer 50 mg SC GP2015 (n=264) or 50 mg SC Enbrel (n=267) twice weekly for 12 weeks. Patients who achieved $\geq 50\%$ improvement in PASI (PASI 50) from baseline at week 12 were re-randomized either to continue the same treatment on a once-weekly dosing schedule (n=301) or to undergo a sequence of three treatment switches (n=196) in both directions between GP2015 and Enbrel at week 12, 18 and 24. Patients then remained on their week 24 treatment through to week 52.

The primary efficacy end point was the PASI 75 response rate after the first 12 weeks of treatment. The treatment response rate at week 12 for GP2015 and Enbrel was -2.3 (73.4% vs. 75.7%; 95%CI: -9.85 to 5.30). The 95% CI was contained within the pre-specified interval (-18 to 18%), suggesting no statistical difference between the efficacy of the two treatment groups. A reduced rate of Injection site reactions (ISRs) were reported in the first 12 weeks with GP2015 (4.9%) compared with the Enbrel group (14.2%). Most ISRs were mild in both treatment groups (4.2% and 12.0%, respectively). Five patients (1.9%) in the Enbrel group had a confirmed positive low-titre non-neutralizing ADA result within the first 4 weeks of treatment. The respective patients had ADA-negative results at all subsequent visits. At all investigated time points from baseline to week 52, the percentage PASI score change was comparable between the continued GP2015 and Enbrel groups. No difference in efficacy was observed between the continued and switched treatment groups at any time point. The rate of treatment-emergent adverse event (TEAE) up to week 52 was comparable between the groups receiving GP2015 (59.8%) or Enbrel (57.3%) only and the groups that switched (initially receiving GP2015 [61%], initially receiving Enbrel [59%]). At week 36, a single patient (1%) in the switched group initially treated with Enbrel was positive for a non-neutralizing ADA (low-titre) but ADAs were not detected in previous or subsequent visits. A composite of adverse events, referred to by the authors as being of "*special interest*" and defined according to the etanercept label (herpes simplex, tinea infection, neutropenia, onychomycosis, hypersensitivity, melanocytic naevus, skin papilloma, herpes zoster, oral herpes, skin candida, tinea versicolour, squamous cell carcinoma of the cervix, anaemia, rash, urticaria, multiple sclerosis), was reported to have occurred more frequently in the GP2015 only group (11.0%) as compared with the Enbrel only group (4.7%) to week 52. Within the patients that underwent switching, this "*special interest*" composite occurred more frequently in those who were treated with GP2015 initially (11.0%) as compared with those treated initially with Enbrel (5%). Any individual outcome contained within the composite measure accounted for a maximum of two events in any treatment group. The authors concluded that; the overall safety profiles of both GP2015 and Enbrel are consistent with previously published Enbrel studies, the rate of ADA development was low and comparable to that of the literature for the originator product, and that switching did not adversely affect safety.

Commentary

The design of this study is particularly noteworthy with regards to switching. In addition to continuing patient on either the potential biosimilar or reference products patients were switched in both directions and on multiple occasions. Patients initially treated with the potential biosimilar were switched to the reference product, back to the biosimilar and then back to the reference product before finishing the study. The opposite occurred for patients initially treated with the reference product. In these arms of the study, this study design resulted in patients undergoing multiple switches and several months of stable treatment with both the reference product and the biosimilar. The outcomes of this study do not indicate that multiple switching, in either direction, resulted in any negative effects on efficacy.

This study included a composite safety endpoint that was referred to as being of “*special interest*”. The authors indicate that this composite was “*defined by*” the special warnings and precautions on the etanercept label. The composite includes a range of outcomes which range from relatively minor, such as fungal nail infections, through to those more serious, such as multiple sclerosis. The interpretation of the clinical significance of the comparison of the rates of this composite outcome between treatment groups is challenging as a result of the diverse nature of the elements comprising the outcome and the fact that there were few events per element.

