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Review

Biopharmaceuticals for rheumatic diseases in Latin America, Europe, Russia, and India: Innovators, biosimilars, and intended copies

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ABSTRACT

A biosimilar is a biopharmaceutical product intended to be comparable to a previously licensed biopharmaceutical agent. The goal of such products is to increase the accessibility of biopharmaceutical therapy for rheumatoid arthritis by reducing costs. They are not like generic drugs, in that they may differ from the reference products in manufacturing, composition, and formulation. Regulatory authorities strive to ensure the absence of clinically meaningful differences between biosimilars and their reference drugs. However, small molecular differences may potentially affect pharmacodynamics (including affinity), pharmacokinetics, and immunogenicity. Intended copies are non-innovator biopharmaceutical products that, unlike biosimilars, do not have enough clinical evidence to demonstrate biosimilarity. For approval of a biosimilar, most countries require preclinical and clinical studies demonstrating comparability with the reference drug. The margin for determining equivalence or non-inferiority is determined on a case-by-case basis in each country, as there are no general criteria. The European Medicines Agency and US Food and Drug Administration have stringent regulatory processes to ensure comparability of biosimilars with their reference drugs. There are also post-marketing surveillance requirements to monitor safety. Only one biosimilar, CT-P13, has been approved for rheumatoid arthritis. However, in countries with less stringent regulation, intended copies are being commercialized and safety problems have been documented. Consequently, in such countries, there is an urgent need for appropriate regulatory processes to be established. Attempts to close the affordability gap of biopharmaceuticals should not open another gap between patients treated with an innovator drug and an intended copy.

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1. Introduction

Biopharmaceutical agents, such as tumor necrosis factor (TNF) antagonists and other immunosuppressive drugs can provide

effective control of rheumatoid arthritis (RA) symptoms in patients who do not respond to first-line therapy with conventional disease-modifying anti-rheumatic drugs (DMARDs). Biopharmaceutical agents are large-molecule medicines manufactured biologically rather than chemically, using a living cell line cultured under highly controlled conditions. Post-translational modifications (e.g. glycosylation and molecular folding) must be strictly controlled to ensure the correct conformation for the intended biological activity [1].

A biosimilar is a biopharmaceutical product intended to be comparable to a previously licensed innovator biopharmaceutical agent. Variations in post-translational modifications may be caused by changes in cell lines and/or manufacturing processes,

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resulting in products that are similar but not identical to approved “reference” agents – hence, the term “biosimilar”, rather than “bioidentical” [2]. These compounds may have minor variations that result in clinically meaningful differences in safety, purity, and potency [3]. Pharmacokinetic and pharmacodynamic studies in humans, clinical immunogenicity data, and clinical knowledge are all necessary to demonstrate similarity to the reference product [3]. Regulatory authorities in Europe and the USA strive to ensure that there are no clinically meaningful differences between a biosimilar and its reference drug. Biosimilars are unlike generics in that there may be differences in the design, manufacture, composition, and formulation versus the reference product [4]. Like generics, biosimilars are only licensed after expiration of the reference drug’s patent. However, unlike generics, substantial clinical data are required for the approval of biosimilars. Intended copies are non-innovator biopharmaceutical products that, unlike biosimilars, do not have enough evidence to demonstrate biosimilarity; these products may therefore exhibit clinically significant differences from the reference drug.

The costs of biosimilars are generally less than those of reference drugs, but because they are designed to have no clinically meaningful differences from the innovator product, they do not provide any clinical advantage [2]. Therefore, patients on innovator biopharmaceutical agents may be inappropriately switched to biosimilars for economic rather than medical reasons [4]. In some countries, this principle is written into official recommendations (e.g. the Hungarian College of Rheumatology) [5]. However, the cost of biopharmaceuticals can be a significant barrier to treatment access in developing countries [6]. Biosimilars can help address unmet medical needs by improving access [7]. In Hungary, for example, only 5% to 6% of RA patients are treated with biopharmaceutical agents compared with an EU average of 12% [5]. The annual cost of TNF antagonist treatment is approximately US \$ 10,000 to \$ 30,000 per patient [2]. The annual treatment cost for the 6000 patients in Hungary who received biopharmaceutical agents in 2011 exceeded 15 billion HUF (approximately US \$ 66,450,000, or \$ 11,000 per patient) [5].

