Chapter

Biosimilar Monoclonal Antibodies in Latin America

Paola Karp, Matías Gatto, María Victoria Batto, Sol Ferrero and Gustavo Helguera

Abstract

In the last decade, the expiration of patents protecting therapeutic monoclonal antibodies opened an opportunity for the development and approval of biosimilar versions of these drugs. The complexity of these biologic molecules required the imposition of strict regulations to establish robust comparability with the antibody of reference in physicochemical, analytical, biological and, when deemed necessary, clinical data. Accordingly, this period coincides with the updating of the requirements and guidelines for the manufacture and approval of biologics in Latin American countries by their respective regulatory agencies. Although the term "biosimilar" does not appear in the official regulatory provisions in most of the countries, it is of general use in Latin America, and several biosimilars of therapeutic monoclonal antibodies were approved based on comparative quality, nonclinical and clinical data that demonstrate similarity to a licensed biological reference registered before in a Regulatory Health Authority of reference. Here, we provide an overview of how the complexities of therapeutic monoclonal antibodies shaped the regulatory landscape of similar biologics, the current status of biosimilar monoclonal antibodies in Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, México, Paraguay, Perú and Uruguay and their potential to reduce the cost of antibody therapies in this region.

Keywords: monoclonal antibody, biosimilar, biologics, Latin America, Argentina, Brazil, Chile, Colombia, México, Perú

1. Introduction

1.1 The evolution of monoclonal antibodies to biologic medicines

Antibodies, also known as immunoglobulins, are complex glycoproteins produced by B-cells against foreign substances as part of the adaptive immune response [1, 2]. The invention of the hybridoma technology in 1975 by Köhler and Milstein allowed the production of monoclonal antibodies with a desired specificity from a unique clone of B cells [3]. In contrast to polyclonal antibodies, monoclonal antibodies are homogeneous, monospecific, and could be produced in unlimited quantities in the laboratory. Since they can be directed against almost any molecular epitope, monoclonal antibodies were early adopted as a diagnostic tool, but took more than a decade until the approval of Muromonab-CD3 (Orthoclone Okt3®), which is the first monoclonal antibody developed with the hybridoma technology commercialized for therapeutic use [4]. However, since antibodies from hybridoma technology

have only murine sequences, in human patients they exhibited limited effector function [5], were immunogenic inducing anti-mouse antibodies, and had a significantly reduced half-life [6]. Therefore, it was not until the development of recombinant monoclonal antibodies in the 1980s and 1990s that a new era of biologic therapy began, with the chimerical [7], humanized [8] and fully human antibodies [9]. Each step involved the gradual replacement of murine segments of the antibody sequence by the corresponding human sequence: in chimeric antibodies the constant region was replaced, and in humanized antibodies, the framework flanking the complementarity-determining regions and the constant region were replaced, and in human monoclonal antibodies the whole sequence is human. Further engineering allowed their customization, creating variants in valence, size, effector functions and with the conjugation of compounds for delivery to targeted cell types such as cancer.

1.2 The emergence of biosimilar antibodies and Latin America

In the last twenty years, therapeutic monoclonal antibodies have been increasingly and consistently approved and by 2021 it is estimated that 106 monoclonal antibodies would have been approved in the United States or European Union for treatment of an expanding spectrum of diseases [10]. The emergence of next-generation therapeutic monoclonal antibodies in the last decade coincides with the expiration of the patents protecting the early recombinant monoclonal antibodies [11]. The approval in 2013 of the infliximab biosimilar Remsima® [12] opened an emerging field of competition all over the world, with the development of biologic copies that exhibit equivalent quality and efficacy compared to the original antibodies. It was also an opportunity for biopharmaceutical companies in Latin America to enter this market, encouraged also by their governments. However, monoclonal antibodies post-translational modifications include different degrees of glycosylation, disulphide bridge variants, or C/N terminal modifications that are dependent on the manufacturing process [13]. Because of this structural complexity, regulatory agencies in Latin America went through profound changes in their standards in order to update the criteria for evaluation and approval of antibody biosimilars, requiring comparability analysis in safety and efficacy. Today, their requirements usually include the provision of detailed physicochemical, pharmaceutical, and biological information regarding critical quality attributes of the active principle and the manufacturing process. In addition, the comparability also requires establishing if there are variations in the type of host cell to produce of the recombinant protein, the amino acid sequence, the secondary, tertiary, and quaternary structure, interactions, post-translational modifications, the formulation, as well as impurities related to the process or storage. The challenge for their approval by regulatory agencies is reshaping the accessibility of these expensive medicines in Latin America. Here we focus our analysis on biosimilars that have been characterized in their physicochemical properties and showed evidence of quality, efficacy and safety published in the scientific literature, and will not include products known as copies or intended copies whose sponsors have failed to present sufficient evidence of their equivalence to the product of reference.

