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University of  
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School of  
**Pharmacy and  
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# Literature Review of International Biosimilar Medicines

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**Sponsor:** National Medicines Policy Section  
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Australian Government

**Authors:** Michael Ward, PhD BPharm(Hons)  
Stephanie Reuter Lange, PhD BSc(Hons)  
Kirsten Staff, PhD, MPharm, PGCertEd  
  
School of Pharmacy & Medical Sciences  
University of South Australia  
CEA-19, GPO Box 2471  
Adelaide, SA, 5001

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## Introduction

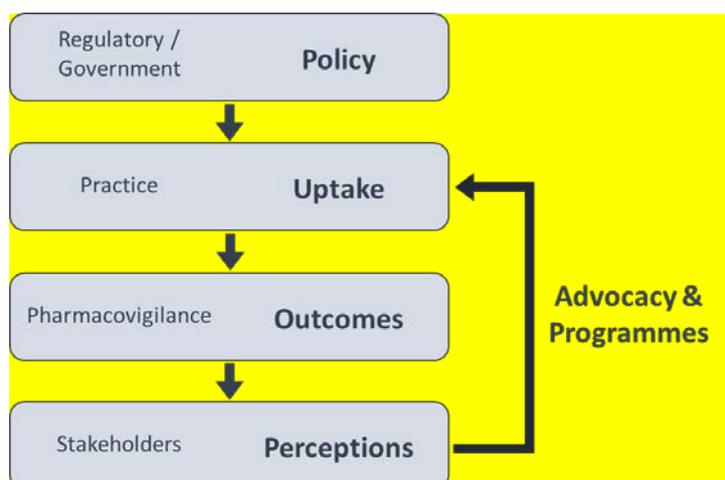
A comprehensive literature search has been undertaken to examine all international and Australian clinical, academic and policy journals and media articles or sources in relation to biosimilar medicines for the purpose of providing evidence which will inform policy development and the communication activities of the Australian Government's Biosimilar Awareness Initiative. A particular emphasis has been literature that discusses issues around the uptake and substitution of biosimilars as part of national or sub-national programmes that encourage the use of biosimilars in order to increase access to medicines and improve the sustainability of government formularies.

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 Biosimilar Medicine Policies to Subsidisation, Switching and Substitution
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 Medicines

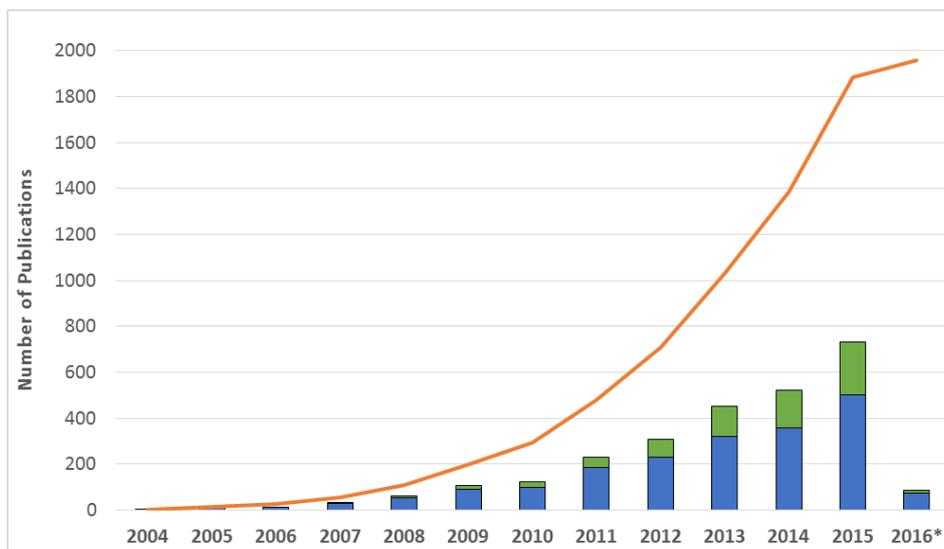
An iterative, systematic, step-by-step approach was applied to ensure that all literature relevant to the themes was identified. Qualitative and quantitative peer-reviewed literature, and relevant grey literature, were included. The literature review was restricted to include publications reported in the English language, between 1 June 2004 and 28 April 2016, coinciding with the commencement of the discussion on the Guideline on Similar Biological Medicinal Products by the Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA). To broadly capture the literature on biosimilars, broad search terms were used which were then combined with additional terms that specifically relate to each of the issues-based themes that have been identified. Additionally, between the 28 April and 6 June 2016, the literature was manually searched to include the most recent relevant publications.

## **Overview of the Published Biosimilar Literature**

This report provides an overview of the most significant literature identified through the literature search process. Since 2010, there has been a significant rise in the rate of peer-reviewed publications related to biosimilars (Figure 2), coinciding with the formulation of regulatory positions around the world and the patent expiry of a number of significant biologic agents. Analysis of these manuscripts identifies the following broad types of contributions:

- Education pieces
- Preclinical and clinical drug development
- Technical/methodological development
- Commentaries and individual opinion pieces
- Investigator-initiated studies and case series
- Conference abstracts

**Figure 2** Number of biosimilar publications (blue) and conference abstracts (green) published annually from 2004 to 2016 (\*until 28 April), and cumulative publications over time (orange)



The most numerous contribution to literature are papers that are of an educational nature. Owing to the fact that biosimilars are an entirely new concept, with distinct and important differences from traditional understanding of generic products as they apply to small molecule drugs, there has existed a significant need and desire for articles to educate the medical and scientific community on this emerging topic. For this reason there are a large number of manuscripts specifically intended for this purpose and as such share a common overall structure and content. These manuscripts typically begin with an articulation of what a biosimilar is and why they need to be considered differently to small molecule generic products. Having established this, these articles then usually go on to discuss the regulatory framework that has been established for the approval of biosimilars. This typically leads to a discussion of the potential benefits of biosimilars, particularly the potential cost implications, and the established areas of uncertainty and challenges that remain to be addressed, particularly the topics including potential immunogenicity, switching/substitution and extrapolation of indication. Owing to the educational nature of these publications, they have not specifically sought to extend or expand the knowledge base in this emerging area, rather they restate what is already known or identified as uncertainties in order to inform the reader of these issues. In general, these articles assume a balanced position on biosimilars adopting neither an excessively pro or anti stance. In the context of this review, these papers do not contribute meaningfully to the specific aims; however, they play an important role in propagating the general understanding within the broader scientific and medical community.

Similarly, there are an increasing number of articles within the literature that specifically describe the results obtained during the commercial development of potential biosimilars. These manuscripts describe the information that regulators require for the approval of a biosimilar agent including the design and results of physicochemical characterisation, preclinical development, phase I pharmacokinetic studies and phase III safety and efficacy clinical trials. Whilst manuscripts of this nature are of clear importance to the development of biosimilars, they do not contribute meaningfully to the aims of this review. Given the authorship of these manuscripts, they typically seek to minimise discussion of the potentially contentious topics pertaining to biosimilars and do so by remaining firmly within the relative shelter of the established regulatory frameworks. Perhaps

the notable exceptions are the most recent publications of open-label extension studies that are beginning to provide evidence of switching.

In addition, there are a number of papers addressing a range of fundamental and technological issues relating to the production and characterisation of biological agents. This includes topics such as assessment of glycosylation patterns and bioanalytical quantification of anti-drug antibodies. Whilst these topics are of clear importance to the development of biosimilars, they do not contribute to the aims of this literature review.

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 Biosimilar Medicine Policies to Subsidisation, Switching and Substitution**

The relevant peer-reviewed literature within this theme is predominantly comprised of commentaries and overviews of the current policy framework within various countries globally; little new information beyond that provided in the corresponding regulatory guidelines is reported.

### **Registration Process**

With the development of guidelines developed by the EMA<sup>1</sup> and the World Health Organization (WHO)<sup>2</sup> setting out principles for biosimilarity determination, the regulation of biosimilars is trending towards global harmonisation as a number of countries move to adopt, or implement their own guidelines based on, those developed by the EMA or the WHO. More recently, the US Food and Drug Administration (FDA) has followed with the release of their own guidance outlining the scientific considerations in demonstrating biosimilarity<sup>3</sup>.

On the other hand, in countries with emerging industries, policies regulating biosimilars are in development. Within South America, the most advanced regulatory framework is present in Brazil where two approval pathways for biosimilars exist depending on the amount of data required; one involving phase I and phase III trials where indication extrapolation is permitted, and the other with lower quality and clinical study requirements but where extrapolation of indication is not allowed<sup>4</sup>. This is in contrast to the registration of bio-copies in Mexico for which no clinical data is required.

Within India, official guidelines outlining biosimilar regulatory approval were released in 2012, after a number of biosimilars were already approved for use under an *ad hoc* abbreviated process. The guidance requires evidence of safety and efficacy, although formal requirements are less stringent than that outlined by the EMA or WHO. It is worth noting that other regulatory pathways in India allow for registration of biosimilars outside of this policy – a biosimilar of Humira (adalimumab) is licensed in India, however Humira is not authorised in India but Indian guidelines permit biosimilar authorisation if the originator has been licensed and widely marketed in a country with a well-established regulatory framework<sup>5</sup>.

## **Extrapolation of Indication**

With strong scientific justification and taking into consideration the overall evidence of biosimilarity, the mechanism(s) of action of the indications and the potential risks in the patient populations, extrapolation of indication is possible within all regions that have adopted biosimilar regulations. For the early biosimilars, this was relatively straightforward, with the same receptors responsible for the pharmacological effects for each of the different indications under consideration; however, for monoclonal antibodies, this is more complex with the effect potentially mediated through multiple mechanisms of action<sup>5</sup>.

Interestingly, despite similar guidelines with respect to extrapolation of indication globally, this has resulted in different regulatory agencies arriving at different conclusions on whether extrapolation of indications is justified for a given biosimilar. Notably, the EMA has recently allowed extrapolation of indication for biosimilar infliximab (Inflectra and Remsima) for rheumatologic and gastrointestinal inflammatory diseases, whereas Health Canada did not approve extrapolation to the inflammatory bowel disease indications (e.g. Crohn's disease and ulcerative colitis) for Remsima<sup>6</sup>.

## **Interchangeability**

Recommendations with respect to the ability of a biosimilar to be used interchangeably with the originator have not been made by the EMA; rather this has been deemed to be outside of the remit of the EMA and therefore decisions regarding whether biosimilars can, or should, be used interchangeably have been left to each EU member country<sup>7</sup>. Regulatory authorities have taken the stance of not recommending switching of biologic products, such as in Belgium or France, or only for specific groups of biologics, such as in Germany, whereas in Italy, Norway and the UK these decisions are left to the discretion of the prescribing physician<sup>8</sup>. Within the Netherlands, treatment interchangeability "is permitted, but only if adequate clinical monitoring is performed and the patient is properly informed"<sup>9</sup>.

The establishment of evidence for the ability of patients to safely switch from an originator biological product to a biosimilar (under physician supervision) through pharmacovigilance monitoring systems could feasibly translate to cost savings for health systems<sup>8</sup>. The Norwegian Medicines Agency is sponsoring an interchangeability trial, known as NOR-SWITCH, to establish whether patients treated with infliximab can safely be switched to a biosimilar<sup>10</sup>; the results of this trial are pending.

The US has adopted a dual licencing pathway for biosimilars – a relatively simplified pathway in which the biosimilar will not be deemed interchangeable with the originator, and a substantially more demanding pathway for interchangeable biosimilars<sup>3</sup>. Despite the obvious limitations for a non-interchangeable biosimilar, interchangeability trials for registration under the second pathway are rarely carried out. To incentivise drug developers to pursue this option, a year of market exclusivity is offered for the first-in-class biosimilar; however, an interchangeable biosimilar under this pathway has yet to be approved<sup>8</sup>.

## Substitution

Within Europe, approximately two-thirds of countries have either laws or guidelines in place that prohibit substitution of biological medicines. On the other hand, France has legislation that permits automatic substitution of biosimilars at treatment initiation<sup>11</sup>, and the Dutch Medicines Evaluation Board recently supported substitution of biosimilars for treatment-naïve patients<sup>9</sup>. Under this framework, prescribing physicians retain the right to request no substitution and must be notified if a substitution is made. Similar guidelines are in place in Germany where substitution at treatment initiation is permitted for specific groups of biosimilars (e.g. epoetins)<sup>8</sup>. Substitution of biological medicines at the pharmacy level is permitted in Estonia and Poland, with Polish reimbursement law not distinguishing between small-molecule generics and biosimilars<sup>12</sup>. No specific regulations regarding biologic product substitution are in place in some countries which could feasibly lead to unintended changes in patient treatment; however, it is worth noting that whilst no formal substitution policy is in place, this does not necessarily mean that this is not regulated in these countries – for example, in Austria, prescribing physicians must prescribe all medications by brand name and pharmacists cannot legally substitute prescribed products at their own discretion, thus substitution of biological agents is not possible despite no specific substitution policy being in place.

While the US FDA oversees approval of biologic medicines and designation of interchangeability, policies governing substitution are covered by state law. Most, but not all, US states have passed legislation to permit substitution of biologic agents<sup>13</sup>. Whilst state legislation varies, these predominantly include requirements that:

- The prescriber is able to prevent substitution by stating “dispense as written” or “brand medically necessary”;
- The prescriber must be notified of any allowable substitution made at a pharmacy;
- The individual patients must be notified that a substitute or a switch has been made; and
- The pharmacist and prescriber must retain records of substituted biologic medications.

Notably, within some states of the US, it is mandatorily required that the state-regulated pharmacist substitute a generic version of the prescribed drug if all prescription requirements are met; within three states (Florida, Massachusetts and Washington) these laws are not invalidated by biosimilar substitution measures.

In Canada, much like that in Europe and the US, the regulatory agency does not declare substitutability but rather the decision is at the provincial level; however, Health Canada “does not support automatic substitution of a SEB [biosimilar] for its reference drug”<sup>14</sup>.

## Naming

There is no current international harmonisation on biosimilar naming. The policies outlined in the WHO International Non-proprietary Names (INN) for Biological and Biotechnological Substances guidelines indicate that non-glycosylated biosimilars should have the same INN as the reference biologic, whereas glycosylated biosimilars are noted with a Greek letter (spelled out in full) added to the INN<sup>15</sup>; however, the naming system remains voluntary.

Within Europe, the same INN should be used for both the reference medicinal products and the biosimilar medicinal products<sup>4</sup>. The prescription of biologic agents by INN can result in unintended

switching of treatment, and while INN prescribing is mandatory or recommended in a number of countries throughout Europe, exemptions from INN prescribing of biologic agents have been introduced in the majority of countries. Conversely, in Portugal, biologic agents are not excluded from mandatory INN prescribing, thus the prescriber must indicate separately that substitution cannot occur<sup>12</sup>.

The FDA has not formally adopted a naming system; however, in the current draft guidance, the FDA proposes that a biosimilar have the same drug substance name as the originator, followed by a unique suffix<sup>16</sup>.

## **Prescribing**

Ultimately physicians, within the bounds of the regulatory environment, have authority over whether to prescribe a biosimilar to their patient. A number of countries have implemented physician-based incentivisation strategies to increase the prescription of biosimilars; given the uncertainty associated with treatment interchangeability, these are generally targeted at prescription of biosimilars to patients initiating treatment<sup>8</sup>.