2. Standards for biosimilars

Several patents for biopharmaceutical agents will expire over the coming years, such as rituximab (EU expiry in 2013; US expiry in 2015), infliximab (EU, 2014; US, 2018), and etanercept (EU, 2015; US, 2028) [8]. Over the same period, an increasing number of biosimilars will become available in various countries. Most countries require preclinical and clinical studies demonstrating comparability with the reference drug. Consistency is also needed between the biosimilar and reference drug with respect to amino acid sequences and high-order structures [9], as well as conformation, post-translational modifications, immunogenicity, affinity for ligand or receptor, and function [10]. In the USA, the Biologics Price Competition and Innovation (BPCI) Act documents the pathway for licensure of biosimilars [11,12]. Some reliance on the evidence supporting the reference drug is possible (indeed, it may avoid unnecessary and therefore unethical testing), although studies demonstrating the safety, purity, and potency of the biosimilar are needed [13]. Even if the product is similar to the innovator agent during all critical steps of manufacture, it cannot be labelled as similar without proper comparative clinical trials [14]. A risk-based approach to evaluating biosimilarity is advocated, analogous to the US Food and Drug Administration (FDA) approach to reducing uncertainty in clinical settings [12,15].

Equivalence or non-inferiority clinical studies are required to demonstrate similarity to the reference drug. The margin for determining equivalence or non-inferiority is determined on a case-by-case basis by each country’s regulatory agency, as there

are no general criteria (Table 1) [16–18]. In some cases, the margin is linked to the extent of reduction in efficacy that patients and their carers would be willing to accept. There is a risk associated with performing only non-inferiority trials: if the biosimilar was found to be better than the innovator (“bio-better”), a reduction in dose would probably be appropriate. Thus, demonstrating only non-inferiority could lead to patients receiving unnecessarily high doses of the “bio-better” with a likely increase in the risk of adverse events.

The number and characteristics of study subjects required for approval vary from drug to drug and from indication to indication. Study design and choice of endpoints also vary among indications. Ideally, regulatory authorities should consider long-term safety data. With RA therapies, for example, not all immunogenic adverse events are immediate [19].

Despite the requirements for comparability, small molecular differences between biosimilars and the reference drug are inevitable. Such differences are likely to relate to aspects, such as glycosylation and conformation [2], and they may potentially affect pharmacodynamics (including affinity), pharmacokinetics, and immunogenicity. Immunogenicity is a possible issue with all biopharmaceuticals, and apparently minor molecular differences can introduce clinically important immunogenicity differences [1].

After approval for one indication, biosimilars may be approved for other indications of the reference drug without substantial clinical data (called indication extrapolation). However, a drug approved for one condition may have a different adverse event profile for another condition, and the differences would likely be observed with biosimilars as with the reference drugs. Extrapolation may represent an efficient means of increasing the use of biosimilars, but it is reliant on a high degree of similarity. For example, etanercept (a soluble TNF receptor) and infliximab (an anti-TNF antibody) both act as TNF inhibitors, and both are indicated for RA. However, infliximab is also approved for treatment of inflammatory bowel disease, whereas etanercept is not effective in this condition [20]. Accurate extrapolation depends on careful selection of patient populations.