1.3 Regulation of biosimilars in Latin America

Aiming to meet the international standards for production and development of biologic medicines, since 2008, Latin American countries began joining the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and today Argentina, Brazil and Mexico are members. This organization sets standards in the international development, implementation and maintenance of harmonized Good

Manufacturing Practices (GMP) and quality systems of inspectorates of medicinal products. Only these three countries in Latin America have developed a biotechnology industry that include private companies with the capacity to manufacture biologic medicines. Meanwhile, today most countries in Latin America have approved specific regulations for the registry of biologic medicines and of similar biotherapeutic products or biosimilars. The World Health Organization uses a definition for these medicines as "biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product" [14]. As expected, each country in Latin America has adopted its own regulatory framework for the registration and approval of biosimilars.

The registration of biosimilar medicines in Argentina is controlled by the National Administration of Drugs, Foods and Medical Devices (Administración Nacional de Medicamentos Alimentos y Tecnología Médica, ANMAT). In 2011 was published provision N° 7729/2011, that "approved the requirements and guidelines for the registration of medicinal specialties of biological origin whose qualitative-quantitative composition, therapeutic indication and proposed route of administration, have precedents in other medicinal specialties of biological origin authorized and registered before this Administration or another Regulatory Health Authority (medicine biological reference or comparator), of which there is evidence of effective commercialization and sufficient characterization of its risk-benefit profile" [15]. The term "biosimilar" is not used in any of the regulatory provisions of ANMAT approved to date [16], referring to these products as "similar biological medicines".

In Brazil, the National Health Surveillance Agency (Agencia Nacional de Vigilancia Sanitaria, ANVISA) is the registry agency in charge of the approval of the biosimilars, which is regulated under the resolution RDC 55/2010 [17, 18]. Although ANVISA does not use the term "biosimilar" in its resolution, its definition is merged with the term "biological product", which is defined as the non-new or known biological medicine that contains a molecule with known biological activity, already registered in Brazil and that has gone through all manufacturing steps (formulation, filling, lyophilization, labelling, packaging, storage, quality control and release of the batch of biological product for use) [17]. The approval of these biological products will require comparability studies with a biological comparator with regard to non-clinical and clinical parameters based on quality, efficacy and safety, in order to establish that there are no detectable differences in terms of quality, efficacy and safety between the products. The biological drug of reference or innovator receives the name of "new biological medicine", and the product of reference "comparator biological product" is a biological product that has already been registered with ANVISA on the basis of a complete dossier and has already been marketed in the country.

The National Medicines Agency (Agencia Nacional de Medicamentos, ANAMED) is the regulatory agency in Chile that regulates the technical standard for sanitary registration of biotechnological products derived from recombinant DNA techniques. In their regulatory technical norm for biologic medicines, the term biosimilar is defined as "the biotechnological medicine that has been shown to be comparable in quality, safety and efficacy to the reference biotechnological product, based on its exhaustive characterization through comparability studies under equal conditions, consisting of quality studies and non-clinical and clinical studies, all of them comparative" [19, 20].