Within Italy, health organisations have put in place policies to increase the use of biosimilar epoetin and decrease treatment costs of renal failure through either the requirements of all prescribers to prescribe biosimilars to all treatment-naïve patients, or through the provision of biosimilars only on hospital-based formularies<sup>17</sup>. However, ultimately this takes the authority of prescription decisions away from the physician.

Financial and/or biosimilar prescription volume targets are often used to incentivise biosimilar prescription amongst physicians, with monitoring systems improving the effectiveness of these initiatives<sup>8</sup>. For example, within Belgium, physician prescription patterns are monitored and financial penalties are enforced where minimum thresholds for low-cost drugs are not met. The epoetin prescription system to facilitate biosimilar uptake within Germany is well recognised, with biosimilar epoetin quotas of up to 60% of total prescription volume in some regions reported. This is through a physician-focussed approach incorporating budget targets, prescription quotas and monitoring systems. Additionally, this is furthered through physician education programs and the active involvement of professional clinical associations. Most likely a result of this multi-faceted approach, German physicians tend to be more knowledgeable and have more progressive views on biosimilars relative to physicians from other European countries<sup>18</sup>.

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

The uptake of biosimilar molecules has occurred progressively since 2006 and is now present in the following five clinical areas in order of their appearance on the market:

1. Human growth hormone (HGH), also known as somatotropin, stimulates growth, cell reproduction and regeneration in humans. It is used to treat children's growth disorders and adult growth hormone deficiency.
2. Epoetin controls red blood cell production and is commonly used in combination with dialysis and oncology treatments.
3. Filgrastim (granulocyte colony-stimulating factor; G-CSF) stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream. Filgrastim is

used with certain cancer patients to accelerate recovery from neutropenia after chemotherapy, allowing higher-intensity treatment regimens.

4. Anti-tumour necrosis factor (Anti-TNF) therapies, specifically infliximab, are monoclonal antibodies used to treat auto-immune diseases such as rheumatoid arthritis, psoriasis and Crohn's disease.
5. Insulin, specifically glargine, which is long acting analogue used for basal dosing in type I and type II diabetes.

The volume of peer reviewed publications addressing the global uptake of biosimilars in practice is currently low. In this section an overview summary of biosimilar uptake more broadly is provided, followed by a review of the peer-reviewed publications within each therapeutic area described above.

## General Uptake

The majority of publically available data relating to the uptake of biosimilars in practice has been collated by the IMS Institute and recorded in their MIDAS (Multinational Integrated Data Analysis System) database. This database monitors national biologic drug utilisation data from 22 member states of the EU, plus Norway and Switzerland. A limited number of peer-reviewed articles and documents have been published reviewing the data contained in this database at various time points since 2006, when the first biosimilar medicines were marketed. Although the IMS is a commercial health data service provider, they have maintained what is currently the most extensive data set on biosimilar uptake.

### ❖ Rovira *et al*, 2011: *The impact of biosimilars' entry in the EU market*<sup>19</sup>

This report, commissioned by the EU in 2011 via a service contract with the European Commission (Directorate-General for Enterprise and Industry), describes the impact of biosimilar introduction upon the European biological therapeutic market between 2007 and 2009. The aim of the report was to provide an analysis of the characteristics of biosimilars and the development of the EU's biosimilars market with a view to improving EU Member States' understanding of the biosimilar market, including the likely impact on future pharmaceutical budgets. Information regarding the launch dates, prices per standard unit and sales volumes of biosimilar somatropin, epoetin and filgrastim in 24 European countries including Austria, Belgium, Bulgaria, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom were obtained from the IMS Institute's MIDAS database and compared for the period 2007-09.

In relative terms, the market of biosimilars was determined to be quite small during this period. By 2009 the total value of the European market for all biological drugs was estimated to account for 20% of the total pharmaceutical market. The sales observed for the biological medicines for which biosimilars had been developed at this point (originator and biosimilar somatropin, epoetin and filgrastim) in the analysis amounted to 3.4% of the total biological market value which was equivalent to only 0.7% of the total pharmaceutical market in the included countries. However, the expansion of the biosimilars market in Europe was notable for the reporting period. Total biosimilar sales increased rapidly from €3.3 million in 2007 to €65.5 million in 2009, interestingly the market for the respective originators fell slightly during this period from €981.2 million in 2007 to €921.2 million in 2009. The authors hypothesised that this data demonstrated changes in prescribing

practice during this period as the total biosimilar market share increased from 0.34% in 2007 to 6.64% in 2009.

The authors reported that large inter-country variability in biologic use and biosimilar penetration was already being observed by 2009. In relation to total pharmaceutical sales, Denmark had the highest biologic market share (30.2%) whereas Lithuania had the lowest (9.3%). With regards to biosimilar uptake in individual countries, Italy had the highest biosimilar market share (1.0% of total market) and Portugal had the lowest (less than 0.1% of total market). The authors did not propose an explanation as to why these differences were being observed. The report concluded that the main appeal for biosimilar development in the European market will be its ability to reduce costs for consumers and payers, and that market penetration will depend on the product characteristics, stakeholder perception and appropriate incentives for doctors and patients. The authors also conclude that biosimilar uptake appeared to have less opposition when being prescribed for new patients, whereas resistance was observed by both doctors and patients to shifting to a biosimilar after a patient had been initiated on the originator.

❖ De Labry *et al*, 2013: *Biosimilars in the European market*<sup>20</sup>

The group that produced the Rovira report<sup>19</sup> published this update on biosimilar uptake across Europe in 2013. The MIDAS database was again utilised to analyse biosimilar usage within the same 24 countries plus the Czech Republic and Estonia, up to December 2010. This research paper was published in the Generics and Biosimilars Initiative (GaBI) Journal. GaBI is an impartial peer-reviewed scientific journal; however it should be acknowledged that the mission of GaBI is to raise the scientific status of generic and biosimilar medicines, and as such could be perceived to have a pro-biosimilar outlook.

This updated report largely reinforced the views expressed in the Rovira report<sup>19</sup> and demonstrated that the Europe-wide trend for increasing biosimilar uptake and decreasing originator use continued into 2010. Additionally, it provided minor correction of the previously reported 2007-2009 data. The new data suggested that total biosimilar sales increased further from €65.5 million in 2009 to €162.2 million in 2010, and the market for the respective originators fell further from €928.8 million in 2009 to €882.7 million in 2010. The total biosimilar market share increased from 6.59% in 2009 to 15.52% in 2010. This data continues the patterns observed in the Rovira report<sup>19</sup> and suggests that the rate of biosimilar uptake in Europe was in fact accelerating during 2010.

Once again the large variability in individual country biosimilar uptake was commented upon. The market penetration figures for 2010 were claimed to range from the high levels of Greece (73%), Romania (41.9%) or Austria (37.2%) to notably low levels in Belgium (2%), Denmark (1.2%) and Czech Republic (1.9%). This data appears to conflict with the Rovira report which observed that high uptake levels were observed in Italy at a rate of 1%, however it is unclear which measure is being used to calculate biosimilar uptake in this report, as it may be compared to total biologic sales or total pharmaceutical sales. As some countries only report the retail (non-hospital) sales this may have a marked effect on the reported uptake levels depending upon the measure chosen. Regardless of these discrepancies it remained evident that large differences exist in biosimilar penetration across countries.

- ❖ Farfan-Portet *et al*, 2014: *Are biosimilars the next tool to guarantee cost-containment for pharmaceutical expenditures?*<sup>21</sup>

In this paper it was noted that prior to 2010 the published literature on biosimilars (epoetin, somatropin and filgrastim) only addressed the authorisation procedures, with little to no commentary on uptake and price erosion. As such the authors attempted to address the effect of biosimilar introduction on biologic competition, price and uptake. They performed a structured literature review in Medline OVID and PUBMED and found only 11 relevant papers addressing biosimilar pricing. As such they concluded that evidence of price differences between biosimilar and originator medicines was limited. An explanation offered was that biosimilar competition at that point was a recent phenomenon with little opportunity for reporting. Broadly, price difference between the originator medicine and the biosimilars ranged between 10% and 35% and data was only reported from Europe, although marked inter-country and inter-drug variation can be observed in this mostly pre-2010 data. The major source of data on biosimilar uptake was the IMS MIDAS database and these findings have already been discussed. The uptake for biosimilar somatropin was observed to be lower across European countries than for filgrastim and epoetin. The authors suggested that the reason for this was related to the fact that somatropin is used as long-term therapy, whereas epoetin and filgrastim are for short-term treatment.

The authors conclude that directly reviewing biosimilar market penetration is only of relevance when a significant price differential exists between the originator its biosimilar and where treatment options are limited to these options. If the therapeutic area in question has products that have been more recently launched then the role of biosimilars must be considered in context of the wider therapeutic options. Ultimately, uptake estimates across Europe were largely provided by the pharmaceutical companies and the review was hampered by a lack of independent analyses of biosimilar use in the studied countries, however most models of future savings were being based upon a 20% price reduction.

- ❖ IMS Institute for Healthcare Informatics, 2014: *Assessing biosimilar uptake and competition in European markets*<sup>22</sup>

The most recently published review of the MIDAS database was produced by the IMS Institute themselves in 2014. Their report summarised biosimilar uptake and market competition in Europe, including prescription data from June 2006 until December 2013, with the aim of assessing the key drivers of biosimilar utilisation. This research was funded by the European Federation of Pharmaceutical Industries and Association. Although conducted independently and without industry or government funding, the analysis of biosimilar uptake evolution in these MIDAS based reports are limited by accurate data availability due to unreported direct sales or parallel exporting, and individual interpretation of treatment practice. Additionally, product pricing measures did not necessarily reflect rebates and discounts which in some countries may be significant. Consistent with previous reports based upon their database, it was noted that biosimilar uptake within accessible markets varies widely between countries and therapy areas.

The range of biosimilar penetration for somatropin was observed to be typically low (2-30% of treatment days in 2013) across Europe. A notable exception was Poland (99% of treatment days in 2013), this finding was explained by Poland's adoption of a tender model for acquisition during 2011. The uptake of biosimilar somatropin in Poland increased from 40% to 99% within a single year as a result. Epoetin biosimilar penetration displayed a narrower range of uptakes across

Europe, from 1% in Croatia to 62% in Bulgaria, which was largely in agreement with previous reports of this database. Filgrastim biosimilar penetration is lowest in Belgium with 2% share and highest, with nearly 100% share of the accessible market in Croatia, Czech Republic, Hungary and Romania. Hungary introduced a tender system for purchasing in the first quarter of 2012 and biosimilar filgrastim uptake increased from 50% within a year. The authors equated Belgium's low uptake of biosimilar filgrastim with the countries use of a competition-driven free market, with minimal payer intervention. Interestingly, Denmark observed low biosimilar filgrastim uptake despite having strict guideline-driven prescribing protocols. The authors suggest that this could be explained by the preference given to long-acting filgrastim products for which there was no biosimilar product, although it should be noted that uptake of biosimilar short-acting products overtook reference short-acting filgrastim products by 2013.

The IMS report also commented upon the evolution of biological medicine price in the investigated countries since the introduction of biosimilars. Medicine price for a molecule is influenced by two factors: firstly, the price of the originator and biosimilar respectively; and secondly, the products mix between the two. They suggested that a measure of the evolution of price within the accessible market provides evidence of whether the reduction in overall costs from competitive price pressure has resulted from the introduction of biosimilars. The authors studied epoetin price reductions since 2016 and observed that accessible market listed price for epoetin products ranged from an 81% reduction in Croatia to 4% in Denmark. Overall, the median reduction from 2006 to 2013 was 35%. An additional investigation into price reduction also factored in volume and access to measure overall medicine cost during this period. Croatia achieved a 68% reduction in total spend on epoetin products, whereas the Czech Republic and Italy observed an increase in excess of 40%. This increase was explained by the expansion of access to these drugs within these countries during this period.

### **Uptake of Specific Biosimilars**

A total of eight peer reviewed original research articles have been published addressing the uptake of individual biosimilars into clinical practice. The published uptake data on individual biosimilar drugs in order based upon their date of market entry is reviewed below.

#### **Somatropin Biosimilars**

There have been no peer reviewed publications analysing the uptake of biosimilar somatropin. Despite being the first biosimilar to be approved in most global markets, the uptake of biosimilar somatropin has been uniformly low across Europe and the wider global markets. With the exception of Poland (99% penetration), typical market penetration has been shown to be 2-10%, as previously described<sup>22</sup>.

#### **Epoetin Biosimilars**

Epoetin alfa biosimilars first entered the European market in August 2007, with the alternative epoetin zeta, which incorporates a different stabilising agent (Tween 80), following shortly after in December of the same year. Epoetin biosimilar uptake has been the best characterised, with a total of six peer reviewed original research articles identified addressing this topic. These studies

report an analysis of prescribing data in a range of countries, with a particularly strong emphasis on the European market.

❖ Bennett *et al*, 2014: *Regulatory and clinical considerations for biosimilar oncology drugs*<sup>4</sup>

These authors undertook an extensive and widely cited review of the clinical and regulatory considerations of biosimilar use. The uptake data presented relied upon the European MIDAS data reported by Rovira *et al*<sup>19</sup> incorporating data up to 2009. As previously described, the IMS report<sup>22</sup> incorporates more current data (until 2013), rendering the data presented in this publication as obsolete.

❖ Menditto *et al*, 2015: *Doctors commitment and long-term effectiveness for cost containment policies: Lesson learned from biosimilar drugs*<sup>23</sup>

This paper reports biosimilar epoetin uptake within the Italian market between 2009 and 2013, comparing data from the Campania region with national epoetin sales across Italy retrospectively. Campania was the first Italian region to encourage the prescription of biosimilars through regional decrees to incentivise prescribers to prefer biosimilars over the originators, in case of equal therapeutic indications and the same administration regimen.

At the national level, the market penetration rate of all biosimilar drugs (epoetin, filgrastim and somatropin) as measured by total biologic comparator consumption, was 2.3% in 2009. This figure reportedly increased steadily to 19.7% by 2012. In the Campania region, the observed increase in total biosimilar usage was accelerated, increasing from 1.6% in 2009 to 40.1% in 2012.

This same effect was also noted for the specific uptake of epoetin in these regions during the studied period. The timing of the implementation of the local decrees in Campania mapped closely with increases in uptake; these increases were not observed at the National level. The authors noted that by April 2012, the consumption of biosimilar epoetins in Campania had exceeded the market share of the reference epoetin products (i.e. biosimilar epoetin uptake was greater than 50%), a period immediately after the issuing of the third decree. Biosimilar epoetin uptake was approximately 20% at this time at the National level. The authors concluded that measures implemented by policy makers to constrain prescribers to achieve cost containment are only effective in combination with adequate incentives for professionals. The authors state three main outcomes for enhancing biosimilar uptake, firstly that adequate education programs for professionals are required to create consensus; secondly, clinician integration via a peer review process should be encouraged and lastly a constant prescribing monitoring system must be established. The main limitation of this study was that the authors had no access to individual patient-level data, which would have allowed the full investigation of indications of use and switches from biosimilar to biological drugs.