Interchangeability or substitutability is standard with small-molecule generic drugs, but there is an ongoing debate about whether pharmacies should consider biosimilars to be automatically interchangeable or substitutable with the reference drugs. Interchangeability can be demonstrated by clinical trials with a crossover design. In the USA, there are separate approval pathways for “highly similar” and “interchangeable” biosimilars, the latter being more rigorous, requiring evidence that clinical results are the same with each product in all clinical circumstances [11,13]. Before prescribing a biosimilar, rheumatologists should understand the evidence supporting its similarity to the innovator, and understand the fundamental criteria that must be met for the compound to be labelled a biosimilar product [14]. Once this has been demonstrated, interchangeable products can be substituted at any time without affecting clinical outcomes [2]. In Europe, however, the European Medicines Agency (EMA) does not have the authority to determine interchangeability. Therefore, policies on automatic substitution are determined by each individual country [9]. World Health Organization (WHO) guidelines state that the interchangeability of an innovator with a biosimilar product should be judged by physicians, not by pharmacists or administrators [16].

Biosimilars must be named in such a way that physicians can easily distinguish them from the reference drug [2]. On the other hand, assigning a different generic name to the biosimilar could cause confusion. Unclear nomenclature could lead to inaccurate reporting of adverse events, which would be particularly problematic for interchangeable biosimilars as there could be uncertainty regarding which drug the patient was actually receiving. National and international registries for biopharmaceutical products should

Table 1
Regulations for biosimilars in Latin America, Europe and India [16–18].

Country	Status	Notes
<i>Latin America</i>		
Argentina	Regulation enacted	Approval pathway is similar to the World Health Organization (WHO) system (comparative data needed at all stages), although extrapolation between indications is not permitted
Bolivia	No biosimilars regulation	
Brazil	Regulation enacted	Two-pathway system: comparability (similar to WHO system; comparative data needed at all stages) and individual development (requirement for some comparative data may be waived, e.g. phase I and phase II)
Chile	Regulation enacted	Each regulatory authority decides on the evidence required for approval. No differentiation is made between novel biopharmaceutical agents and biosimilars Regulations do not address the question of interchangeability
Colombia	Regulation drafted or in development	Approval pathway similar to WHO system (comparative data needed at all stages), although data on manufacture/chemistry needed as for a new drug
Cuba	Regulation enacted	Extrapolation between indications is possible Etanar [®] approved for use via processes used for small-molecule generic drugs
Dominican Republic	No biosimilars regulation	
Ecuador	No biosimilars regulation	
Guyana	No biosimilars regulation	
Honduras	No biosimilars regulation	
Jamaica	No biosimilars regulation	
Mexico	Regulation enacted	Data are mostly needed as for a new drug in relation to manufacturing, preclinical studies, and phase I studies Comparability data is sufficient for phase II and phase III studies (in some cases, phase III comparability data may not be required) No extrapolation is permitted between indications
Nicaragua	No biosimilars regulation	
Paraguay	No biosimilars regulation	
Suriname	No biosimilars regulation	
Uruguay	No biosimilars regulation	
Venezuela	Regulation enacted	Data are mostly needed as for a new drug, although comparability data may suffice for phase I and phase II studies Biosimilars are considered to be biopharmaceuticals and need the same documentation as biopharmaceuticals to be registered No extrapolation is permitted between indications
<i>Europe</i>		
Albania	No biosimilars regulation	
Belarus	No biosimilars regulation	
European Union (EU)	Regulation enacted	European Medicines Agency (EMA) is the first regulatory body to issue guidance for biosimilars Preclinical data are required to show comparability; pharmacokinetic and pharmacodynamic studies are also needed, as well as head-to-head clinical trials demonstrating clinical equivalence in most cases Extrapolation between indications is allowed Hungary is a member of the EU and therefore applies EU regulation to biosimilars
Hungary	Regulation enacted	
Moldova	No biosimilars regulation	
Norway	No biosimilars regulation	
Russia	Regulation drafted or in development	Formal guidelines are not in place, but EMA guidelines are followed in practice Two sets of regulations have been drafted (one by the medical community and one by the pharmaceutical industry), but they have not yet been enacted. Biosimilars are currently assessed according to regulations for small-molecule generics Draft regulations are based on the EMA guidelines but not yet finalized
Ukraine	Regulation drafted or in development	
<i>Other countries</i>		
India	Regulation enacted	

be encouraged to develop standardized terminology for clear differentiation between innovator products and biosimilars.