The regulatory agency responsible for the approval of biologic medicines in Colombia is the National Drug and Food Surveillance Institute (Instituto Nacional de Vigilancia de Medicamentos y Alimentos, INVIMA). In 2014, the Decree N° 1782 [21] that describes the registration pathway for biosimilars in that country was published. Even though the directive does not use the term "biosimilar", it refers to them as "similar biotherapeutic products" and established a specific regulatory system for their registry. This application requires a series of tests comparing the

attributes of quality, safety and efficacy between the biosimilar and the biologic reference medicine to demonstrate that the drug under evaluation is highly similar to the reference drug [21].

The regulation of biologic medicines in Ecuador is overseen by the Regulatory, Control and Surveillance National Agency (Agencia Nacional de Regulación, Control y Vigilancia Sanitaria, ARCSA). The Health Ministry approved in 2019 the agreement 385 that regulates the commercialization of biological medicines for human use and consumption in Ecuador, as well as to establish the general procedure for obtaining the Sanitary Registry. In this directive, the biosimilars are defined as a biological medicinal product that has been shown by the comparability exercise to be similar in terms of quality, safety and efficacy to the reference biological medicinal product [22, 23].

Mexico is another country where the term "biosimilar" is not used in their regulatory norms for approval of biologic medicines. The Federal Commission for Sanitary Risks Protection (Comisión Federal para la Protección contra Riesgos Sanitarios, COFEPRIS) is the agency in Mexico responsible for regulating the approval, manufacture and commercialization of biologic medicines. The norm NOM-257-SSA1-2014 establishes the regulatory framework for biotechnological medicines and refer to "biocomparable biotechnological medicine", as the non-innovative biotechnological medicine that proves to be comparable in terms of safety, quality and efficacy of the reference biotechnological medicine through biocomparability studies [24, 25].

The registration of biological medicines in Paraguay is regulated by the National Directorate for Sanitary Surveillance (Dirección Nacional de Vigilancia Sanitaria, DINAVISA). The Decree N° 6611 approved in 2016 established the requirements for the approval of biologic medicines and includes the definition for similar biologic medications or biosimilars [26]. In this decree, biosimilars are defined as a biological medicine product that demonstrates similarity in terms of safety, quality, efficacy and immunogenicity to the reference biological medicinal product through the comparability exercise [26].

In Peru, the General Directorate of Pharmaceuticals, Devices and Drugs (Dirección General de Medicamentos, Insumos y Drogas, DIGEMID) is the agency in charge of the regulations and norms regarding approval and certification of biologic medicines. In 2016 the Supreme Decree N° 013-2016-SA that regulates the registration of biological products, which choose the path of similarity, or similar biologic products was approved [27]. In this norm, they are defined as the biological product, which in terms of quality, safety and efficacy, is similar to a biological reference product [27].

Most of the remaining countries in Latin America do not have dedicated agencies or specific norms that regulate the approval and surveillance of biosimilars, and therefore will not be included in this analysis [25].

2. Biosimilar monoclonal antibodies approved in Latin America

Currently there are five therapeutic monoclonal antibodies registered in Latin America whose patents expired in recent years and have biosimilar versions commercialized in the region (**Figure 1**). Those are rituximab, trastuzumab, infliximab, adalimumab and bevacizumab, and only Argentina, Brazil and Colombia have at least one biosimilar version approved for each monoclonal antibody (**Figure 1**). With more than ten biosimilars approved, Argentina and Brazil are the countries in Latin America with more biosimilar monoclonal antibodies approved. Next are Colombia, Peru, Paraguay, Mexico and Chile, with 3 to 5 biosimilars of monoclonal antibodies, and the lowest adoption of biosimilars is in Ecuador, Bolivia and Uruguay