❖ Bocquet *et al*, 2015: *Biosimilar versus patented erythropoietins: Learning from 5 years of European and Japanese experience*<sup>24</sup>

This study focused on biosimilar epoetin uptake between 2007 and 2012, providing a country-by-country analysis using a methodology they previously developed during a similar study reviewing the uptake of biosimilar filgrastim<sup>25</sup> (as described in the filgrastim sub-section). This study sourced data from the IMS MIDAS database on the use of biosimilar epoetin in five European countries with

large pharmaceutical markets (Germany, France, Spain, Italy, UK) and Japan. The authors justified studying these countries by claiming they have similar legislative procedures towards biosimilars and are therefore comparable. The use of biosimilars in these countries was described in terms of their retail market structure, market size, rates of biosimilar uptake and national incentives for biosimilar use. Countries were classified into three categories, i.e. those with a dominant retail distribution, a dominant hospital distribution, or an equally-shared distribution between retail and hospital markets.

Japan had the biggest retail and hospital epoetin market among countries studied, although epoetin consumption per capita was observed to be lower than in Italy and France. Biosimilar epoetin rapidly gained market penetration in the Japanese retail market in terms of volume (10.3% of defined daily dose [DDD] in 2012), while it was rarely included in hospital formularies resulting in low uptake (3.2% DDD in 2012). The high uptake (68.0% DDD in the retail market and 78.3% DDD in hospitals) of second-generation epoetins such as darbepoetin for which there was no biosimilar was stated as a likely reason. Physicians were not incentivised to prescribe biosimilars and National guidelines stated that the substitution of originators for biosimilars by pharmacists should be avoided during the post-marketing surveillance period. Although the biosimilar to reference price difference was observed to be the largest of all the studied countries (-26.9% in 2012), the global biosimilar epoetin uptake was low (6.8% DDD).

France, a retail market, ranked second among EU countries for epoetin consumption per capita, behind Italy. Biosimilar epoetin penetration was 7.0% (DDD in 2012) of the retail market in volume, while biosimilar epoetin uptake was almost negligible in hospitals (0.8%). It was suggested that the high second generation consumption (49.9% DDD in the retail market and 68.6% in hospitals) may explain why biosimilar uptake remained globally low (5.8% DDD). In 2012, no substitution was authorised and no incentive for physicians to prescribe biosimilars was offered in France. With the first marketing of a biosimilar, the French Health Ministry applies a biosimilar discount of 20% versus the price of the originator, which is decreased by approximately 10%. The authors state that these price cuts gradually lead to a convergence between biosimilar and reference prices (-14.0% in 2012).

The Italian epoetin market is a hospital market and was equivalent in volume to France. Epoetin consumption per capita was observed to be the highest. In 2012 as described by Menditto *et al*<sup>23</sup> above, some regions had enacted the principle of incentivising use of a biosimilar first for naïve patients, leading to locally high biosimilar uptake. Italy is often portrayed as the largest European biosimilar accessible market, however the global biosimilar epoetin uptake was moderate (8.6% DDD) at the National level. In 2012, the difference between biosimilar and reference price in Italy was the highest among all EU countries (-22.2%), but biosimilar uptake remained fairly low.

The Spanish epoetin market had an exclusively hospital distribution. In 2012, Spain ranked second among countries in terms of global biosimilar epoetin uptake (11.5%), in spite of offering the lowest biosimilar price differences of all countries (-3.6%). The authors noted that the financial crisis in Spain had prompted the government to decrease medicines prices and to promote the use of biosimilars, greatly affecting their uptake.

Germany is a retail market and the epoetin consumption per capita is 70% lower compared with France. The epoetin market is the oldest and the market on which biosimilar epoetin penetrates to the greatest extent (30.4% globally). The authors describe that individual health insurance funds (Krankenkassen) possess a strong influence upon the biosimilar market as they are allowed to

negotiate price directly with key stakeholders. Biosimilar and reference price differences were shown to have diminished in recent years (-30.3% in 2007 vs. -10.8% in 2012) due to decreases in reference prices.

Epoetin consumption in the UK per capita is much lower than other countries (nearly 93.0% smaller than Japan and France). The authors explain that this is due to the National Institute for Health and Care Excellence (NICE) recommending against the use of epoetin in cancer and local formularies often requiring a sub-cutaneous route of administration, an indication that some biosimilar epoetin products do not possess. This policy resulted in very low biosimilar epoetin uptake (2.0% globally in 2012).

The authors highlighted that each epoetin market is highly country-specific. No link was found between biosimilar epoetin uptakes, epoetin market distribution mixes, and epoetin consumption. The authors state that the implementation of national prescription and substitution incentives appeared to be determining factors of biosimilar uptake; however, the heterogeneity of the national markets made it impossible to outline country profiles for significant biosimilar penetration. As such, the authors conclude that markets should be analysed on a therapeutic class-by-class and country-by-country basis to gain a real understanding of the local uptake.

❖ Perfetti *et al*, 2015: *Diffusion of biosimilar hemopoietic growth factors use in oncology practice: An Italian experience*<sup>26</sup>

The authors described the results of a pilot collaborative project to promote the use of biosimilar epoetin and filgrastim in an Italian oncology setting during 2012 and 2013. The findings for epoetin are discussed here, whereas the filgrastim findings are discussed in the filgrastim sub-section. Therapeutic planning records detailing the treatment plan of oncology patients were monitored before and after a physician intervention including a meeting with the head of pharmaceuticals and an education session, as a measure of biosimilar uptake. A change in epoetin prescribing pattern was observed after the intervention, showing a sharp increase in biosimilar drug records (from 23% to 72%) and an increase in the total number of patients treated with epoetin (69 in 2012, 98 in 2013). Notably, the second generation epoetin darbepoetin, for which there is no biosimilar available, was most affected with a decrease in usage recorded (from 47% to 11%). The authors reported a follow-up on biosimilar usage a year later showed the changes in epoetin biosimilar prescribing behaviour were sustainable with biosimilar epoetin usage remaining above 90%.

❖ Ingrasciotta *et al*, 2015: *How Much Are Biosimilars Used in Clinical Practice? A Retrospective Italian Population-Based Study of Erythropoiesis-Stimulating Agents in the Years 2009-2013*<sup>27</sup>

As described by the Menditto *et al*<sup>23</sup> above, Campania was the first region in Italy to impose use of biosimilars for first choice treatment of naïve patients, followed by Tuscany and Veneto in 2010, and Sicily in 2014. The aim of this population-based database study was to evaluate the prescribing patterns of biosimilar and reference epoetin in four large Italian geographic areas (2009-2013), where different health policy interventions promoting biosimilar use were adopted. The authors stated that a report on medicine use in Italy in 2013 showed that at the National level 41.0% of patients newly treated with epoetin alpha were treated with biosimilar epoetin alpha, an increase in uptake of 71.6% compared with the previous year. During the study period, medicines usage by more than 10% of the entire Italian population was monitored using public prescribing data. Approximately 50,000 (0.8% of the monitored group) patients received at least one dose of

epoetin; of these, 83.4% were naïve users of epoetin. Most patients started therapy with originators (78.5%) and much less frequently with biosimilars (21.5%). The authors reported an increase in biosimilar uptake from 1.8% of in 2010 to 33.6% in 2013, with larger increases observed in Treviso (from 0.0% to 45.0%) and the Tuscany region (from 0.7% to 37.6%) than in Caserta (from 7.5% to 22.9%) and Palermo (from 0.0% to 27.7%). These regional differences observed in this uptake were explained by differences in incentivisation and education programs. The switching patterns across different epoetin products during the first year of treatment were observed. Switching between different products was very frequent (17.0%). It was observed that users switched more frequently toward an originator (84.1%) than toward a biosimilar (15.9%). Most biosimilar uptakers were naïve patients (>6 months since last dose), and only a very small proportion represented originator ESA users switching toward a biosimilar.

❖ D'Amore *et al*, 2016: *Switching between epoetins: A practice in support of biosimilar use*<sup>28</sup>

A retrospective drug utilisation study of patients who received their first epoetin prescription between 1 July 2011 and 31 December 2014 was conducted in the Umbria region of Italy. In this study, switching was defined as any transition between different epoetins in two consecutive prescriptions. Overall, 3258 subjects received a prescription for epoetin of which 2896 had at least two prescriptions. Of these, 354 (12.2%) experienced one or more switches. The probability of switching depended on the duration of treatment, with approximately 15% of users switching within 12 months of observation and 25% switching within 2 years. Switching was not limited to reference and biosimilar epoetins and it was suggested to affect patent and off-patent epoetins equally.

### **Filgrastim Biosimilars**

In its first three years post-launch (September 2008), the biosimilar version of filgrastim achieved a significant market share in Europe's most populous countries. A total of two peer reviewed original research articles were identified addressing the uptake of biosimilar filgrastim.

❖ Bocquet *et al*, 2014: *Biosimilar granulocyte colony-stimulating factor uptakes in the EU-5 markets: A descriptive analysis*<sup>25</sup>

In this study, the authors utilised the same country-by-country methodology to investigate filgrastim uptake in 2011, as was later used to investigate epoetin uptake as described previously. Germany, France, Italy, Spain and the UK were analysed using the IMS MIDAS database. Japan was not included in the analysis as there were no filgrastim biosimilars launched by the end of 2011.

Filgrastim consumption is between 1.7 and 2.6 times greater per capita in France, compared with the other countries. France is a retail market-oriented distribution system: 93.6% of filgrastim sales by volume were made via retail pharmacies in 2011. Global biosimilar filgrastim uptake was determined to be 5.4% (DDD) in 2011, a low level. This may be explained by the small price difference between biosimilar and originator (-5.4%, stable 2007 to 2011).

The German filgrastim market was split almost equally between retail and hospital markets. The biosimilar filgrastim penetration in the retail market was relatively high (9.6% DDD in 2011), with the authors attributing this to incentives for physicians to prescribe biosimilars that are well established. The German market is often portrayed as the largest biosimilar market in Europe, this was not found to be the case for filgrastim with only a moderate global uptake (8.5% DDD in 2011).

Again, this may be explained by the moderate price difference between biosimilar and originator (-10.0% in 2011 down from -21.3% in 2008).

The Italian filgrastim market was smaller than the French and German markets and was mainly a hospital market (12.7% for the retail market and 87.3% for the hospital market DDD in 2011). There is a 1.0% difference between the German and the Italian global biosimilar uptake (7.5% in Italy DDD in 2011) despite a much greater difference in biosimilar price (-23.6%) compared to the reference.

In Spain, the exclusive filgrastim distribution was via the hospitals. The market size was small, likely as a result of tenders in hospitals, however biosimilar price discounts are high (-31.8%). The authors stated that this most likely explained the comparatively large global biosimilar uptake in 2011 (12.4% DDD in volume). It was again noted that Spain's drastic economic slowdown and financial crisis prompted the government to significantly decrease all medicines prices, including filgrastim, and to promote the use of biosimilars.

The UK filgrastim market was similar in size to the Spanish market. The distribution was almost exclusively the hospitals; only 1.6% of filgrastim in volume were distributed via retail pharmacies in 2011. The biosimilar uptake was the highest of all the markets in 2011 (20.4% DDD in volume). The authors attributed this to local decisions to include biosimilars in the therapeutic formulary. The author also noted that in the UK retail market there was no PEG-filgrastim, and the biosimilar market share was 17.7% in 2011, i.e. the highest of all EU-5 countries.

❖ *Perfetti et al, 2015: Diffusion of biosimilar hemopoietic growth factors use in oncology practice: An Italian experience*<sup>26</sup>

As previously discussed for the epoetin context, this study reported the results of a pilot collaborative project to promote the use of biosimilar agents in an Italian oncology setting. Therapeutic planning records detailing the treatment plan of oncology patients were monitored before and after a physician intervention including a meeting with the head of pharmaceuticals and an education session. Similar outcomes were observed for filgrastim as were observed for epoetin

A change in filgrastim prescribing pattern is observed after the intervention, showing a sharp increase in biosimilar drug records (from 3% to 66%). Notably, Lenograstim and PEG-filgrastim, for which there are no biosimilars available, were greatly affected with a decrease in usage recorded from 14% to 5% and 80% to 26% respectively. In contrast to the epoetin data, the number of patients being treated with filgrastim decreased by 18% during the study duration from 115 to 94 patients. The authors reported a follow-up on biosimilar usage a year later showed the changes in filgrastim biosimilar prescribing behaviour were sustainable with biosimilar filgrastim usage remaining above 90%.

Two critical moments in the timelines were noted by the authors, the first a negative impact in biosimilar uptake at Month 2 where a shortage in biosimilar to the clinic supply was observed, resulting in reduced prescribing rates for about one month prior to the study intervention at Month 6. The second critical moment was the first intervention at Month 6, which resulted in marked increase in biosimilar epoetin and filgrastim uptake which was sustained throughout the remainder study.

## **Infliximab Biosimilars**

The first monoclonal antibody biosimilar, infliximab, was launched in Central and Eastern Europe in late 2013, but was only approved in Western Europe in February 2015. Biosimilar infliximab was introduced earlier in South Korea with a market entry of November 2012. As it has only been marketed for a short period, only a single peer-reviewed article addressing the usage and uptake of biosimilar infliximab has been identified.

- ❖ Kim *et al*, 2016: *Brief Report: Utilization of the First Biosimilar Infliximab Since Its Approval in South Korea*<sup>29</sup>

This study used claims data from April 2009 to March 2014 from the Korean Health Insurance Review and Assessment Service database, which includes the entire South Korean population, to assess the number of claims for biosimilar infliximab. In total, 20,976 TNF inhibitor users were identified from the South Korean claims database, including 983 with a prescription claim for biosimilar infliximab. Among all of the claims for any version of infliximab, the proportion of biosimilar infliximab claims increased steadily to 19% of global infliximab usage through March 2014. The authors noted that after November 2012, there were significant changes in uptake, with additional increases in the use of branded and biosimilar infliximab (9 more claims per month) and decreases in the use of etanercept (-52 claims per month) and adalimumab (-21 claims per month). During the first 15 months since its introduction in South Korea, one-fifth of all infliximab claims were for the biosimilar version. Introduction of biosimilar infliximab may affect the use of other TNF inhibitors, and the magnitude of change in usage will likely differ in other countries.

## **Insulin**

Biosimilar insulin glargine has only been available on the market since September 2014. As such no peer reviewed articles addressing its uptake have yet been published.

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

A total of 12 manuscripts were identified that describe the outcomes associated with larger scale, multi-centre use of biosimilars. This relatively limited number of publications is complemented by an increasing number of small, single-centre, investigator-initiated studies and case series reports. These smaller studies have utilised a number of study designs ranging from simple case series through to case-control studies, typically utilising historical controls and rarely, randomised trials. Resultantly, these studies rank lowly in the NHMRC Evidence Hierarchy<sup>30</sup> and where statistical analysis has been performed this is typically underpowered to provide meaningful results. Further, these study designs are frequently susceptible to bias which cannot be fully assessed from the material provided. However, these publications contribute to the body of literature on biosimilars and their overall tone provides an indication as to clinician attitude towards, and acceptance of, biosimilars. These publications have the capacity to influence the attitudes of readers and, for these reasons, these studies have been presented in this report in a tabular format that is intended to provide a summary of the type of results reported, particularly as they relate to creating an overall impression of the outcomes associated with biosimilar utilisation.