3. Manufacturing process for biosimilars

Molecules used for treating RA (monoclonal antibodies and soluble receptor constructs) are large, complex proteins. Their clinical profile depends on factors, such as conformational structure, immunogenicity, and interaction with target antigens, and is highly sensitive to changes not only in the sequence(s) of amino acids but also molecular folding and post-translational changes. Purity is another key consideration in the manufacture of biosimilars [21].

After biopharmaceutical agents are produced from cell lines, purification and formulation steps are required. Because biosimilars are not manufactured in exactly the same way as the reference drugs, minor molecular differences are almost inevitable.

Furthermore, manufacturing processes for all biopharmaceutical products are liable to change as improvements/efficiencies are sought [13]. Such changes can affect the drug's clinical profile and its degree of similarity to the reference drug. Both innovator products and biosimilars have been shown to exhibit variations in the nature of the molecule following adjustments in manufacturing [22]. Clinical trials may be needed to confirm that a molecule's efficacy and safety are unchanged by alterations in manufacturing. However, such investigations are expensive and the required techniques may not be available in all countries. Therefore, consortia of countries (e.g. European Union) should co-ordinate evaluation efforts wherever possible [23].

The fundamental premise of development of a biosimilar is therefore the establishment of comparability based on analytics. This can take multiple iterations in early-stage development and takes more time than is normally required of an innovator product

early in development. This process is followed by preclinical and clinical trials appropriate to document biosimilarity on all levels [7]. Ultimately, the product is defined by the manufacturing process.

4. Clinical implications of differences between biosimilars and their reference drugs

All biopharmaceuticals are immunogenic to some extent, and the degree of immunogenicity is a key determinant of their clinical profile. Immunogenicity is not unique to biosimilars [7]. Immunological reactions may be caused by impurities (e.g. endotoxins, denatured proteins) stimulating a T-cell response and B-cell activation, or by the biopharmaceutical forming insoluble aggregates that stimulate a B-cell response [24]. As discussed above, minor differences in molecular structure of the product (e.g. protein sequence, degree of glycosylation) can have significant consequences for antigenic sites or solubility, which can lead to immunogenicity-related side effects. Loss of clinical efficacy is perhaps the most frequent manifestation of immunogenicity, and has been reported with both TNF inhibitors [2] and interferon-alpha and beta [24]. In two studies comparing biosimilar and innovator infliximab, both agents were immunogenic. Levels of anti-drug antibodies (ADAs) were similar for the two studied biopharmaceuticals in both patients with ankylosing spondylitis and those with rheumatoid arthritis. The proportion of clinical responders was lower among those with ADAs [10]. It may be possible to restore efficacy by increasing the dose, but adverse effects such as anaphylaxis may result [24].

A risk of thromboembolic events has been documented with adalimumab in RA as well as psoriatic arthritis [2]. This may be attributable to the formation of adalimumab–antiadalimumab antibody immune complexes and subsequent activation of platelets, although the precise mechanism is unknown [25]. Development of ADAs has been reported with other drugs, such as infliximab [26,27], rituximab [28], and tocilizumab [29], although with tocilizumab the antibodies had no clinically meaningful effect on the dose–response relationship.

There are several other examples of immunologically mediated adverse reactions to biopharmaceuticals in RA and other settings. For example, pure red cell aplasia (PRCA) has been reported with the biosimilar erythropoietin HX575 in renal anemia [1], and with a formulation change relating to the recombinant erythropoietin Eprex® [1,24,30]. Changes in an antibody's binding affinity for the target antigen can cause a particular dose to be less efficacious (reduced affinity) or more efficacious (increased affinity). The frequency of adverse events may also increase with increasing affinity [4].