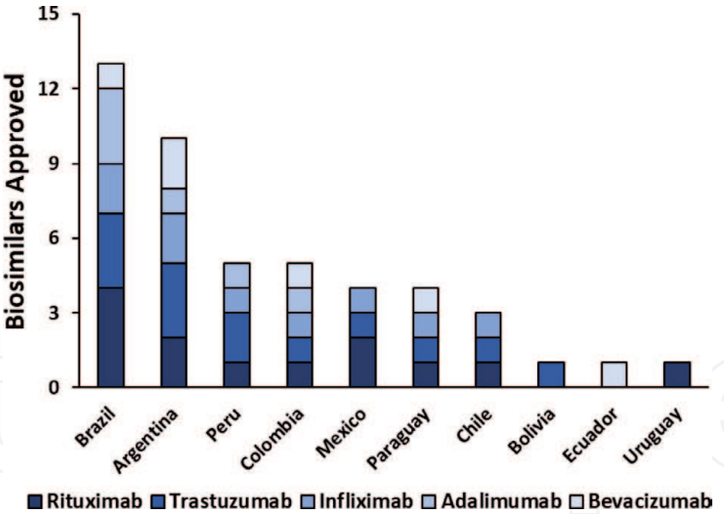

Figure 1.
Comparative plot of the number of biosimilars approved in Latin American countries.

(**Table 1** and **Figure 1**). Recent reports indicate that in Brazil the prices in U.S. dollars of original biologics, including therapeutic monoclonal antibodies, have been declining significantly in the last decade. The emergence of competition by biosimilars, with their lower prices may strengthen this trend [28]. It is expected that the approval of more biosimilar monoclonal antibodies will increase the competition, decreasing the healthcare costs and expanding the accessibility of this class of drugs.

2.1 Rituximab

Developed by Genentech in the United States, rituximab is marketed with the brand name Rituxan® (also known as MabThera®) and is currently commercialized by Roche. Rituximab is a murine/human chimeric monoclonal antibody with IgG1 / κ isotype directed against the CD20 antigen expressed by B cells used for the treatment of non-Hodgkin´s lymphoma (NHL), chronic lymphocytic leukaemia (CLL) [29], and rheumatoid arthritis [30]. Rituximab was approved by the FDA in 1997 for the treatment of B-cell Lymphomas and was the first chimeric recombinant monoclonal antibody approved against cancer. Several biosimilars of rituximab have been developed over the years, and by 2021 there are five different biosimilars of rituximab approved in Latin America, with nine different brand names commercialized in Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, Paraguay, Peru and Uruguay (**Table 1**).

2.1.1 Ruxience® (Pfizer)

PF-05280586 (Ruxience®) is a biosimilar of rituximab developed in the United States by Pfizer and commercialized in Brazil as Ruxience® by Wyeth Industria Farmaceutica. It is a monoclonal antibody used in the treatment of various types of cancer and immunological indications. In Brazil, PF-05280586 was approved with the same therapeutic indications approved for the reference rituximab.

Comparative biochemical and functional characterization were carried out to determine the level of physiochemical similarity, tryptic peptide maps were generated for both PF-05280586 and rituximab-EU and resolved by reverse-phase high-performance liquid chromatography Ryan [31]. This study proved that PF-05280586 has an identical primary amino acid sequence to rituximab. Additionally, it was demonstrated to be highly similar based on the comparison of physicochemical critical attributes, and non-clinical *in vitro* functional characteristics [31].