## Epoetin Biosimilars

There are two large studies, from Bavaria and France, which have evaluated the outcomes associated with the use of biosimilar epoetin. These studies have focussed upon different patient groups and so specific results are not directly comparable. However, given the commonality of the fundamental underlying biological effects of epoetin within these different patient groups the outcomes reported for each study are complementary. Overall, these studies report a positive overall impression from the use of biosimilar epoetin products, including those switching from an originator product, as a result of a lack of evidence of negative outcomes identified. The findings of these studies are described below.

- ❖ Horbrand *et al*, 2013: *A population-based study comparing biosimilar versus originator erythropoiesis-stimulating agent consumption in 6,117 patients with renal anaemia*<sup>31</sup>

Epoetin utilisation was investigated using a population-based database of accounting information of Bavarian physicians and pharmacy claims data in chronic haemodialysis outpatients between January 2008 and December 2010. This study included 6,177 patients who had received epoetin for six or more continuous accounting quarters, of which 35.7% of patients received a biosimilar epoetin. This included 507 patients who switched therapy between an originator and biosimilar. The population of switchers included those who switched from an originator to a biosimilar (88.8%) and those who were switched from a biosimilar to an originator (11.2%). The manuscript reports that the prescribed daily dose (PDD) was “comparable” for biosimilar (defined daily dose [DDD]=444, IQR=294–648) and originator epoetin (DDD=414, IQR 288–594) and did not increase in patients who switched from originator to biosimilar epoetin. As a result of the nature of the data source utilised in this study, the clinical endpoints of haemoglobin concentration or haematocrit value are not reported. However, in the context of clinical practice of titrating treatment to effect, the absence of a difference in PDD is consistent with attaining equivalent clinical outcomes.

- ❖ Michallet *et al*, 2014: *BiOsimilaRs in the management of anaemia secondary to chemotherapy in Haematology and Oncology: Results of the ORHEO observational study*<sup>32</sup>

The ORHEO study was an observational, longitudinal, multicentre study performed in France to evaluate the efficacy and safety of biosimilar epoetins for the treatment of chemotherapy-induced anaemia. This study included patients who were eligible for treatment with an epoetin alfa biosimilar but excluded those who switched to another epoetin treatment between baseline and Month 6 of the study. This study provided results on range of clinical measures associated with epoetin treatment including haemoglobin, haematocrit and additional parameters such as iron studies and blood pressure values. Overall, 2333 patients >18 years (mean age 66.5 years) with chemotherapy-induced anaemia (haemoglobin <11 g/dL) in association with solid tumours, lymphoma or myeloma and eligible for biosimilar epoetin treatment were included. 99.9% of patients received epoetin zeta (median dose 30,000 IU/week). The majority of patients who discontinued treatment during the study did so on the basis of positive treatment outcomes including attainment of satisfactory haemoglobin (39.5%), changes to chemotherapy regimen no longer necessitating epoetin (26.6%), or a combination of attaining target haemoglobin and cessation of chemotherapy (14.9%) whilst 10.8% stopped as a result of a lack of efficacy. The rate of adverse effects was considered “similar” to that previously reported for epoetin zeta with only

1.9% of patients stopping treatment due to an adverse effect and thromboembolic events (3.55%) were “lower than reported previously” for epoetin zeta (4.2%) and epoetin alfa (4.0%)”.

❖ Investigator-Initiated Studies/Case Series

There are two small studies of this nature reported within the literature that focus on different patient groups and as such are not directly comparable. Both of these studies provide overall positive conclusions regarding the use of biosimilar EPO. These studies are described in Table 1.

**Table 1: THEME 3 (Outcomes) Summary of Investigator-Initiated Studies/Case Series for Epoetin**

Agent	Reference	Indication(s)	Number of Patients	Comments on Outcomes	NHMRC Evidence Assessment <sup>30</sup> Level of Evidence	NHMRC Evidence Assessment <sup>30</sup> Generalisability	NHMRC Evidence Assessment <sup>30</sup> Applicability
Epoetin zeta	33	Renal transplant recipients	10 switches 10 naïve	<ul style="list-style-type: none"> <li>• Amongst switchers epoetin dose at 1 month was slightly higher than at baseline but not statistically significant (127± 99 vs. 117± 73 UI/kg per week)</li> <li>• No drug-related adverse effects</li> </ul>	IV	A	A
Epoetin alfa (Binocrit)	34	Elderly low-risk myelodysplastic syndrome patients	24	<ul style="list-style-type: none"> <li>• 15 patients (62.5%) became transfusion independent and remained free from transfusion requirement for at least 3 months</li> <li>• Conclusion: Binocrit is promising for the treatment of anaemia of MDS patients</li> </ul>	IV	A	A

## Filgrastim Biosimilars

There are 3 multicentre studies that report on the outcomes associated with the use of biosimilar filgrastim.

- ❖ Gascon *et al*, 2016: *Treatment patterns and outcomes in the prophylaxis of chemotherapy-induced (febrile) neutropenia with biosimilar filgrastim (the MONITOR-GCSF study)*<sup>35</sup>

The MONITOR-GCSF study is an international (12 countries), multi-centre (140), prospective, observational, open-label, pharmaco-epidemiologic study of cancer patients (n=1447) treated with myelosuppressive chemotherapy across a total of 6,213 cycles and receiving prophylaxis with Zarzio. The outcomes of interest were related to the grades of severity of chemotherapy-induced neutropenia, febrile neutropenia and hospitalisations associated with these events. The study inclusion/exclusion criteria make no reference to prior exposure to filgrastim.

The rates of chemotherapy-induced neutropenia (grade 4) and febrile neutropenia episodes, associated hospitalisations, chemotherapy disturbances, adverse events/reactions were considered to be “statistically within the range of rates reported historically”. The authors conclude that “the effectiveness and safety results of this study should address prescribers’ concerns about biosimilars”.

Whilst this study utilised biosimilar filgrastim, the manuscript itself does not have a strong focus on biosimilar issues, beyond reporting the rates of events of interest. Instead the focus is predominantly upon factors such as the impact of different chemotherapy regimens and clinical practice issues related to the use of growth factor support in this patient group, particularly the appropriateness of primary versus secondary prophylaxis.

- ❖ Nahon *et al*, 2016: *Zarzio, biosimilar of filgrastim, in prophylaxis of chemotherapy-induced neutropenia in routine practice: A French prospective multicentric study*<sup>36</sup>

The aim of this observational, prospective, longitudinal, and multicentric study conducted in France was to assess the efficacy, safety, and use of Zarzio in prophylaxis of chemotherapy-induced neutropenia in cancer patients. The objective of the study was to describe, under the conditions of use in current clinical practice, the incidence of severe neutropenia and to collect safety data. Prior exposure to filgrastim was not specifically reported but the exclusion criteria included hypersensitivity to Zarzio or to any other filgrastim indicating that prior filgrastim exposure was possible. The intended primary endpoint of the study was a comparison of the incidence of severe neutropenia at nadir between the 1<sup>st</sup> and the 4<sup>th</sup> chemotherapy cycles but this was not possible due to deficiencies in the availability of neutrophil nadir data. The authors report that neutrophils decreased between cycles 1 and 2 but then remained stable within the normal range (>2000 neutrophils/mm<sup>3</sup>) and that this was considered to be consistent with the results of phase III trials conducted for this product in breast cancer patients. Ultimately the authors conclude that “the results obtained in real-life conditions of this study confirm that Zarzio is efficient and well tolerated in cancer patients”.

- ❖ Tesch *et al*, 2015: *Prevention and treatment of chemotherapy-induced neutropenia with the biosimilar filgrastim: A non-interventional observational study of clinical practice patterns*<sup>37</sup>

The HEXAFIL study was an observational study that assessed the clinical usage, safety and efficacy of the biosimilar filgrastim in routine clinical practice in Germany. The primary objective of the study was to evaluate the safety and tolerability of biosimilar filgrastim. The secondary objectives included treatment efficacy, through assessment of the occurrence of neutropenic complications, and evaluation of the patterns of biosimilar filgrastim clinical utilisation. Data including neutropenic complications and adverse events were documented for up to 3 consecutive cycles. A total of 1,337 cancer patients received the biosimilar filgrastim for primary prophylaxis, secondary prophylaxis, or interventional treatment plus chemotherapy. A total of 114 patients (7.7%) experienced at least 1 treatment-emergent adverse event with a possible relation to filgrastim. Consistent with the manuscript of Nahon *et al*<sup>36</sup> the authors concluded that the safety profile of the biosimilar filgrastim was “generally in line with that reported in the phase III clinical trial and in clinical studies of the originator filgrastim” and that their study “provides further reassurance that the efficacy of this biosimilar observed in the clinical trial setting is maintained in clinical practice.”

- ❖ Investigator-Initiated Studies/Case Series

A significant focus of the publications of this nature is upon the extrapolation of biosimilar filgrastim to indications beyond those included for registration purposes. The nature of these studies reflects the diversity and sometimes specialised applications for filgrastim in haematology and oncology. In these settings, patient characteristics can be drastically different from those that were included in the studies presented for registration. Further, whilst the biological effects of filgrastim for the prevention/management of chemotherapy induced neutropenia are easily measured, particularly within the studies that were utilised for registration purposes, there exist additional uncertainties regarding the effect of filgrastim in these additional applications and this has driven the publications in these areas. For example, in the mobilisation of haematopoietic stem cells for autologous or allogeneic transplantation, there are additional questions regarding the attributes of the stem cells that are mobilised. These attributes are not easily measured but may impact upon clinical outcomes following transplantation of these cells. For this reason there has been interest in reporting both the effects of filgrastim that can be readily measured, such as cell yields, and also in reporting clinical outcomes in these settings. In many instances these reports will relate to a relatively small number of patients, something which typifies research in these specific patient groups more generally.

The results of these studies are described in Table 2. In general, these reports provide a favourable impression of the outcomes associated with biosimilar filgrastim, either in terms of readily quantifiable measures, such as attainment of CD34+ cell targets, or in some instances the associated clinical outcomes. These studies most frequently utilised comparison against historical controls from the same institution that were treated with the originator product prior to availability of the biosimilar. A single prospective trial is reported, but the randomisation procedure was not discussed which results in a downgrading of the evidence rating for this study<sup>38</sup>.

**Table 2: THEME 3 (Outcomes) Summary of Investigator-Initiated Studies/Case Series for Filgrastim**

Agent	Reference	Indication(s)	Number of Patients	Comments on Outcomes	NHMRC Evidence Assessment <sup>30</sup> Level of Evidence	NHMRC Evidence Assessment <sup>30</sup> Generalisability	NHMRC Evidence Assessment <sup>30</sup> Applicability
Filgrastim (Tevagrastim)	39	Allogeneic Hematopoietic Stem Cell Mobilisation and Transplantation in Patients with Acute Myelogenous Leukaemia/Myelodysplastic Syndromes	48 total  24 Tevagrastim 24 Neupogen	<ul style="list-style-type: none"> <li>• Similar yields of CD34+ stem cells were mobilised in the Tevagrastim (<math>10.2 \times 10^6</math>, range: 2.52 to 35.4) group and the filgrastim (<math>9.35 \times 10^6</math>, range: 3.7 to 30.6) historical control group</li> <li>• Similar engraftment kinetics, hematopoietic reconstitution, and transplantation outcome were noted</li> <li>• Donor side effects were mild, transient and not different groups</li> </ul>	III-3 (historic controls)	B	B
Filgrastim (Zarzio)	40	Post Autologous Hematopoietic Stem Cell transplant to facilitate engraftment  Mobilisation of Peripheral blood stem cell (PBSC) in patients undergoing autologous stem cell transplantation (AHSCT)	110 total  70 post AHSCT  40 PBSC mobilisation prior to AHSCT	<ul style="list-style-type: none"> <li>• Biosimilar filgrastim following AHSCT is effective and generally well tolerated in the engraftment setting</li> <li>• Kinetics of PBSC mobilisation and yield of CD34+ cells were comparable to the originator</li> </ul>	IV	B	B

Agent	Reference	Indication(s)	Number of Patients	Comments on Outcomes	NHMRC Evidence Assessment <sup>30</sup> Level of Evidence	NHMRC Evidence Assessment <sup>30</sup> Generalisability	NHMRC Evidence Assessment <sup>30</sup> Applicability
Filgrastim (Zarzio)	41	Peripheral blood stem cell (PBSC) mobilisation in healthy matched donors for allogeneic stem cell transplantation (allo-HSCT)	36 total 18 Zarzio 18 Neupogen	<ul style="list-style-type: none"> <li>• No significant differences in the collection of the optimal cell dose</li> <li>• 3/18 (16.6%) donors that received Zarzio failed to mobilise the optimal cell dose compared with 0% in the Neupogen group</li> <li>• Platelet and neutrophil median time to engraftment was comparable between the two groups</li> </ul>	III-3 (retrospective)	B	B

Agent	Reference	Indication(s)	Number of Patients	Comments on Outcomes	NHMRC Evidence Assessment <sup>30</sup> Level of Evidence	NHMRC Evidence Assessment <sup>30</sup> Generalisability	NHMRC Evidence Assessment <sup>30</sup> Applicability
Filgrastim (Nivestim)	42	Mobilization of Peripheral blood stem cell (PBSC) patients undergoing autologous stem cell transplantation (AHSCT)	98 total  60 Nivestim 38 Neupogen	<ul style="list-style-type: none"> <li>• No difference in CD34+ count at first leukapheresis (<math>47 \times 10^6</math> cells/L v <math>60 \times 10^6</math> cells/L, <math>p=0.48</math>)</li> <li>• No difference in total CD34+ collected (<math>5.37 \times 10^6</math>/kg v <math>4.59 \times 10^6</math>/kg, <math>p=0.22</math>)</li> <li>• Nivestim group required fewer median number of leukapheresis sessions (1 v 2, <math>p=0.0003</math>).</li> <li>• Nivestim use associated with longer median time to neutrophil engraftment (15 v 13.5 days, <math>p=0.09</math>)</li> <li>• Nivestim use associated with longer time to platelet (PLT) engraftment (20 v 18 days, <math>p=0.01</math>) but did not result in increased PLT transfusions (2 v 3, <math>p=0.2</math>) or impact significantly on hospitalisation time for admissions within 30 days post-transplant</li> </ul>	III-3 (retrospective)	B	B