- ❖ Hegg et al, 2016: A phase III, randomized, non-inferiority study comparing the efficacy and safety of biosimilar filgrastim versus originator filgrastim for chemotherapy-induced neutropenia in breast cancer patients[17]

A phase III, randomized, non-inferiority study comparing the efficacy and safety of a biosimilar filgrastim (Fiprimas, Eurofarma), the first biosimilar drug manufactured by the Brazilian industry, versus reference filgrastim (Granulokines, Roche) for chemotherapy-induced neutropenia in 217 breast cancer patients. The primary endpoint was the rate of grade 4 neutropenia in the first treatment cycle. Secondary endpoints included the rates of febrile neutropenia and neutropenia of any grade, the duration of grade 4 neutropenia, the generation of anti-filgrastim antibodies, and the frequency of adverse events and laboratory abnormalities. There was no difference in the rate of grade 4 neutropenia between biosimilar filgrastim (Fiprimas, Eurofarma) and reference drug in the first chemotherapy cycle (90% CI for difference in rate: -12.67-12.61). With regard to the secondary endpoint, the number of patients with grade 4 neutropenia was 56 (51.4%) for the biosimilar and 59 (54.6%) for the reference. The authors conclude that “*The efficacy and safety profile of the test drug were similar to those of the originator product based on the rate of grade 4 neutropenia in the first treatment cycle*”.

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

- ❖ Manolis *et al*, 2016: Biosimilars: Opportunities to promote optimization through payer and provider collaboration[18]

Reporting the perceived challenges of biosimilar use and development of practical solutions to promote optimal utilisation through payer-provider collaboration, this supplement summarises the consensus of a panel representing health plan organisations within the US. This paper sought to highlight the potential collaborative opportunities between payers and providers that could help optimise the economic value associated with biosimilars, *“assuming a cost-saving opportunity is available”*. The supplement was developed by CDMI/Magellan Rx and was funded by Hospira (acquired by Pfizer).

According to the panel, *“payers and providers must carefully consider economic implications and cost-effectiveness in order to increase the acceptance or understanding of biosimilars in clinical practice”*. Three major challenges surrounding biosimilar adoptions were identified: (1) provider confidence in biosimilar education and clinical value, (2) provider confidence in reimbursement for new biosimilars, and (3) creating shared payer and provider cost-savings. The group posed potential solutions to these issues to assist with biosimilar adoption.

One of the key challenges identified related to provider confidence. Whilst provider and payers have much experience with reference products, some are not aware of biosimilars in general. The overall acceptance of biosimilars, particularly in the context of extrapolation of indication, will have a major impact on the management, adoption and the ability to optimise the savings potential of biosimilars. In this context, the shift to biosimilars will require a major educational component. Importantly, it was also identified that the education and acceptance of patients with respect to biologics is crucial.

It was agreed that the biosimilar manufacturer must invest a substantial amount of effort into the education of all health care stakeholders; however, with the opportunity of substantial cost savings, the payer should also be willing to supplement education efforts. The panel recommended a series of webinars educating providers would be beneficial to increase understanding. Materials and tools should also be disseminated in order to support patient education. The panel proposed that the endorsement of educational materials by specialty societies and organisations may be helpful, however further justification for this recommendation was not offered.

Critically, responsive communication with providers will provide valuable insights into attitudes and behaviours. Market penetration of biosimilars is likely to be highly variable, with therapies for acute and supportive care likely to more easily transition compared with chronic therapies. In the instance of the latter, providers may choose to utilise biosimilar products for treatment-naïve patients only; feasibly this first-hand experience would provide a level of comfort in order to begin switching patients from originator treatment to the biosimilar where appropriate. However, despite this, the patient may provide resistance

to switching from the originator where they are already responding well; this highlights the importance of patient education as part of biosimilar adoption.

The panel also recognised challenges of financial aspects relating to biosimilar use, including complexities of provider reimbursement and cost sharing initiatives. For the most part these relate specifically to a US healthcare environment; however, the key facilitating factor is likely to be early engagement of payers with providers to start dialogue, determine the level of understanding, and assess best strategies to enhance biosimilar adoption.

❖ Arato, 2016: Japanese regulation of biosimilar products: Past experience and current challenges[19]

This paper reviews the data packages of biosimilar products in Japan with those overseas, and examines the challenges in the development of biosimilar products in Japan. Whilst this review examines these challenges from a Japanese perspective, for the most part, the issues are not unique to a Japanese regulatory environment; these include the selection of an appropriate reference product, varying indications and dosages of reference product and the selection of an appropriate study population that is sensitive to detecting potential differences between treatments. However, within the context of a Japanese regulatory environment, the necessity of Japanese data provides another challenge. The Questions and Answers (Q&A) document, released by the Japanese Ministry of Health, Labor and Welfare (MHLW) in December 2015 for a better understanding of the “Guideline for the quality, safety and efficacy assurance of biosimilar products”, specifically states that either a comparative pharmacokinetic study or a phase III study should include a Japanese population. However, in this review the author notes that *“the focus of such a biosimilarity exercise is to demonstrate similar efficacy and safety compared with reference products, and ethnic differences have already been demonstrated in some reference products; therefore, it is questionable whether the Japanese data are scientifically necessary”*.