The biological function of biopharmaceuticals can of course be affected by molecular structure independent of immunogenicity. For example, glycosylation patterns during the production of encept (p55TNF-R:Ig) were found to be variable, resulting in inconsistencies in pharmacokinetics and treatment efficacy; product development was discontinued [2]. It must be acknowledged that a degree of variability exists between different batches of all biopharmaceuticals, for both innovators and biosimilars [22]. Batch consistency controls are needed as part of the manufacturing process to minimise this variability [22].

5. Regulatory status for biosimilars in rheumatic diseases

The EMA and US FDA have stringent regulatory processes to ensure comparability of biosimilars with their reference drugs [2,13,15]. Although there are differences between the EMA and FDA processes, fundamentally they both require demonstration that physicochemical properties and clinical safety and efficacy of the biosimilar are similar to the reference drug [2,12,31]. The FDA

requires evidence that there are no clinically meaningful differences in safety, purity or potency, although formulation differences are permissible [21]. Guidelines from the EMA stipulate that the safety of a biosimilar should be assessed using identical parameters as were used for the reference drug, and that at least one equivalence trial is performed with a large enough number of patients to compare frequencies of adverse events with the two products [9]. The WHO guidelines for biosimilars share the same principles as the FDA and EMA guidelines in requiring comparative data for chemistry/manufacturing, non-clinical, and clinical studies [16–18].

After initial approval, the FDA and WHO advocate approval of biosimilars for additional indications by extrapolation from the reference drug and data for the biosimilar in a primary indication [2,9,17]. However, caution is required when extrapolating between diseases (e.g. RA versus inflammatory bowel disease), particularly, if they have different etiologies (e.g. inflammation versus malignancy). It remains to be seen whether physicians will be comfortable with prescribing a medication for an indication without full phase III data [32].

Regulation of manufacturing and approval of biosimilars differs considerably among countries. Regulations are in development in some countries, such as Russia.

There is a general trend among Latin American countries (e.g. Argentina and Brazil) to follow the WHO guidelines, although Brazil has a two-pathway system (one for individual development and one for establishing comparability with an existing product) [17]. In several Latin American countries (Chile, Mexico, Venezuela), chemistry/manufacturing data are required as for a new drug. A common issue with guidelines in Latin America is that individual regulatory authorities can require different levels of evidence for the approval of a given drug [14,33].

In India, guidelines for biosimilars provide comprehensive coverage of physicochemical and biological characteristics, but they are less strict than FDA/EMA/WHO requirements [34], and only short trials are required to assess bioequivalence for licensing procedures [14]. The latest guidelines state that comparative pharmacokinetic and pharmacodynamic studies should be performed with assessment of immunogenicity [35]. However, the need for a clinical safety and efficacy study may be waived if similarity has been established preclinically and by clinical pharmacokinetic and pharmacodynamic data.

Although Eastern Asia is outside the scope of this review, it should be noted that in 2012, Korea approved CT-P13 (Remsima™), an infliximab finished product, which is the first biosimilar in rheumatology to demonstrate comparability to the innovator in a clinical study. The trial that led to this license appears to be well designed and powered to detect differences in efficacy and safety [14]. Recently, the EMA has given the product marketing authorization, but it can only be commercialized in the EU after patent expiration of infliximab in 2014 [10].

Less stringent systems in developing countries have enabled the approval of intended copies (e.g. copies of rituximab in Bolivia, Chile, India, Peru, and Mexico, and copies of etanercept in Colombia and China) [2,13,14,33]. Regulations for biosimilars are in development in Colombia, a country in which Etanar® (a “me-too” drug that is an intended copy of etanercept) was approved without clear guidelines and is already in use [33,36]. Intended copies have the potential for inferior efficacy and/or safety compared with the reference drugs [2,13,33].