Agent	Reference	Indication(s)	Number of Patients	Comments on Outcomes	NHMRC Evidence Assessment <sup>30</sup> Level of Evidence	NHMRC Evidence Assessment <sup>30</sup> Generalisability	NHMRC Evidence Assessment <sup>30</sup> Applicability
Filgrastim (Zarzio)	43	Mobilisation of Peripheral blood stem cell (PBSC) in multiple myeloma patients undergoing autologous stem cell transplantation (AHSCT)	77 total 40 Zarzio 37 Neupogen	<ul style="list-style-type: none"> <li>No difference in mean number of CD34+ cells/mL in the peripheral blood in the biosimilar and originator (<math>199.6 \pm 207.4</math> v <math>192.8 \pm 154.7</math>, <math>P=0.87</math>)</li> <li>No difference in the median number of CD34+ cells/kg collected in the biosimilar and originator groups (<math>11.5 \pm 5.8</math> v <math>12.3 \pm 5.3</math>, <math>P=0.51</math>)</li> <li>Mobilisation failure rates in the biosimilar and originator groups were 2.5% and 2.7% respectively (<math>P=NS</math>)</li> <li>No statistically significant differences in hematopoietic recovery parameters and transplant-related toxicities</li> <li>No significant differences in side effects were observed</li> </ul>	III-3 (historic controls)	B	B
Filgrastim (Zarzio)	44	Paediatric Allogeneic - Hematopoietic Stem Cell transplant (Allo-HSCT) or autologous Hematopoietic Stem Cell Transplantation (AHSCT)	58 total 29 Zarzio 29 Neupogen	<ul style="list-style-type: none"> <li>No difference in CD34+ blood count at first mobilisation, Patients achieving blood CD34+ cell peak <math>\geq 20 \times 10^6/L</math> (90% v 79%, <math>p=0.5</math>) or number of leukapheresis procedures.</li> <li>Higher incidence of fever of unknown origin in the biosimilar group (45% v 17%, <math>p = 0.02</math>)</li> <li>No difference was observed in comparison with historical control group mobilised with originator filgrastim.</li> </ul>	III-3 (historic controls)	B	B

Agent	Reference	Indication(s)	Number of Patients	Comments on Outcomes	NHMRC Evidence Assessment <sup>30</sup> Level of Evidence	NHMRC Evidence Assessment <sup>30</sup> Generalisability	NHMRC Evidence Assessment <sup>30</sup> Applicability
Filgrastim (Zarzio)	38	Autologous Hematopoietic Stem Cell Transplantation (AH SCT)	108 total 54 Zarzio 54 Neupogen	<ul style="list-style-type: none"> <li>• No statistically significant differences between groups in the mean number of mobilised CD34+ cells/mL in peripheral blood (biosimilar 62.0 [2–394] v originator 47.5 [2–370]) or the number of CD34+ cells/kg body weight.</li> <li>• Both groups had a median of one apheresis</li> <li>• Five patients (9%) in the originator filgrastim group and six patients in the biosimilar filgrastim group (11%) did not mobilise sufficient CD34+ cells.</li> <li>• Similar occurrence of neutropenic fever between biosimilar and originator (11 v 10)</li> <li>• Similar occurrence of bone pain between biosimilar and originator (17 v 19)</li> </ul>	III-1 (randomisation method not provided)	B	B
Filgrastim (Leucostim)	45	Autologous Hematopoietic Stem Cell Transplantation (AH SCT)	84 total 68 Neupogen 16 Leucostim	<ul style="list-style-type: none"> <li>• Leucostim was comparable to Neupogen for PBSC mobilisation in patients who underwent autoHSCT</li> </ul>	III-3	B	B

Agent	Reference	Indication(s)	Number of Patients	Comments on Outcomes	NHMRC Evidence Assessment <sup>30</sup> Level of Evidence	NHMRC Evidence Assessment <sup>30</sup> Generalisability	NHMRC Evidence Assessment <sup>30</sup> Applicability
Filgrastim (Zarzio)	46	Primary or secondary prophylaxis of chemotherapy induced neutropenia	102 total 77 Zarzio 25 Neupogen	<ul style="list-style-type: none"> <li>• Trend toward increased primary prevention with biosimilar implementation (52% v 36% of patients) possibly enabled by the lower cost</li> <li>• No unexpected safety findings were observed.</li> <li>• Biosimilar filgrastim was effective and prevented dose reductions or discontinuation in the majority of patients.</li> </ul>	IV (no direct formal comparison between groups)	A	A
	47	PBSCT in lymphoma or multiple myeloma	88 total 38 biosimilar 50 Neupogen	<ul style="list-style-type: none"> <li>• No significant differences could be detected in 12 clinical and biological parameters.</li> </ul>	III-3	B	B
Filgrastim (Tevagrastim)	48	Peripheral blood stem cells (PBSC) mobilisation in combination with plerixafor in patients with lymphoma or multiple myeloma	14 total	<ul style="list-style-type: none"> <li>• All patients able to collect <math>\geq 2.0 \times 10^6</math>/kg CD34+ cells</li> <li>• Median of one apheresis procedures</li> <li>• We were able to show that mobilisation with biosimilar filgrastim and plerixafor is a very efficient strategy for stem cell mobilisation and allows collection of adequate quantities of CD34+ for autologous transplantation.</li> </ul>	IV	B	B

Agent	Reference	Indication(s)	Number of Patients	Comments on Outcomes	NHMRC Evidence Assessment <sup>30</sup> Level of Evidence	NHMRC Evidence Assessment <sup>30</sup> Generalisability	NHMRC Evidence Assessment <sup>30</sup> Applicability
Filgrastim (Zarzio)	49	Lymphoma or multiple myeloma autologous PBSC mobilisation	81 total 40 Zarzio 41 Neupogen	<ul style="list-style-type: none"> <li>• No difference in median PB CD34+ cell concentration before the first leukapheresis was (biosimilar: 55.5/μL (range 1-196) with biosimilar and 60/μL (range 13-432) with originator (P=0.71))</li> <li>• Both groups required a median of one leukapheresis sessions to attain target CD34+ cell count</li> <li>• Median number of days to absolute neutrophil count recover <math>\geq 0.5 \times 10^9/L</math> was 14 days (range 9-21) in the biosimilar group and 15 days (range 7-20) in the originator group</li> </ul>	III-3 (historic controls)	B	B

## Infliximab Biosimilars

There are 5 multicentre studies that report on the post-marketing outcomes associated with the use of biosimilar infliximab. Two of these studies are open-label extension studies of the phase III clinical trials for CT-P13 in rheumatoid arthritis and ankylosing spondylitis. Importantly, these studies provide evidence for the outcomes associated with switching.

- ❖ Yoo *et al*, 2016: *Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study*<sup>50</sup>

This open-label extension study, which included 302 patients who had previously completed the PLANETRA study, sought to investigate the efficacy and safety of switching from the infliximab originator to the biosimilar CT-P13 in patients with rheumatoid arthritis, and to provide data on extended duration treatment with only the biosimilar. Overall findings of the study suggested comparable efficacy and safety between those continuing biosimilar treatment and those who switched. Efficacy endpoints assessed American College of Rheumatology 20% (ACR20) response, ACR50 and ACR70, with response rates comparable between the maintenance and switching groups, as illustrated by ACR20 (71.7% vs. 71.8% respectively), ACR50 (48.0% vs. 51.4%, respectively) and ACR70 (24.3% vs. 26.1%, respectively). With regards to the formation of antidrug antibodies (ADA), 40.3% of maintenance group patients and 44.8% of switch group patients were ADA positive at study conclusion ( $p = 0.48$ ). The proportion of patients with at least one positive ADA result during the extension study were similar between the treatment groups (57.2% for the maintenance groups vs. 64.3% for the switch group) and there were no differences in the number of patients with sustained ADA responses. Additionally, no differences in the proportion of patients experiencing treatment-emergent adverse events were observed (53.5% vs. 53.8% for the maintenance and switch groups respectively).

- ❖ Park *et al*, 2016: *Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study*<sup>51</sup>

In a study with very similar design to Yoo *et al*<sup>50</sup>, this open-label extension to the PLANETAS study, examined the long-term safety and efficacy of CT-P13 in 174 patients with ankylosing spondylitis, which included a treatment arm of patients switching from the reference infliximab to the CT-P13 biosimilar. Again, overall findings of the study suggested comparable efficacy and safety between those continuing biosimilar treatment and those who switched. Efficacy was determined according to the Assessment of SpondyloArthritis International Society (ASAS)20, ASAS40 and ASAS partial remission. End of study response rates were comparable between maintenance and switching groups for ASAS20 (80.7% vs. 76.9% respectively), ASAS40 (63.9% vs. 61.5%, respectively) and ASAS partial remission (19.3% vs. 23.1%, respectively). As for the PLANETRA extension study<sup>50</sup>, the proportion of ADA positive patients were similar between the treatment groups (end of study: 23.3% vs. 27.4% for maintenance and switching groups, respectively), and the proportions with a sustained ADA response were similar (85.7% for maintenance group vs. 88.9% for switch group). Notably, the ADA incidence within the switching group did not increase after the switch occurred (26.2% in Week 54 vs. 27.4% in Week 102). A

higher proportion of treatment-emergent adverse events were observed in the switch group during the extension study (71.4% c.f. 48.9% in the maintenance group), with those deemed by the investigator to be related to the study treatment reported as 22.2% for the maintenance group and 39.3% for the switching group. Most adverse events were mild or moderate in severity, and adverse events leading to discontinuation of the study treatment were similar between the treatment groups (3.3% for the maintenance group vs. 4.8% for the switching group).

The remaining 3 infliximab outcomes studies focussed upon the extrapolation of indication to the inflammatory bowel disease indications of Crohn's disease (CD) and ulcerative colitis (UC). These studies each conclude that biosimilar infliximab appears to be similar to the originator in these extrapolated indications.

❖ Gecse *et al*, 2016: *Efficacy and Safety of the Biosimilar Infliximab CT-P13 Treatment in Inflammatory Bowel Diseases: A Prospective, Multicentre, Nationwide Cohort*<sup>52</sup>

This prospective, multi-centre, observational cohort study was designed to examine the efficacy, safety, and immunogenicity of CT-P13 infliximab biosimilar in the induction treatment of Crohn's disease and ulcerative colitis. The study included 210 patients with inflammatory bowel disease (Crohn's disease n = 126; ulcerative colitis n = 84). None of the patients had received infliximab treatment with the originator within 12 months prior to the initiation of biosimilar infliximab, but 22.3% had previously undergone induction with originator infliximab. The primary objective was to assess early clinical remission at Week 14. Secondary endpoints of the maintenance phase included sustained clinical remission and response, biochemical response, mucosal healing, immunogenicity, and safety, evaluated at Week 54.

At Week 14, 81.4% of Crohn's disease and 77.6% of ulcerative colitis patients demonstrated a clinical response and 53.6% of Crohn's disease and 58.6% of ulcerative colitis patients were considered to be in clinical remission. Clinical remission rates at Week 14 were significantly higher in patients who were infliximab naïve, compared with those who had previously undergone induction with the originator compound ( $p < 0.05$ ) likely as a result of the significantly higher baseline ADA positivity in both Crohn's disease and ulcerative colitis patients previously treated with originator infliximab. At Week 30, there was no difference in clinical remission or in clinical response between naïve patients and those with previous infliximab exposure (60% vs. 38.9%,  $p = 0.13$  and 75% vs. 50%,  $p = 0.06$ , respectively). With regards to safety, infusion reactions occurred in a significantly higher proportion of patients with previous infliximab exposure compared with naïve patients (27% vs. 2.5%,  $p < 0.001$ ).

The authors conclude that "this prospective multicentre cohort shows that CT-P13 is effective and safe in the induction of clinical remission and response in both CD [Crohn's disease] and UC [ulcerative colitis]" and that the "efficacy and safety of CT-P13 reported herein is comparable to those of observational studies of the originator compound".

❖ Farkas *et al*, 2016: *Efficacy of Infliximab Biosimilar CT-P13 Induction Therapy on Mucosal Healing in Ulcerative Colitis*<sup>53</sup>

This multi-centre prospective study aimed to evaluate the efficacy of CT-P13 induction therapy on mucosal healing at 14 weeks in 63 patients with ulcerative colitis. Of these patients, two had

previously received originator infliximab, but not within the preceding 12 months. Cumulative clinical response and steroid-free remission at Week 14 were achieved in 82.5% and 47.6% of the patients, respectively. Sigmoidoscopy revealed steroid-free mucosal healing in 47.6% of the patients, and complete mucosal healing was present in 27%. Trough concentration of CT-P13 were significantly higher in patients who achieved mucosal healing or steroid-free mucosal healing than in patients who did not achieve endoscopic remission. Anti-infliximab antibody positive patients presented with undetectable trough levels. Previous anti-TNF therapy was not predictive of a loss of response in this study. Anti-infliximab antibodies were detectable in seven patients at Week 14 however, none of these patients had received anti-TNF- $\alpha$  therapy previously.

The authors conclude that “infliximab biosimilar CT-P13 represents a promising treatment option for patients with UC not only regarding clinical activity, but also in achieving mucosal healing”.

❖ *Park et al, 2015: Post-marketing study of biosimilar infliximab (CT-P13) to evaluate its safety and efficacy in Korea*<sup>54</sup>

This post-marketing study included patients with active moderate-to-severe Crohn’s disease, fistulising Crohn’s disease, or moderate-to-severe ulcerative colitis who were treated with CT-P13 and followed for 30 weeks. This study included patients who were both treatment naïve and those who switched to the biosimilar from the originator. The publication provides results between January 2013 and November 2014. A total of 145 patients were included in the efficacy population (moderate-to-severe Crohn’s disease n = 70; fistulising Crohn’s disease n = 10; moderate-to-severe ulcerative colitis n = 65). The majority of infliximab-naïve patients (102/113 [90.3%]) were exposed to at least three doses of treatment which spanned a 6-week induction period whilst 52/60 (86.7%) patients in the switch group received three doses of CT-P13. Overall 41% of patients underwent dose escalation from the initial dose of 5 mg/kg. There were no notable differences in dose escalation between infliximab-naïve and switched patients. There were no notable differences in proportions of patients experiencing adverse effects at different doses in the infliximab-naïve group compared with the switch group. Overall, 27 (87.1%) patients with moderate-to-severe Crohn’s disease who switched from the infliximab originator did not experience disease worsening and therefore were considered to have disease control. The authors noted that the rate of infusion reactions in this study is possibly lower than that reported historically with the originator but the numbers in the study are small. It was considered that CT-P13 was well tolerated with no unexpected adverse effects observed. The authors concluded that “the tolerability profile observed with CT-P13 in IBD [Inflammatory Bowel Disease] appears to be at least in line with what has previously been reported with RMP [originator]”, that “CT-P13 is efficacious in this population of patients” and that “clinical outcomes such as safety and efficacy are comparable for CT-P13 and RMP [originator]”.

❖ Investigator-Initiated Studies/Case Series

Within the review period four studies have reported the outcomes associated with the use of biosimilar infliximab at single institutions for the management of inflammatory bowel disease. The details of these studies are provided in Table 3. These studies have included clinical outcomes such as remission and mucosal healing. A number have also investigated infliximab concentrations and the presence of ADA. Some of these studies have included patients that have previously received treatment with originator infliximab. Overall, the response to biosimilar infliximab has been

considered to be consistent with that of the originator product. It notable that in these studies a number patients did experience adverse effects or lack of efficacy, often as a result of the presence of ADA, but that this was not limited to patients who have been treated with the originator product prior to receiving the biosimilar and that the authors did not attribute these events to the use of the biosimilar.