❖ Cesarec & Likic, 2016: Budget impact analysis of biosimilar trastuzumab for the treatment of breast cancer in Croatia[20]

The predicted economic impact of the introduction of biosimilar trastuzumab into Croatia was examined by the authors. The budget impact analysis model was built on the approvals for trastuzumab breast cancer treatment in Croatia in 2015, using information extracted from the Croatian Health Insurance Fund (CHIF) databases. The developed model only examined relative drug acquisition costs over a 1 year period and was based on cost-efficient use of vials, such that no unused portion was wasted. Doses and administration regimens were based on standard treatment recommendations for patients with early or metastatic breast cancer, and patient body weight was assumed to be 70kg. The manuscript investigated the impact of biosimilar cost modelled at three levels (85%, 75% and 65% of originator cost) in trastuzumab-naïve patients, with the intravenous biosimilar uptake rate set at 50%. Based on the 479 patients treated, the model predicted a cost saving of €0.26-0.69 million in Croatia over the 1 year period. In this setting, this equated to an additional 3-10% patients treated if the projected drug cost savings were reinvested in treatment with trastuzumab.

- ❖ Brodzsky *et al*, 2016: A budget impact model for biosimilar infliximab in Crohn's disease in Bulgaria, the Czech Republic, Hungary, Poland, Romania and Slovakia[21]

Using a budget impact model, the authors examined the predicted economic savings achieved with the introduction of biosimilar infliximab for the treatment of Crohn's disease in Central and Eastern Europe. The relative drug acquisition costs of 3 scenarios were compared: (1) no biosimilar available; (2) biosimilar available to treatment-naïve patients only (no switching); (3) biosimilar available to treatment-naïve patients and switching of originator-treated patients (switching allowed). The developed model examined relative drug acquisition costs over a 3-year period and was based on cost-efficient use of vials, such that no unused portion was wasted. The model was based on existing data of patients treated with infliximab and adalimumab in the six countries; doses calculated on body weight were based on survey results of Hungarian Crohn's disease patients. The cost of biosimilar infliximab was modelled at 75% of originator cost. The model examined an uptake rate of 75% biosimilar infliximab for infliximab treatment-naïve patients, and a 25% uptake in patients eligible for adalimumab therapy. In the switching scenario, it was assumed that 80% of patients would switch from originator infliximab to the biosimilar; no switching from biosimilar to originator was included. Based on the 2013 population of 4737 patients with Crohn's disease in the six countries, over a 3 year period, the model predicted cost savings of €8.0 million and €16.9 million in the non-switching and switching scenarios, respectively. Based on this cost saving, an additional 722 (no switching) and 1530 (switching allowed) patients with Crohn's disease could receive biosimilar infliximab therapy if savings were reinvested.

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

During the review period, there were no manuscripts published that contributed new information relevant to this theme.

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 four publications that specifically examine this theme.

Erythropoietin

- ❖ Kurtz *et al*, 2016: Biosimilar epoetin for the management of chemotherapy-induced anemia in elderly patients[22]

An exploratory sub-analysis of the ORHEO observational study, described in detail in previous biosimilar literature review reports, was conducted to compare the tolerability and effectiveness of epoetin biosimilars in the management of chemotherapy induced anaemia (CIA) in younger patients (<70 years old, n=1301) versus elderly patients (≥70 years old, n=1009), the majority of whom received biosimilar epoetin zeta (Retacrit, 99.9%). Results were consistent with previous findings, with both age groups responding well to treatment with biosimilar epoetin (79.8% vs 84% responding at 3 months, and 86.3% vs 86.8% responding at 6 months among younger and elderly cohorts respectively) and indicate that biosimilar epoetin was an effective and well-tolerated treatment for managing CIA in elderly cancer patients.

Filgrastim

- ❖ Fruehauf *et al*, 2016: Compatibility of biosimilar filgrastim with cytotoxic chemotherapy during the treatment of malignant diseases (VENICE): A prospective, multicenter, non-interventional, longitudinal study[23]

This manuscript reports an observational study describing the ‘real-world’ outcomes of biosimilar filgrastim (Nivestim®) in 386 patients (81% female, median age = 61 years, range [22–92]) adult patients with solid tumours (87%) or hematologic malignancies (13%) who received cytotoxic chemotherapy. The results provided are restricted to relatively high level descriptive data such as number of chemotherapy cycles completed and median neutrophil counts which significantly limits the conclusions that can be drawn. However, the authors conclude that *“Biosimilar filgrastim was effective and well-tolerated in both the primary and secondary prophylactic settings”* which, on the basis of the study design and the data presented, reflects their clinical judgement.