6. Post-marketing surveillance/pharmacovigilance

The EMA and FDA emphasize the need for post-marketing surveillance of biosimilars to more completely characterize their safety profile [2]. However, in the absence of evidence that their safety differs from that of reference drugs in practice, it has been

Table 2
Innovators, biosimilars, and intended copies in rheumatoid arthritis [2,6,18,36].

Drug	Manufacturer/promoter	Reference molecule	Development status	Countries using the drug
<i>Innovators</i>				
Rituximab (Rituxan, MabThera)	Biogen Idec, Genentech, Hoffmann-La Roche, Chugai Pharmaceuticals	N/A	Marketed	Worldwide, including USA, Canada, EU, Japan
Etanercept (Enbrel)	Amgen, Pfizer, Wyeth, Takeda Pharmaceuticals	N/A	Marketed	Worldwide, including USA, Canada, EU, Japan
Infliximab (Remicade)	Janssen Biotech, Mitsubishi Tanabe Pharma, Xian Janssen, Schering-Plough	N/A	Marketed	Worldwide, including USA, China, EU, Japan
Adalimumab (Humira)	Abbott Laboratories	N/A	Marketed	Worldwide, including USA, Canada, EU, Japan
<i>Biosimilars</i>				
BI695501	Boehringer-Ingelheim Pharmaceuticals	Adalimumab	Phase I	N/A
TNFcept (LBEC0101)	LG Life Sciences	Etanercept	Phase I	N/A
PRX-106	Protalix Biotherapeutics	Etanercept	Preclinical	N/A
HD203	Hanwha Chemical	Etanercept	Phase III	N/A
TuNEX	Mycenax Biotech	Etanercept	Phase III	N/A
Avent	Avesthagen	Etanercept	Preclinical	N/A
TNFmab (LBAL)	LG Life Sciences	Infliximab	Preclinical	N/A
CT-P13 (Remsima)	Celltrion	Infliximab	Newly approved by EMA	N/A
TL011	Teva Pharmaceutical Industries Ltd	Rituximab	Phase II	N/A
GP2013	Sandoz Biopharmaceuticals	Rituximab	Phase II	N/A
CT-P10	Celltrion	Rituximab	Phase I	N/A
BCD-020	Biocad	Rituximab	Phase III	N/A
PF-05280586	Pfizer	Rituximab	Phase I	N/A
<i>Intended copies^a</i>				
Reditux	Dr Reddy's Laboratories	Rituximab	Marketed	Bolivia, Chile, India, and Peru
Kikuzubam	Probiomed	Rituximab	Marketed	Bolivia, Chile, Mexico, and Peru
Etanar	Shanghai CP Goujian Pharmaceutical Co	Etanercept	Marketed	Colombia
Yisaipu	Shanghai CP Goujian Pharmaceutical Co	Etanercept	Marketed	China

EU: European Union; N/A: not applicable.

^a Not subject to current European Medicines Agency/Food and Drug Administration standards for biosimilarity at time of approval.

suggested that extensive post-marketing surveillance may not be needed with all biosimilars [1].

Comparison of post-marketing surveillance data from a biosimilar with data from the reference drug may help to confirm biosimilarity. Assessment of the incidence, persistence, and time to formation of ADAs will be particularly important, as clinical trials are unlikely to provide comprehensive insight on this outcome [19]. Surveillance programs may also be valuable for detecting unexpected effects of formulation changes. For example, pharmacovigilance enabled detection of PRCA following an adjustment to the manufacturing process for recombinant erythropoietin (Eprex[®]) [1]. Clarity of product nomenclature is especially critical for accurate post-marketing surveillance [2].