**Table 3: THEME 3 (Outcomes) Summary of Investigator-Initiated Studies/Case Series for Infliximab**

Agent	Reference	Indication(s)	Number of Patients	Comments on Outcomes	NHMRC Evidence Assessment <sup>3</sup> Level of Evidence	NHMRC Evidence Assessment <sup>30</sup> Generalisability	NHMRC Evidence Assessment <sup>3</sup> Applicability
CT-P13	55	inflammatory bowel disease	25 total  CD=19 UC=6	<ul style="list-style-type: none"> <li>CT-P13 was used for induction (naïve – 13) or maintenance treatment (switch – 12) in patients with moderate-to-severe IBD</li> <li>CT-P13 induction treatment for IBD seems to be as effective as IFX</li> <li>The switch from IFX to CT-P13 was largely safe, and patients showed clinical relapse and adverse event rates similar to those reported for IFX</li> </ul>	IV	A	A
CTP-13	56	inflammatory bowel disease	78 total  CD (n = 46) UC (n = 32)	<ul style="list-style-type: none"> <li>6 patients switched from Remicade (CD=4, UC=2)</li> <li>79% of CD and 56% of UC patients achieved remission at week 14</li> <li>Four CD patients and four UC patients had trough levels of 0 mg/L. Two of these patients had high ADA levels (≥80 AU/L), five had medium/high ADA levels (&lt;80 AU/L), and one had low ADA levels (&lt;10 AU/L). One of these had received originator infliximab 18 months prior.</li> <li>No unexpected immunogenicity or safety findings arose during the current study. AEs were consistent with those previously observed with CT-P13 and infliximab RMP</li> <li>CT-P13 was efficacious in both CD and UC patients, achieving similar clinical responses to those observed with the RMP in large randomised studies</li> </ul>	IV	A	A

Agent	Reference	Indication(s)	Number of Patients	Comments on Outcomes	NHMRC Evidence Assessment <sup>30</sup> Level of Evidence	NHMRC Evidence Assessment <sup>30</sup> Generalisability	NHMRC Evidence Assessment <sup>30</sup> Applicability
CT-P13	57	inflammatory bowel disease	39 total  CD=18 UC = 21  2 patients switched	<ul style="list-style-type: none"> <li>Clinical response and remission were achieved in 37.5% and 50% of patients with CD</li> <li>Clinical response and remission was achieved in 20% and 66.7% of patients with UC</li> <li>Mucosal healing was achieved in 73.3% of UC patients who underwent induction therapy followed by sigmoidoscopy</li> <li>Mean serum IFX levels were significantly lower in patients who developed ATI compared to patients who did not develop ATI (12.8 vs 1.73 µg/ml, p = 0.005)</li> <li>One patient was previously treated with IFX and developed hypersensitivity reaction with high antibody level. Slightly elevated ATI were identified in this patient who had previously developed antibodies against the originator IFX</li> <li>Adverse reactions included mild arthralgia, one hypersensitivity reaction and the need for colectomy in one patient in UC.</li> <li>Induction with CT-P13 is safe and effective</li> </ul>	IV	A	A

Agent	Reference	Indication(s)	Number of Patients	Comments on Outcomes	NHMRC Evidence Assessment <sup>3</sup> <sup>0</sup> Level of Evidence	NHMRC Evidence Assessment <sup>30</sup> Generalisability	NHMRC Evidence Assessment <sup>3</sup> <sup>0</sup> Applicability
CT-P13	58	inflammatory bowel disease	17 total  CD=8 UC=9  9 patients switched	<ul style="list-style-type: none"> <li>• Mean number of CT-P13 administrations was <math>4.2 \pm 1.9</math> (range 1–7)</li> <li>• Clinical response and remission at 8 weeks were achieved in seven patients (UC =5, CD=2)</li> <li>• One CD patient did not respond to CT-P13</li> <li>• Amongst the 9 switchers 8 patients showed a similar clinical outcome compared with the originator. One CD patient experienced loss of response</li> <li>• CT-P13 may have biosimilarity and interchangeability with its originator in inflammatory bowel disease.</li> </ul>	IV	A	A

## ❖ Conference Abstracts

Owing to the relative recency of the availability of biosimilar infliximab, publication lag and the unique considerations with this molecule as compared with previous biosimilars published conference abstracts were reviewed for inclusion. The abstracts detail the use of biosimilar infliximab for a broader range of indications than the above published papers and includes rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis and Crohn's disease. The details of these abstracts are provided in Table 4. These abstracts include reports of the outcomes of patients that have switched from originator to biosimilar. However, because these are only available in abstract form it is not possible to rigorously assess their content. In this context though, conference abstracts provide an overview of general nature of the outcomes that are beginning to be reported with the use of biosimilar infliximab.

Overall, these abstracts present a generally positive view of the outcomes associated with the use of biosimilar infliximab although a notable example, reporting on the use in inflammatory bowel disease with the use of historic controls, provides a dissenting view concluding that "our results suggest that biosimilars may not be as efficacious as the reference medicine"<sup>59</sup>. This abstract was presented at a conference held in February of 2015 but has not been subsequently published as a full manuscript in a peer reviewed journal.

**Table 4: THEME 3 (Outcomes) Summary of Conference Abstracts for Infliximab**

Agent	Reference	Indication(s)	Number of Patients	Comments
Not stated	<sup>60</sup>	Switching in rheumatic diseases  RA=15 SPA/axial spondyloarthritis= 14 psoriatic arthritis= 7 juvenile RA=2 chronic reactive arthritis =1	39 total	<ul style="list-style-type: none"> <li>• Aim: report clinical experience of the use of biosimilar infliximab in patients with rheumatic diseases who were switched from originator</li> <li>• Eleven patients (28.2%) discontinued biosimilar: in 3 patients, INX-antibodies were found (before the 1st biosimilar infusion)</li> <li>• Latent tuberculosis activated in one patient after receiving two infusions. Patient had received infliximab for 12 months before switch.</li> <li>• One patient was diagnosed with neurofibromatosis after two biosimilar infusions and had received infliximab for almost 5 years before switch</li> <li>• Six patients discontinued biosimilar for subjective reasons without objective deterioration of disease, in whom a nocebo effect cannot be ruled out (perceived as "a cheap copy")</li> <li>• Effectiveness of biosimilar appeared similar to originator over a median of 11 months in patients who switched.</li> <li>• No immediate safety signals were observed.</li> </ul>
Inflectra/Remsima	<sup>61</sup>	Anti-drug antibody (ADA) reactivity	256 total 131 ADA positive	<ul style="list-style-type: none"> <li>• The purpose of the study was to determine if antibodies to infliximab (ATI) in RMC-treated patients cross-react with the biosimilar.</li> <li>• Promonitor-ANTI-IFX CE marked kit cross linking with either biosimilar brand</li> <li>• ATI of RMC-treated patients cross-react with either IFT or RMS</li> </ul>
Not stated	<sup>62</sup>	Rheumatoid Arthritis	98 total  52 biosimilar 46 originator	<ul style="list-style-type: none"> <li>• Prospective biologic DMARDs registry in Korea: BIOlogics Pharmacoepidemiologic StudY (BIOPSY)</li> <li>• Aim: to compare the characteristics of RA patients who use biosimilar infliximab with those of patients who start original infliximab and to identify the effectiveness and safety of biosimilar infliximab for RA</li> <li>• Biologics-naive patients were more common in biosimilar users but not significant statistically (92.3 % vs. 84.8 %, P=0.39)</li> <li>• DAS28-ESR remission rate observed in 6 or 9 months after starting biosimilar and original infliximab were 18.6% and 15.6%, respectively (P =0.75). HAQ-DI changes were not different between two groups (0.4 +/- 0.8 vs. 0.4 +/- 0.7 P=0.85).</li> <li>• Most common reason of drug discontinuation was ineffectiveness in both groups (61.5% in biosimilar and 68.2% in original infliximab).</li> </ul>

Agent	Reference	Indication(s)	Number of Patients	Comments
CT-P13	<sup>63</sup>	Ulcerative colitis	12	<ul style="list-style-type: none"> <li>• Aim: to examine the efficacy of CT-P13 induction therapy on mucosal healing in patients with ulcerative colitis (UC)</li> <li>• Two patients discontinued therapy after the second infusion. One patient previously treated with infliximab developed high antibody level experienced a hypersensitivity reaction. One developed septic complications.</li> <li>• At week 6 remission achieved in 5 patients and clinical response in 2. Two did not respond. One non-responder was previously treated with infliximab</li> <li>• Results indicate that the induction with CT-P13 can result mucosal healing in similar proportion as the originator infliximab</li> </ul>
Remsima	<sup>64</sup>	Crohn's Disease (CD) and Ulcerative Colitis (UC)	106 total CD=55 patients (32 switched) UC=51 (10 switched)	<ul style="list-style-type: none"> <li>• Aim: to assess the efficacy and safety of Remsima in Korean patients with IBD</li> <li>• At week 8 in anti-TNF naive CD patients the rates of clinical response and remission were 91% and 78% at week 8</li> <li>• At week 8 in anti-TNF naive UC patients the rates of clinical response, clinical remission, and mucosal healing were 87%, 31%, and 54%</li> <li>• Three patients (2.8%) discontinued Remsima because of an adverse event</li> <li>• The efficacy of Remsima was maintained in 86% of patients with CD and in 67% of patients with UC after switching from Remicade.</li> <li>• Remsima showed an excellent short-term clinical response and a good safety in both moderate to severe CD and UC.</li> </ul>
Remsima	<sup>65</sup>	Paediatric ulcerative colitis	6	<ul style="list-style-type: none"> <li>• Disease activity (PUCAI) and laboratory values (CRP, ESR, platelet count) was assessed at the start of the biological therapy and at week 10</li> <li>• For one patient it was the second course of biological treatment (3 doses of the reference product received 9 months prior)</li> <li>• 2 patients (33%) discontinued treatment, 1 due to lack of response after first dose (disease flare), 1 due to anaphylactic reaction during dose 3 infusion (second course of infliximab)</li> <li>• Initial observations point to efficacy and safety of biosimilar infliximab in the treatment of paediatric patients with ulcerative colitis</li> </ul>

Agent	Reference	Indication(s)	Number of Patients	Comments
Remsima/Inflectra	<sup>66</sup>	Paediatric Crohn's disease	12	<ul style="list-style-type: none"> <li>• Five out of 12 patients were previously treated with a biologics (4 with reference infliximab, 1 with adalimumab)</li> <li>• Time of previous treatment was 6-59 months with biologic-free interval of 7-72 months</li> <li>• 10/12 patients (83%) response was observed as assessed by significant PCDAI and inflammation markers decrease</li> <li>• Treatment was discontinued in 2/12 patients (17%) after first dose due to lack of response, accompanied by adverse event in one patient and withdrawal of consent in second patient</li> <li>• Adverse events during infusion were observed in 2/12 patients (17%): one anaphylactic reaction leading to treatment discontinuation and one blood pressure rise that resolved after infusion rate lowering</li> <li>• Appears to be safe and efficacious in inducing remission in Crohn disease paediatric patients</li> </ul>
CT-P13	<sup>67</sup>	Paediatric Crohn's disease	32	<ul style="list-style-type: none"> <li>• Six patients had been previously treated with a biologic: infliximab (5) or adalimumab (1).</li> <li>• Mean number of originator INF infusions before the switch to biosimilar was 9.9 (median 8.0; range 4-29)</li> <li>• The occurrence of sporadic mild adverse events did not differ significantly when were measured before and after switching</li> </ul>
CT-P13	<sup>68</sup>	Ulcerative colitis (UC) or Crohn's disease (CD)	17	<ul style="list-style-type: none"> <li>• Twelve patients in maintenance with originator were switched to CT-P13</li> <li>• Eleven patients experienced no ADR or loss of response during study period</li> <li>• Disease flare-up was observed in 1 CD patient</li> <li>• Mean number of CT-P13 administrations was 4.2+/-1.9.</li> </ul>

Agent	Reference	Indication(s)	Number of Patients	Comments
Inflectra	<sup>59</sup>	Inflammatory Bowel Disease	36  14 Inflectra (January to July 2014)  22 Remicade (Dec 2011 to Dec 2013)	<ul style="list-style-type: none"> <li>• 29% of patients in Inflectra group required surgery versus 0% in the infliximab group (p= 0.02)</li> <li>• 80% of the Inflectra group required hospital readmission versus 5% of the infliximab (remicade) group. (p=0.00004).</li> <li>• 60% of patients in the Inflectra group needed steroid augmentation of standard steroid tapering protocol with 50% requiring multiple increases in steroid dose versus 8% of patients in the Infliximab (p-value = 0.0007)</li> <li>• Over the course of 8 weeks, 93% of patients in the Inflectra group had an increase in CRP with 7% remaining unchanged whereas 100% of patients in the infliximab group had a decrease in CRP (p=&lt;0.001)</li> <li>• Our results suggest that biosimilars may not be as efficacious as the reference medicine.</li> <li>• The results found reflect the ECCO statement position that the use of most biosimilars in IBD will require testing in this particular patient population [3] and cannot be extrapolated from other disease populations.</li> </ul>

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

### **Prescribers**

Six studies have sought to investigate the attitudes of prescribers to biosimilar medicines. These manuscripts have used a variety of methodologies including anonymous surveys through to focus groups.

- ❖ Hallersten *et al*, 2016: *Physicians prefer greater detail in the biosimilar label (SmPC) - Results of a survey across seven European countries*<sup>69</sup>

The European Associations for Bioindustries (EuropaBio) commissioned a survey of 210 physicians across 7 European countries, examining preferences on biosimilar label information, and information sources when prescribing biologic agents. Data from this study indicated that the Summary of Product Characteristics (SmPC) is a frequently used information source for 55% of surveyed physicians, particularly when prescribing the medicine for the first time. When presented with modified SmPC documents incorporating additional information with respect to pharmacodynamic properties, posology and method of administration and undesirable effects, in all cases the majority (approximately 4 out of 5) physicians preferred to be provided with the additional information. However, it remains unclear how the inclusion of this additional information is likely to affect decisions regarding the use of biosimilars.

- ❖ Dolinar *et al*, 2014: *Biosimilars naming, label transparency and authority of choice – survey findings among European physicians*<sup>18</sup>

This study, conducted in 2013 by The Alliance for Safe Biologic Medicines, recruited 470 prescribers from France, Germany, Italy, Spain and the UK with clinical experience in the use of biologicals and assessed biosimilar knowledge and awareness using a 15-minute web-based survey. Respondents were from the specialties of nephrology, rheumatology, dermatology, neurology, endocrinology and oncology. Approximately half (54%) of respondents that they were “familiar with a basic understanding” of biosimilar medicines, whilst 20% were unable to define biosimilars and 4% had never heard of them. Thirty-seven percent of respondents believed that all indications for which a biosimilar has been approved have undergone clinical testing. With regard to pharmacist substitution, 62% of respondents considered that it was not acceptable for the pharmacist to decide which biological (originator or biosimilar) to dispense, 35% considered it acceptable and 3% considered it totally acceptable.

- ❖ Molinari *et al*, 2016: *Global survey of physicians’ attitudes toward biologic and biosimilar therapies*<sup>70</sup>

This conference abstract which was published in conjunction with, but not presented at, the 2016 American Society of Clinical Oncology Annual Meeting (June 3-7) describes the results of an online survey of physicians attitudes toward and understanding of biologics and biosimilars. A total of 1245 physicians from various practice settings in the US, Latin America (Colombia, Mexico, Brazil, and Argentina), and Europe (Italy, France, Germany, UK, and Spain) completed the survey.