- ❖ Argnani *et al*, 2016: Outpatient experience with biosimilar filgrastim in patients with lymphoid neoplasm: Lessons from daily clinical practice[24]

This letter reports on the retrospective observational outcomes of the use of biosimilar filgrastim (Zarzio®) in 141 patients with a range of lymphoid neoplasms within a single Italian institution. High level descriptive data such as treatment interruption/delay were reported. The authors conclude that *“Our results are similar to those reported in clinical trials and in large observational prospective studies conducted in routine practice”*.

- ❖ Becker *et al*, 2016: Healthy donor hematopoietic stem cell mobilization with biosimilar granulocyte-colony-stimulating factor: Safety, efficacy, and graft performance[25]

In a study looking at an extrapolation of indication of filgrastim, this manuscript reports on the use of biosimilar filgrastim (Sandoz®) for the mobilisation of stem cells in healthy donors for transplant. The study is designed as a 10 year non-interventional safety study, with this manuscript reporting on mobilisation, graft transfusion and with a mean follow-up period of 433.3 days (range, 2-1528 days). Stem cell mobilisation and harvest results, the pattern and intensity of adverse events, and engraftment outcomes were consistent with those expected for the reference biological medicine.

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

Four original research articles were published during the review update period addressing the topic of biosimilar perception amongst healthcare professionals. Three of these articles investigated the perception of biosimilars amongst specialist physicians including gastroenterologists, rheumatologists, dermatologists, haematologist-oncologists, medical-oncologists, and nephrologists. Thakur *et al*[26] investigated the perceptions and preferences amongst nurses for the different auto-injector devices used to deliver etanercept, comparing the reference device Enbrel® with the device used to deliver the biosimilar agent Benepali®. This study specifically investigated nurses’ perceptions of the administration device and not the drugs they administered or their effect.

- ❖ Cohen *et al*, 2016: Awareness, knowledge, and perceptions of biosimilars among specialty physicians[27]

This original research article reports the baseline findings of a 19-question survey created by the Biosimilars Forum investigating US physician awareness, knowledge and perception of biosimilars. The Biosimilar Forum is a collection of biosimilar sponsors with a declared interest in biosimilar promotion within the US. In order to minimise bias the group employed an independent organization to conduct the survey and the respondents were not made aware of the source of the survey until after they completed the survey. 1201 specialists responded from specialties including gastroenterology, rheumatology, dermatology, haematology-oncology, medical-oncology, and nephrology; however, the breakdown of response by specialty was not disclosed. Physician awareness of biological drugs in general was examined by providing a list of drugs commonly used (not disclosed) within their specialty and respondents were asked to identify the biological agents. Dermatologists and gastroenterologists provided the greatest number of 'correct' responses (>90%), with medical oncologists the least able to identify biological agents (63% correct).

Five major knowledge gaps were identified by the authors: defining biologics, biosimilars and biosimilarity; understanding the approval process; understanding comparable safety and immunogenicity between biosimilar and the originator; understanding extrapolation of indication; defining interchangeability and substitution. The authors were surprised by the lack of understanding of what defines a biological drug, particularly given that physicians who do not prescribe biological drugs were excluded from the study. Differences in the levels of understanding of the key concepts associated with biosimilar use were identified across the different specialties. Haematologist-oncologists appeared to have the greatest knowledge of the regulation of biosimilars (58% correctly identifying how long biosimilars have been marketed within the US) which is unsurprising as this is currently the only specialty that possesses an approved and marketed biosimilar in the US. Rheumatologists appeared to possess the lowest level of knowledge, with only 34.6% correctly identifying the current position of biosimilars in the US. Overall, 44.8% of respondents believed that "*biosimilars will be safe and appropriate for use in naïve and existing patients*"; however, this varied across the specialties ranging from 34.5% of rheumatologists to 57.0% of haematology-oncologists.

The authors concluded that "*although physicians across specialties have generally positive attitudes toward biosimilars, dermatologists and rheumatologists appear to be less enthusiastic about biosimilars*". The investigators acknowledged that a weakness is the relative infancy of biosimilars in the US market and plan to repeat the survey in 2-3 years to investigate changes in biosimilar perception in the US from this baseline.