Non-proprietary name	Antibody name	Brand name (country)	Manufacturer (country)	Distributor (country)
Rituximab		#Rituxan® / #Mabthera®	Roche (SW)	Roche
	PF-05280586	Ruxience® (BR)	Pfizer (US)	Wyeth (BR)
	RTXM83	Novex® (AR, PA, UR) Rigetuxer® (ME)	mAbxience (AR)	Laboratorios Elea (AR) Laboratorios PISA (ME) Laboratorios Bioéticos (PA) Urufarma (UR)
		Vivaxxia® (BR)	Libbs (BR)	Libbs (BR)
	GP2013	Rixathon® (AR) Riximyo® (BR) Arasamila® (ME)	Sandoz (AU)	Novartis (AR) Sandoz (BR, ME)
	CT-P10	Truxima® (BR, CH, CO)	Celltrion (SK)	Celltrion (BR, CO) Saval (CH)
	Zytux	Zaytux® (PE)	AryoGen (IR)	PeruLab (PE)
Trastuzumab		#Herceptin®	Roche (SW)	Roche
	ABP 980	Kanjinti® (AR, PE)	Amgen (US)	Varifarma (AR, PE)
	MYL-1401O	Ogivri® (CO) Tuzepta® (AR) Zedora® (BR) Bisintex® (BO, CH, PA, PE)	Biocon (IN)	Laboratorios Raffo (AR) Libbs (BR) PharmaTech Boliviana (BO) Recalcine (CH) Mylan (CO) Pharma International (PA) Abbott (PE)
	PF-05280014	Trazimera® (AR, BR)	Pfizer (US)	Pfizer (AR) Wyeth (BR)
	CT-P6	Herzuma®(BR)	Celltrion (SK)	Celltrion (BR)
Infliximab		#Remicade®	Janssen (US)	Janssen
	CT-P13	Remsima® (AR, BR, CH, CO, EC, ME, PA) Flixceli® (PE)	Celltrion (SK)	Gobbi-Novag (AR) Celltrion (BR, CO, ME, PA) Saval (CH) Oxialfarm (EC) AC Pharma (PE)
	PF-06438179 / GP1111	Ixifi® (AR) Xilfya® (BR)	Pfizer (US)	Pfizer (AR) Wyeth (BR)
Adalimumab		#Humira® / #Trudexa®	AbbVie (US)	AbbVie
	ABP 501	Amgevita® (AR, BR, CO, PE)	Amgen (US)	Amgen (AR, BR, CO) TecnoFarma (PE)
	GP2017	Hyrimoz® (BR)	Sandoz (GE)	Sandoz (BR)
	PF-06410293	Xilbrilada® (BR)	Pfizer (US)	Wyeth (BR)
Bevacizumab		#Avastin®	Roche (SW)	Roche
	BEVZ92	Bevax® (AR, EC, PA)	mAbxience (AR)	Laboratorios Elea (AR) Grünenthal (EC) Laboratorios Bioéticos (PA)
	ABP 215	Mvasi® (AR, BR, CO)	Amgen (US)	Amgen (CO)

#Reference Monoclonal Antibodies. Countries: Argentina (AR); Austria (AU); Bolivia (BO); Brazil (BR); Chile (CH); Colombia (CO); Ecuador (EC); Germany (GE); India (IN); Iran (IR); Mexico (ME); Paraguay (PA); Peru (PE); Russia (RU); South Korea (SK); Switzerland (SW); Uruguay (UR); and United States (US).

Table 1.
Biosimilar monoclonal antibodies approved in Latin America.

In a randomized 3-way pharmacokinetic (PK) similarity study in subjects with active rheumatoid arthritis, PK equivalence was demonstrated between PF-05280586 and rituximab-EU, PF-05280586 and rituximab-US, and rituximab-EU and rituximab-US. This study also demonstrated comparable CD19-positive B cell depletion, pharmacodynamic (PD) responses, safety and immunogenicity profiles for all treatments [32–34].

A phase III study was carried out to compare the safety and effectiveness of PF-05280586 versus rituximab-EU in patients with CD20-positive, low tumour burden follicular lymphoma [35]. This study proved that the effectiveness of PF-05280586, as measured by the Overall Response Rate, is similar to that of rituximab-EU [35].

2.1.2 Novex® / Rigetuxer® / Vivaxxia® (mAbxience)

RTXM83 (Novex® / Rigetuxer® / Vivaxxia®) is a rituximab biosimilar developed in Argentina by PharmADN (today mAbxience) and is the first biosimilar therapeutic monoclonal antibody to be developed by a local biopharmaceutical company in Argentina. RTXM83 is commercialized in Argentina with the brand name Novex® by Laboratorios Elea. In Paraguay, RTXM83 is marketed as Novex® by Laboratorios Bioéticos, and in Uruguay it is also sold as Novex® by Urufarma. In Mexico, RTXM83 is commercialized with the brand name Rigetuxer ® by Laboratorios PISA. In Brazil, RTXM83 is manufactured by Libbs and marketed by the same laboratory as Vivaxxia® [36, 37].

RTXM83 is authorized for NHL with clinical trial, and by extrapolation for the following therapeutic indications to CLL, rheumatoid arthritis, adult patients with Wegener's granulomatosis (GW) and microscopic polyangelitis (PSM).