These physicians represent a diverse range of specialties including oncology, rheumatology, neurology, dermatology, nephrology, and endocrinology. When asked about substitution of biosimilars by the pharmacist 80% of US, 87% of Latin American, and 77% of European physicians believed that it was critically or very important for the prescriber to be notified. With regards to switching, those from the US were 45% and 64% more likely than Latin American and European physicians, respectively, to believe that switching is likely to result in the same result. The authors conclude that particularly within physicians from the US there is a “lack technical knowledge and understanding about the effects of biologics and biosimilars sharing the same non-proprietary name” and that “educational initiatives should aim to dispel the misconception that biologics and biosimilars are structurally and therapeutically identical, and to promote a better understanding of their differences”.

### **Gastroenterologists**

Two studies have investigated the attitude of gastroenterologists toward biosimilars. This is a particularly important group of as they are somewhat unique amongst the potential prescriber biosimilars at present for the following reasons:

1. They prescribe the most complex biologic structure to have received biosimilar registration; the monoclonal antibody infliximab is significantly more complex than epoetin or filgrastim
2. The biological effects of the treatment cannot be measured as a marker of treatment response; haematocrit and white cell counts provide clear response outcomes for epoetin and filgrastim but no such measure exists for inflammatory bowel disease
3. They are reliant upon extrapolation of indication; the phase III biosimilar infliximab studies were conducted in rheumatoid arthritis and ankylosing spondylitis and not inflammatory bowel disease and there are differences in the mechanism of action of the drug between these indications.

#### ❖ *Baji et al, 2016: Treatment preferences of originator versus biosimilar drugs in Crohns disease; Discrete choice experiment among gastroenterologists*<sup>71</sup>

A discrete choice experiment was performed in a group of 51 Hungarian gastroenterologists. The study was conducted in May 2014 to explore preferences of gastroenterologists for biosimilar drugs in Crohn’s disease. In this study, 65% of respondents were specialists from inflammatory bowel disease centres that administer biologics and as such represents was considered to represent a significant proportion of the specialists prescribing the biologicals for this indication in Hungary, estimated to be in the order of 50–60 doctors. When interpreting these results of this study it is important that they are considered within the regulatory context within Hungary which requires that patients initiating treatment must receive the biosimilar in order to receive reimbursement and that whilst “mandatory switching” is not recommended those who relapse greater than 12 months after last receiving infliximab should also receive biosimilar in order to be eligible for reimbursement.

In this study clinicians were faced with seven hypothetical choice sets of two treatment options and asked to choose the one they prefer. All choice sets contained an originator treatment option, under the reimbursement conditions at that time, and an alternative biosimilar option in which a variety of reimbursement conditions were offered. The responses provided indicated that in cases

where the patient had already started treatment, the current therapy product, either originator or biosimilar, was considered to be the most important determinant of choice by the prescriber. In contrast, in the case of biological-naïve patients the availability of continuous medicine supply was considered to be the most important determinant of product choice.

Within this group, ten clinicians (20%) indicated having absolutely no concerns with using biosimilars in Crohn's disease, whilst thirty-three (65%) clinicians indicated some concerns about using biosimilars in Crohn's disease. Of those that expressed concern, two had concerns about efficacy, seven had concerns about safety and 21 had concerns both with efficacy and safety. At the time of this study, six (12%) clinicians indicated that they did not support the use of biosimilars in Crohn's disease at all on the basis of a lack of evidence from randomised controlled trials for this indication.

❖ Danese *et al*, 2014: *Viewpoint: Knowledge and viewpoints on biosimilar monoclonal antibodies among members of the European Crohn's and Colitis Organization*<sup>72</sup>

In late 2013 a 15-question multiple choice anonymous web survey of members of the European Crohn's and Colitis Organisation (ECCO) was conducted to evaluate the awareness of biosimilar monoclonal antibodies amongst inflammatory bowel disease specialists and to assess their readiness to use these agents. A total of 307 inflammatory bowel disease specialists responded to the survey. Of these, 87% were experienced in the use of biologicals having prescribed them autonomously for a period of greater than two years. The majority of respondents (70%) were aware that a biosimilar is a similar copy, but not considered "equal" to the originator. However, 19% responded that a biosimilar is identical to the originator. A further 8% were of the understanding that the term biosimilar refers to drugs within a therapeutic class (e.g. within the anti-TNF agents adalimumab would be considered a biosimilar with infliximab). Only 6% of responders thought that the originator and biosimilar monoclonal antibody were interchangeable; however, 28% would consider replacing the originator with a biosimilar.

With respect to the potential problems associated with the use of biosimilars, 67% of responders considered potential differences in immunogenicity to be the most significant issue. Only 6% of respondents stated that there are no additional issues. 62% agreed that monoclonal antibodies are more complex than other biologics and therefore there is a greater risk that they are not "similar enough". This belief is further reflected by the 65% that consider well-designed clinical trials, with validated endpoints, in each medical specialty are required. Further, 54% respondents noted a requirement for more accurate post-marketing pharmacovigilance and 67% agreed that biosimilars should carry distinct INN to aid traceability.

Most responders considered cost-sparing (89%) to be the major advantage of biosimilars with 50% agreeing that biosimilars had the potential to significantly reduce costs. However, 27% of respondents expected that biosimilars would only have a marginal impact on cost whilst 6% expected that the additional costs associated with matters such as regulation and pharmacovigilance could offset any potential savings. 16% conceded they did not know what the cost implications might be.

When the respondents were presented with the scenario of an inflammatory bowel disease patient that was in prolonged remission under treatment with an originator monoclonal antibody, 63% indicated that they disagreed with switching the patient to the biosimilar on the basis of a lack of

disease-specific evidence of interchangeability whilst 22% agreed with the switch. Those who agreed with the switch stated that they would provide detailed information to their patient regarding the limited data on the safety of the biosimilar.

When asked about automatic substitution by a pharmacist, 64% of respondents were against the practice but 18% would agree to such substitutions for treatment-naïve patients. It should be noted that the authors describe 64% of respondents who were against automatic substitution as “an overwhelming majority” perhaps suggesting a strongly held position on behalf of the authors.

When respondents were asked if they would be confident in prescribing biosimilars, 61% felt little or no confidence in using biosimilars in their everyday clinical practice, 26% felt confident enough to use biosimilars, 8% were very confident, and 5% were totally confident. Again, it should be noted that the 61% who felt little or no confidence were described as “most”.

Most responders (73%) thought that patient organisations should be involved in these processes and 40% of respondents said that there should be joint position statements by physicians and patients' associations to regulators. However, 22% believed that this was a matter for expert physicians and regulatory agencies only. Most clinicians believed that medical societies should promote information about biosimilars (66%), collaborate with health institutions on the development of rules on the use of biosimilars (78%), verify and disseminate data regarding the registration process for biosimilars (61%), develop multi-specialty practice guidelines (57%), and create multi-specialty international safety registries to monitor safety and effectiveness (81%).

The exact wording of the questions employed in this study is not provided and as such it is not possible to comment on the validity of the questions. It is possible that the questions were of a leading nature and this may have influenced the nature of the responses provided. As has been highlighted, the wording at times in this manuscript is perhaps a little stronger than the results might suggest, particular in the context of statements that are of negative nature.

❖ Danese *et al*, 2016: *Changes in biosimilar knowledge among European Crohn's Colitis Organization (ECCO) members : A updated survey*<sup>73</sup>

In a follow-up to the Danese *et al*<sup>72</sup> ECCO survey, this study examined 118 specialists' attitudes towards biosimilars after one year of availability in the EU. Within this updated publication, the questionnaire content was included as part of the supplementary material. Concerns regarding immunogenicity have decreased (27.1% in 2015 c.f. 67.1% in 2013); however, it is worth noting that the question assessing this point could be considered to be leading through the use of the wording “boost immunogenicity” rather than adopting a more neutral terminology. Additionally, there was a reduction in the proportion of respondents who held a belief that biosimilars can work differently from the originator (16.9% in 2015 c.f. 43.1% in 2013). There has been little change in the resistance towards automatic substitution by the pharmacist, with 89.8% of respondents disagreeing with the practice (compared with 84.8% in 2013). Confidence in the use of biosimilars increased with the greatest changes reported for those who were either totally confident (28.8% in 2015 c.f. 5.0% in 2013) and those who were not confident at all (9.3% in 2015 c.f. 32.3% in 2013); overall, the proportion of respondents who were at least “enough confident” in the use of biosimilars increased from 39.0% in 2013 to 80.5% in 2015.

## Rheumatologists

- ❖ Grabowski *et al*, 2015: *Attitudes towards subsequent entry biologics/biosimilars: A survey of Canadian rheumatologists*<sup>74</sup>

The objective of this study, conducted in February of 2014, was to identify gaps in knowledge and attitudes towards biosimilars among Canadian rheumatologists. The survey consisted of 29 questions in two sections. The first section captured information on basic respondent information, biologic drug prescribing practices, familiarity with biosimilars and levels of agreement regarding attitudes towards prescribing new drugs. The final section consisted of ten clinical scenario questions where respondents were asked to provide comments. For most questions, responses were captured using a 5-point Likert scale. Respondents were given the opportunity to enter free text comments after most questions, and at the end of the survey. In contrast with Danese *et al*<sup>72</sup>, the full survey questions are published. Eighty-one rheumatologists completed the survey and were included in the analysis. This represented a response rate of 22% for the 369 who were contacted. Over 45% of respondents indicated that they had been practicing for more than 20 years. At the time of the survey, the majority of respondents either strongly agreed or agreed (94%) that they were generally comfortable prescribing biologic drugs but only 31% agreed or strongly agreed that they would be comfortable prescribing a biosimilar if they were available at that time. Rheumatologists with greater than 20 years of experience were significantly more likely to be familiar with biosimilars but no significant association was found between biosimilar familiarity and attitudes towards automatic substitution, pricing considerations, or long-term safety and efficacy profiles.

When presented with the scenario of a biologic-naïve patient for whom an anti-TNF $\alpha$  biologic is indicated and where cost is not an issue, 72% of respondents were unlikely or very unlikely to offer a biosimilar as the initial therapy. Only 11% of respondents were likely or very likely to offer a biosimilar as initial therapy whilst 16% were neutral. Greater familiarity with established brand name drugs and uncertainty over the long-term safety of biosimilars were cited as reasons by those reported that they were unlikely or very unlikely to prescribe a biosimilar in this scenario. Exploring further the impact of clinical trial evidence upon perceptions and attitudes, when presented with a scenario where a phase III head-to-head trial had demonstrated similar safety and efficacy at 30 weeks, 49% of respondents were not confident in the long-term sustainability profile of the biosimilar whilst 19% were confident or very confident, and one third were neutral.

In considering indication extrapolation, when presented with a scenario relating to the treatment of patients with psoriatic arthritis or ankylosing spondylitis with a biosimilar that had demonstrated equivalent safety and efficacy in a well-designed head-to-head trial with the reference biologic in rheumatoid arthritis patients only, 54% disagreed or strongly disagreed with the use of the biosimilar for these indications whilst 14% were neutral. Thirty-two percent of respondents agreed or strongly agreed that they would be comfortable with using a biosimilar to treat the extrapolated indications.

When asked about the impact of financial considerations, 42% of respondents indicated that a 30% price reduction would be reasonable before payers mandated the use of biosimilars over brand name biologics whilst one third indicated that a  $\geq 50\%$  price reduction was more appropriate. In a scenario where the payer mandated using a biosimilar of an anti-TNF $\alpha$  biologic not typically prescribed by the respondent, half of respondents (54%) were likely or very likely to offer the biosimilar to the patient.

In considering substitution by a pharmacist without the prescribers approval, 88% of respondents expressed concern with this practice.

### **Oncologists**

- ❖ Lammers *et al*, 2014: *Barriers to the use of trastuzumab for HER2+ breast cancer and the potential impact of biosimilars: A physician survey in the united states and emerging markets*<sup>75</sup>

This survey examined access to trastuzumab and identified potential barriers to its use in the US, Mexico, Turkey, Russia and Brazil via physician survey. Across all regions, 45% of prescribers reported that they would increase the use of HER2 antibody therapy if a lower cost biosimilar version of trastuzumab were available (US = 29%; Brazil = 53%; Mexico = 63%, Turkey = 23%, Russia = 81%). Among those who indicated that a biosimilar version would not increase their use of HER2 antibody therapy, the most common reason was cited was that they “already always use it in all the appropriate patients/situations” (overall = 35%).

### **Pharmacists**

- ❖ Fernandez-Lopez *et al*, 2015: *Assessment of pharmacists' views on biosimilar naming conventions*<sup>76</sup>

This survey, conducted in November and December of 2014, sought to assess pharmacists on their level of awareness and preferences concerning naming conventions of biosimilars. Respondents were asked to rate their familiarity with biosimilars on a level of 1 to 5, with 1 being the least familiar and 5 being the most familiar. A combined total of 93 respondents participated in the survey. Sixty-six percent of respondents identified a biosimilar familiarity level of 4 or 5. When asked about the familiarity with interchangeable biosimilars this value decreased to 50.6%. Subsequently, when asked about their confidence in substituting interchangeable biologics under different naming scenarios, pharmacists felt most comfortable with a scenario in which the originator and the biosimilar shared the same non-proprietary name, with 56 respondents (74.6%) being confident or very confident. In contrast, in a scenario with different non-proprietary names this value decreased to 19 (25.3%) respondents indicating a confidence level of 4 or 5. In a scenario in which originators and biosimilars did not share a non-proprietary name because of a prefix or suffix, 28 (37.3%) indicated a confidence level of 4 or 5. When asked whether prescriber post-dispensing notification requirements would impact upon their willingness to dispense an interchangeable biosimilar, 52.7% of respondents reported that this would not affect their likelihood to substitute, 19.4% of respondents indicated that it would make them less likely to substitute; and 23.7% were not sure how this would affect their substitution practices.

### **Patients, Caregivers and Public**

- ❖ Jacobs *et al*, 2016: *Patient attitudes and understanding about biosimilars: an international cross-sectional survey*<sup>77</sup>

This study focussed specifically upon understanding the attitude towards biosimilars of a diverse range of individuals including patients with a range of conditions in which biosimilars are currently available, or are likely to be available in the near future including autoimmune diseases and malignancies, those belonging to advocacy groups, caregivers and the general population. The results of interviews conducted with 3,198 individuals internationally is described. The study

utilised 56 close-ended and open-ended question interviews conducted online. The authors report that awareness of the term "biologic" was significantly higher in the diagnosed, advocacy and caregiver groups (45-78%) than the general population (27%;  $p < 0.05$ ) and that similarly, the awareness of biosimilars was significantly higher among respondents in the diagnosed, advocacy and caregiver group (20-30%;  $p < 0.05$ ) than the general population (6%).

The questions included in the interview are not presented. However, it is noted that the respondents expressed concern about assignment to placebo in clinical trials which in the context of biosimilar phase III clinical trials that utilise head-to-head designs raises questions as to the specific nature of the survey questions that elicited this response. The paper does, however, conclude that the results obtained indicate that "patient education programs, developed in partnership with advocacy groups should provide patients with the necessary information to make informed decisions about the use of these products".