- ❖ Baji *et al*, 2016: Perceived risks contra benefits of using biosimilar drugs in ulcerative colitis: Discrete choice experiment among gastroenterologists[28]

This original research investigated the perception of biosimilar use to treat ulcerative colitis (UC) amongst Hungarian gastroenterologists. A discrete choice experiment survey was undertaken during the May 2014 Hungarian Gastroenterology Society Meeting. Biosimilar infliximab has been covered by the National Health Insurance in Hungary since May 2014 for the treatment of severe UC (Mayo score >9) for a duration of no more than 12 months regardless of benefit, whereby treatment can be delayed for a month if there is a medicine supply shortage. Newly initiated infliximab therapy must be undertaken with a biosimilar drug. All 200 attendees of the meeting were invited to participate and 51 undertook the survey. Participants

were asked to imagine a series of hypothetical scenarios whereby the National Health Insurance limitations for prescribing infliximab were relaxed if the biosimilar is used and asked whether the hypothesised relaxation of limitations would influence their decision to initiate biosimilar therapy and/or change patients already treated with the reference medicine to the biosimilar agent. These hypothetical rule changes included 1) the inclusion of patients with moderate disease (MAYO score >6) or 2) treatment beyond 12 months or 3) an uninterrupted supply, and various combinations of these three rules. 84% of respondents chose a biosimilar option for use in a naïve patient in at least one of these hypothetical scenarios and 61% chose a biosimilar option for patients already on a biological drug. A baseline attitudes survey determined that 67% of respondents had concerns with biosimilar safety and efficacy. A sub-analysis of this group determined that the willingness to use biosimilars in the hypothetical situations dropped by 4 and 8%, for naïve and current biological treatment respectively amongst this sceptical population. Overall, the predicted probability of the physician selecting a biosimilar drug using the currently reimbursed Hungarian National Health Insurance system is 52% for naïve patients and 29% for those currently receiving biological therapy. Once offered the hypothetical benefits of biosimilar prescribing this increased to 85% and 63% for naïve and current biological treatment respectively. The authors concluded that most gastroenterologists were willing to consider biosimilar treatment options if better national access to biological drugs is offered in exchange and an overall benefit to society is obtained.

- ❖ Beck *et al*, 2016: Rheumatologists' perceptions of biosimilar medicines prescription: Findings from a French web-based survey[29]

A web-based survey of French rheumatologists was conducted between June and August 2015 to investigate knowledge, experience and opinion regarding biosimilar use in France. 500 rheumatologists nationwide were invited to undertake the survey and 116 participated, approximately 5% of the total population. Many French rheumatologists were not familiar with and felt poorly informed about biosimilar medicines, more than half of respondents described themselves as having little or no knowledge of biosimilars. The major concerns regarding biosimilar use were a lack of available data about tolerability, extrapolation of efficacy and safety from one therapeutic indication to all indications of the reference biological product, and substitution by the pharmacist of a reference medicinal product with its biosimilar product. At the time of the survey, only eight responding rheumatologists had already prescribed at least one of the following biosimilar medicines available in France: biosimilar epoetin, filgrastim, somatropin or infliximab. The authors concluded that further work is needed to enhance understanding and to overcome misperceptions of biosimilar medicines among rheumatologists.

- ❖ Thakur *et al*, 2016: Perceptions and preferences of two etanercept autoinjectors for Rheumatoid arthritis: A new European Union-approved etanercept biosimilar (Benepali®) versus etanercept (Enbrel®) - Findings from a nurse survey in Europe[26]

Benepali® (manufactured by Biogen) is the first etanercept biosimilar to be marketed within the EU, however it utilises a different auto-injector delivery device to the reference product Enbrel®. This original research article compared the preference between these two devices amongst nurses in France, Germany, Italy, Spain and the UK who have had recent experience with the administration of Enbrel®. 149 nurses participated in this Biogen sponsored survey during December 2015 – February 2016 and were asked to evaluate the delivery device in terms of usability and preference in comparison with the reference device.

Importantly participants were instructed to consider only the auto-injector device itself and not the medicine it is delivering. The results suggest that nurses preferred the Benepali® injector device on the basis of attributes including ease of operation, weight, grip and size. It was reported that the majority of nurses (86% of those surveyed) claim that their patients would prefer the Benepali® auto-injector.

Commentary

In the context of biosimilar medicines this is the first publication that specifically focusses on the delivery device rather than the active pharmaceutical ingredient. As compared with generic formulations of traditional small molecules that are usually administered orally as tablets, biologics require the use of an administration device. Patient acceptability of these devices is an important consideration. This manuscript identifies that the delivery device can influence user perception.

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APPENDIX 1

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

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APPENDIX 2

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