7. Clinical experience

Table 2 shows a summary of innovators, biosimilars, and intended copies that are in development or in current use [2,6,18,36]. As noted above, only one biosimilar has been cleared for marketing for the treatment of RA: the EMA announced approval of CT-P13 for RA and several other indications in June 2013. Nonetheless, some intended copies are being commercialized in some countries without stringent regulatory requirements, or where regulations are not sufficiently enforced [2]. Although positive experiences have been reported with such intended copies, safety problems have also been documented. Etanar[®] has been shown to be effective in reducing disease activity score and Health Assessment Questionnaire score in a non-comparative study among RA patients, with side effects reported in 10% of cases [37]. However, there is no evidence that it is equivalent or non-inferior to the innovator product and more data are needed for a comprehensive assessment. In Mexico, the regulatory agency has issued a warning to health professionals concerning anaphylactic reactions associated with rituximab when the innovator product and its intended copy are interchanged [3,38]. Questions have also been raised about the molecular similarity of a Mexican intended copy

of interferon-beta-1b and the innovator compound [39]. The EMA recently required the makers of a copy of interferon-beta-1a to conduct clinical studies of the product for multiple sclerosis because differences between the active substance and other interferon-beta medicines prohibited comparisons with published results on the innovator product [40].

The requirements for clinical data on biosimilars represent an important topic currently under discussion. For example, it is not clear whether non-inferiority trials or equivalence trials are preferable. Criteria for determining whether a product may be classed as a biosimilar, or better or worse than the reference drug, have not generally been agreed, allowing different interpretations depending on the drug (potential variability in criteria for potency, efficacy, etc.), indication, and regulatory requirements which vary between countries. These differences introduce a risk of classifying a drug as a biosimilar despite clinically meaningful differences that physicians and patients may not accept as reasonable.

Unfortunately, there is currently a lack of high-quality, randomized, controlled trials of biosimilars for RA. A PubMed search for clinical trials with the terms biosimilar, randomised/randomized, and rheumatoid yielded only two publications at the time of writing. One was a crossover comparison of etanercept with a biosimilar TNF receptor performed in 23 male healthy volunteers, showing that the Korean criteria for bioequivalence were met [41]. The more recent study, sponsored by the South Korean company Celltrion, demonstrated in 606 patients with RA that the efficacy of CT-P13 was equivalent to that of infliximab, and that the safety profiles of the two products were similar [42]. Equivalence of CT-P13 with infliximab has also been shown in patients with ankylosing spondylitis [43].

There have been examples of safety issues with non-innovator biopharmaceuticals used for indications other than RA, including the recombinant insulin Wosulin in Chile [17] and epoetin alpha and beta in Thailand [1]. These examples, all from developing countries, may be attributable to a lack of strict regulatory processes for ensuring biosimilarity [1]. Importantly, products without clinical

evidence of biosimilarity should be considered as intended copies, as opposed to biosimilars [2]. As yet, there are no data showing the efficacy or safety of a biosimilar in patients with RA previously receiving the reference drug.

8. Conclusions

Biopharmaceuticals are key to the management of RA patients, and evidence suggests the feasibility of using biosimilars for products with expired patents. The potential cost savings are of particular significance in developing countries. However, biosimilarity needs to be demonstrated via appropriate studies, to establish a lack of impairment of safety or efficacy compared with the reference drug. Post-marketing surveillance is also needed for assurance regarding the safety of biosimilars. To ensure that these conditions are met, there is an urgent need for appropriate regulatory processes to be established in many developing countries, which would avoid the potential risks of using intended copies as opposed to biosimilars. Moreover, once implemented, regulatory processes must be enforced. The attempt to close the affordability gap of biopharmaceuticals should not open another gap between “first class” and “second class” patients treated with an innovator drug and an intended copy, respectively.

Disclosure of interest

G.C.-H. has received consultancy fees from AbbVie, Astra-Zeneca, Bayer, MSD, Novartis, Pfizer, Roche, Sanofi, Sandoz and Laboratorios Sophia.

E.M. is a research investigator for innovator and biosimilar drugs for phases I–III, and is a member of Clab-Bio.

V.F.A. is an advisory board member (biosimilars) for Pfizer, AbbVie, and Merck Serono.

M.G. has participated in advisory boards and/or received speaker honoraria from Roche Laboratories, Bristol-Myers Squibb, Pfizer, and Abbott Laboratories.

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