❖ Wilkins *et al*, 2014: *Patient perspectives on biosimilar insulin*<sup>78</sup>

Examining patient perspectives on biosimilar insulin, this study surveyed 3214 patients with either type 1 or type 2 diabetes mellitus. When questioned "if in the future there was a less expensive 'generic' (sometimes called 'biosimilar') version of your insulin that your healthcare provider approved, would you switch?", approximately two-thirds of patients indicated that they would definitely use (27%) or would be likely to use (39%) a biosimilar, whereas 17% reported that they were unlikely to use or would definitely not use. The most common patients concerns raised when asked "aside from cost, what question would you ask first about a generic insulin alternative?" were around whether biosimilars had comparable efficacy and safety profiles, and associated with the design of the delivery device. This research suggests that patients are willing to consider the use of biosimilar insulin; however, efficacy, safety and drug administration concerns should be addressed.

**Table 5: Professional and Patient Organisations**

Organisation	Year	Quotations from Statement Defining Position
American College of Rheumatology <sup>79</sup>	2016	<ul style="list-style-type: none"> <li>• The collection of long-term post-marketing data for each individual biosimilar is necessary to monitor for less common but nevertheless important adverse events</li> <li>• Post-marketing surveillance studies are needed in children as well as adults, as toxicities and long-term sequelae may be different in these disparate populations</li> <li>• The decision to substitute a biosimilar product for a reference drug should only be made by the prescribing provider</li> <li>• The patient should be notified immediately when a substitution is made</li> <li>• Providers must retain the right to write “dispense as written”</li> <li>• Does not endorse switching stable patients to a different medication (including a biosimilar) of the same class for cost saving reasons without advance express consent from the prescribing provider and knowledge of the patient</li> <li>• Biosimilars must have distinct names allowing them to be distinguished from each other and their originators</li> <li>• Extrapolation of indications for biosimilars should not be routinely granted by the FDA based solely on FDA-approved indications of the originator and in the absence of safety data specific to the biosimilar agent and the patient population in question</li> <li>• FDA labels (package inserts) should clearly indicate whether a biosimilar is interchangeable with the reference (originator) biologic</li> </ul>
American Academy of Dermatology <sup>80</sup>	2012	<ul style="list-style-type: none"> <li>• Supports a prohibition on generic therapeutic and biosimilar substitution unless all of the following minimal thresholds are met: <ul style="list-style-type: none"> <li>- the biosimilar has a unique nonproprietary name to eliminate confusion</li> <li>- the biosimilar has been designated by the Food and Drug Administration as interchangeable with the prescribed biologic for the specified indicated use</li> <li>- the prescribing physician provides explicit permission to the pharmacist that a generic therapeutic or biosimilar may be used as a substitute to the original</li> <li>- the patient (or patient’s authorized representative) must be informed and educated about a generic therapeutic or biosimilar substitution at the point of sale</li> <li>- the pharmacist notifies the prescriber in writing or electronic communication within 24 hours prior to the substitution</li> <li>- upon notification of a substitution, the pharmacy and the prescribing physician are encouraged to retain a permanent record in the patient’s medical record of the generic therapeutic or biosimilar substitution</li> </ul> </li> </ul>
Canadian Association of Gastroenterologists <sup>81</sup>	2013	<ul style="list-style-type: none"> <li>• SEBs represent a potentially effective and cost saving option for the management of IBD that may serve to enhance access to biologic therapy.</li> <li>• SEBs should be regarded as stand-alone products, and should be supported by well-designed nonclinical and clinical studies in a population relevant to Canadian patients.</li> <li>• SEBs cannot be regarded as interchangeable with the RBD.</li> <li>• Prescriptions for RBDs should not be automatically substituted for less expensive SEBs by dispensing pharmacies.</li> <li>• SEBs should be supported by long-term pharmacovigilance data in a fashion similar to RBDs.</li> <li>• Companies bringing SEBs to the Canadian market should be committed to improving patient care by acquiring new scientific data beyond that which is required as a minimum to satisfy regulatory authorities and their commercial imperatives.</li> </ul>

Organisation	Year	Quotations from Statement Defining Position
European Crohn's and Colitis Organisation <sup>82</sup>	2013	<ul style="list-style-type: none"> <li>• Different biological and biosimilar medicines targeting the same molecule are neither identical in efficacy nor toxicity, even in the same clinical entity</li> <li>• A biosimilar proven effective and safe for one indication may not necessarily be effective and safe for a second indication for which the reference biological has been shown to be safe and effective</li> <li>• Specific evidence obtained in patients with IBD should be required to establish efficacy and safety for this specific indication, because experience with currently licensed biological medicines has already shown that clinical efficacy in IBD cannot be predicted by effectiveness in other indications, such as rheumatoid arthritis</li> <li>• Clinical trials should be of large enough size to detect common adverse events and powered to show equivalence with a reference biological agent, or conventional superiority</li> <li>• Post-marketing collection of data in both children and adults is necessary to confirm safety by recording less common but important potential adverse effects, as well as identifying any increase in frequency of predictable adverse events contingent on wider access to treatment</li> <li>• Any decision to substitute a product should only be made with the prescribing health care provider's specific approval and patient's knowledge</li> <li>• Names of biosimilars need clearly to differ from their reference biological medicine in order to facilitate the collection of data on safety and efficacy, which would be impossible if confusion between names will occur</li> </ul>
Polish National Consultant in Gastroenterology <sup>83</sup>	2014	<ul style="list-style-type: none"> <li>• The Polish National Consultant in Gastroenterology, in the absence of data regarding bioequivalence in patients with IBD, does not recommend replacing original biological medicine with its biosimilar analogue in the course of treatment</li> <li>• Introduction of such medicine should be done after acquiring the patient's consent</li> </ul>
National Psoriasis Foundation <sup>84</sup>	2015	<ul style="list-style-type: none"> <li>• The National Psoriasis Foundation urges that the patient-provider relationship remain at the center of all treatment planning and recommends that the following minimal thresholds are met for biosimilar substitution to occur: <ul style="list-style-type: none"> <li>- the biosimilar has been designated by the Food and Drug Administration as interchangeable with the prescribed biologic for the specified indicated use</li> <li>- the biosimilar has a unique nonproprietary name to eliminate confusion, to allow providers to accurately track the therapeutic agent in a patient's permanent record, and to allow for the collection of adverse event information</li> <li>- the biosimilar product follows the same route of administration and dosage form as the originator</li> <li>- the pharmacist notifies the prescriber in writing or electronic communication of the intention to substitute within 48 hours of the substitution</li> <li>- the prescribing physician has not indicated the patient must be treated with the prescribed biologic (via instruction to the pharmacist to dispense as written)</li> <li>- The patient (or patient's authorized representative) must be informed and educated about a biosimilar substitution at the point of sale upon notification of a substitution, the pharmacy and the prescribing physician are to retain a permanent record in the patient's medical record of the biosimilar substitution</li> </ul> </li> </ul>

Organisation	Year	Quotations from Statement Defining Position
Arthritis Foundation (USA) <sup>85</sup>	2014	<ul style="list-style-type: none"> <li>• Supports legislation that provides a pathway for biosimilar substitution and should provide the following: <ul style="list-style-type: none"> <li>- Communication to the patient upon substitution</li> <li>- Communication to the prescriber within 48 hours of the substitution</li> <li>- Retention of substitution records for a minimum of 5 years</li> <li>- Permit a physician override to substitution where patients are stable on a prescribed biologic</li> <li>- Biosimilar medications must be approved by the FDA as therapeutically equivalent and interchangeable to the original biologic</li> <li>- Biosimilar medications must have an individualized and unique name noticeably different than the reference biologic</li> </ul> </li> </ul>
Crohn's and Colitis Foundation <sup>86</sup>	Not stated	<ul style="list-style-type: none"> <li>• CCFA supports the principals: <ul style="list-style-type: none"> <li>- encourages the FDA to ensure that all biologics and biosimilars undergo thorough human testing and meet the highest safety standards. Consideration should be given to the application of the biosimilar in pediatric patients</li> <li>- When considering interchangeability with the biosimilar, provide reasonable proof that switching from the originator to the biosimilar would not incur immunogenicity or loss of response to the originator (and vice versa)</li> <li>- Risk of cross reactivity of anti-drug antibodies from the originator agent to the biosimilar must be clearly understood, defined, and listed on the label and prescribing information</li> <li>- The risk of immunogenicity should be noted on the label and in prescribing information</li> <li>- Each biosimilar should have a unique identification number, name or else use international non-proprietary names standards to eliminate patient and provider confusion</li> <li>- Records of substitution should be tracked by the pharmacist and provided upon request to the provide</li> </ul> </li> <li>• The prescribing provider should have the following rights: <ul style="list-style-type: none"> <li>- Be notified prior to the substitution of the originator agent with a biosimilar (or vice versa).</li> <li>- Be able to prevent substitution by indicating "dispense as written" or "brand medically necessary."</li> </ul> </li> <li>• When not otherwise specified in the prescription of these agents, patients, or their designated caregivers, as well as the treating providers, should be asked to provide approval for the substitution of an originator agent with a biosimilar.</li> </ul>
Arthritis Australia <sup>87</sup>	2015	<ul style="list-style-type: none"> <li>• Advice to patients: <ul style="list-style-type: none"> <li>- Talk to your rheumatologist about your biologic medication and whether a biosimilar is available and might be right for you.</li> <li>- Decide in consultation with your rheumatologist whether you should keep taking the same brand of biologic/biosimilar medicine or whether you could consider substitution.</li> <li>- If both you and your doctor decide that you need to keep taking the same brand of medication, make sure your rheumatologist ticks the 'Brand substitution not permitted' box on your script. Tell your pharmacist that you want the medication that is on the script and that you do not authorise any substitution.</li> <li>- Keep a record of the medicine you are taking and advise your rheumatologist if there is any change in the brand you receive from the pharmacy or infusion clinic. An easy way to do this is to keep the packaging of the medicine or take a photograph and show it to your rheumatologist at your next consultation.</li> </ul> </li> </ul>

Organisation	Year	Quotations from Statement Defining Position
Crohn's and Colitis Australia <sup>88</sup>	Not stated	<ul style="list-style-type: none"> <li>• Prescribers and patients both have the right to choose the brand of medicine they will receive at pharmacy level, but it is a choice that should be an informed one.</li> <li>• Talk to your treatment team about your medication, and whether a biosimilar is available as an alternative to your current biologic treatment</li> <li>• Decide in consultation with your gastroenterologist whether you should stay on your current biologic, or consider substituting it for a biosimilar</li> <li>• If you will stay on your current biologic, ensure your doctor ticks the "Brand Substitution Not Permitted" box on your script. This will ensure no substitutions happen at pharmacy level</li> <li>• Keep records of your medication, and immediately advise your treatment team if there is any change to the brand you receive from the pharmacy. This can simply be done by keeping the packaging, or taking photographs</li> </ul>
Gastroenterological Society of Australia (GESA) and Australian Inflammatory Bowel Disease Association (AIBDA) <sup>89</sup>	2015	<ul style="list-style-type: none"> <li>• GESA and AIBDA look forward to the introduction of biosimilars to the Australian market and the price competition that will ensue, enabling more efficient use of the finite health budget</li> <li>• There are, however, no data to support the safety and long-term efficacy of switching between an originator molecule and its biosimilar. Despite the proven similarity it cannot be assumed that there might not be significant and clinically relevant differences between the originator and biosimilar drugs.</li> <li>• GESA and its specialist IBD association, the Australian Inflammatory Bowel Disease Association (AIBDA) does not support the substitution of biologic agents with biosimilars, or vice versa, at the pharmacy level.</li> </ul>
Pharmaceutical Society of Australia <sup>90</sup>	2015	<ul style="list-style-type: none"> <li>• Pharmacists follow substitution principles which respect the choice of prescribers and patients.</li> <li>• PSA believes a holistic, nationally-coordinated and outcomes focussed approach is essential for a strong pharmacovigilance program</li> <li>• Pharmacists have a fundamental role in pharmacovigilance activities.</li> </ul>

Organisation	Year	Quotations from Statement Defining Position
Pharmacy Guild of Australia <sup>91</sup>	2015	<ul style="list-style-type: none"> <li>• The Pharmacy Guild of Australia supports the Australian Government’s policies that encourage the use of biosimilar medicines to contain the cost of the Pharmaceutical Benefits Scheme (PBS) and acknowledges that substitution is cost-saving to both government and patients as well as facilitating market competition.</li> <li>• The Guild believes that where a biological medicine has been ‘a’ flagged the patient should be informed of the availability of an alternative</li> <li>• The Guild accepts that the substitution of biosimilars can be a complex and developing area of clinical practice and that some prescribers and/or patients may choose not to change their medicine regimens and this choice should be respected</li> <li>• The Guild supports this principle and in cases where the prescriber wishes to have a particular brand dispensed the prescriber can tick the “Brand substitution not permitted” box.</li> <li>• The patient might also request that the prescriber tick this box after discussing their preferences or experience.</li> <li>• Where the patient requests substitution against the stated intention of the prescriber, (i.e. the ‘Brand substitution not permitted’ box on the prescription is marked), the pharmacist should either discuss the matter with the prescriber or refer the patient back to the prescriber</li> <li>• The Guild encourages pharmacies to have protocols for their staff to use when engaging with their customers to maintain consistency and avoid patient confusion in relation to biosimilars, in line with the Quality Care Pharmacy Program (QCPP) Professional Standard on Brand Substitution and the Pharmaceutical Society of Australia’s (PSA) Competency Standard for Dispensing Prescription Medicines.</li> </ul>
Patients for Biologic Safety and Access <sup>92</sup>		<ul style="list-style-type: none"> <li>• PBSA believes that prescribers and patients should have all the information necessary to make a fully informed choice about whether to use an innovative biologic or biosimilar.</li> <li>• There must be adequate information about biosimilars available to prescribers and patients in a format that allows them to make an informed choice.</li> <li>• Biosimilar labeling to include the following information: <ul style="list-style-type: none"> <li>- Statement that the product is a biosimilar.</li> <li>- Statement about whether or not the product has been approved as interchangeable with the originator.</li> <li>- Indications of approved use (and any differences from the originator).</li> <li>- Statement of any indications approved on the basis of indication extrapolation.</li> <li>- Other pertinent data derived from studies of the biosimilar that formed the basis of FDA approval of the product.</li> <li>- Adverse event information specific to the biosimilar, if any exist.</li> </ul> </li> </ul>
European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) <sup>93</sup>	2015	<ul style="list-style-type: none"> <li>• EMA approved the use of biosimilars for infliximab for all indications, including adult and paediatric IBD. The ESPGHAN paediatric IBD Porto group advocates giving high priority to performing paediatric trials with long term follow-up to support this decision. (97% agreement)</li> <li>• Treatment of a child with sustained remission on a specific medication should not be switched to a biosimilar until clinical trials in IBD are available to support the safety and efficacy of such a change. (94% agreement)</li> <li>• Post-marketing surveillance programs for efficacy, safety and immunogenicity in children with IBD should be a mandatory requirement for the marketing of biologics and biosimilars with respective indications. (100% agreement)</li> </ul>

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