Comparability studies have shown similar physicochemical properties between RTXM83 and reference rituximab in primary sequence and disulphide bonds, N-terminal and C-terminal amino acid modifications, thermal stability, charge variants, glycosylation pattern, presence of higher order aggregates, purity, and binding affinity to the neonatal receptor and other Fc receptors [38]. Further comparability studies of biological activity *in vitro* were performed, showing similarity in tests of potency of antibody-dependent cell mediated cytotoxicity (ADCC), and binding to the molecular target CD20 [39]. In addition, in vivo studies in cynomolgus monkeys showed similarity in pharmacokinetics (PK) including area under the concentration-time curve (AUC), maximum drug concentration and pharmacodynamics (PD) including the depletion of CD20 and CD40 cells [40].

Data from the phase III clinical trial NCT02268045 in patients with diffuse large B-cell lymphoma has shown similarity comparing the PK parameters in patients treated with RTXM83 and with reference rituximab (in both cases co-administered with cyclophosphamide, doxorubicin, vincristine, and prednisone - CHOP) [41]. In addition, PD was assessed in terms of CD20-positive and CD19-positive B-cell count depletion, length of suppression and time to recovery, with similar profile observed for both treatment arms [41]. In addition, the randomized, double-blind, phase III study comparing RTXM83 versus reference rituximab, both in combination with CHOP showed no obvious differences in the safety profile in terms of nature, frequency and severity of adverse events, and in efficacy in terms of tumour response. The immunogenicity was assessed as the incidence of anti-drug antibodies, which was low and similar between RTXM83 and reference rituximab, with ≤ 4% in both arms [41].

ANMAT in Argentina has established a prospective Treatment Registry as part of its pharmacovigilance program for the detection, evaluation, understanding and prevention of adverse effects derived from the use of medicines, and in 2014, it started to collect data from patients treated with RTXM83. Physicians have sent

information to this registry between 2014 and 2017 from patients treated with RTXM83 for Follicular NHL, diffuse large B-cell NHL, CLL and off-label clinical indications [42]. This active pharmacovigilance program of RTXM83 allows the continuous monitoring of the safety profile of this biosimilar, and its 4% ICSR frequency is comparable to the safety profile of the reference product [42].

2.1.3 Rixathon®/Riximyo®/ Arasamila® (Sandoz)

GP2013 (Rixathon® /Riximyo®/ Arasamila®) is a rituximab biosimilar developed by Sandoz in Austria. GP2013 was registered in Argentina by Novartis with the brand name Rixathon®. GP2013 was registered by Sandoz in Brazil as Riximyo® and was also registered by Sandoz in Mexico with the brand name Arasamila®. It has been in clinical use for the treatment of patients with NHL, CLL, rheumatoid arthritis and other autoimmune conditions [43].

According to a physicochemical and functional comparability with the reference rituximab, GP2013 amino acid sequence and molecular mass were shown to be identical between them [44]. Furthermore, specific amino acid modifications and the glycan pattern were indistinguishable from originator rituximab [44]. The bioassays and the binding assays to measure the functionality revealed a similar result for the biosimilar and the reference antibody, especially the ADCC potency, which was tested *in vitro* and *in vivo* [44, 45]. The preclinical comparability exercise performed in cynomolgus monkeys revealed that pharmacokinetics and pharmacodynamics were comparable between GP2013 and reference rituximab [45].

A randomized double-blind clinical study was performed where patients with rheumatoid arthritis with inadequate response or intolerance to Tumor Necrosis Factor-α (TNFα) treatment received GP2013 or reference rituximab along with methotrexate and folic acid [46]. In this clinical trial, efficacy, safety and immunogenicity profiles were similar between GP2013 and originator rituximab, in addition to the equivalence showed in the pharmacokinetics and pharmacodynamics parameters [46].

Further studies of efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of GP2013 plus cyclophosphamide, vincristine and prednisone (GP2013-CVP) compared with reference rituximab were performed in a multinational, double-blind, randomized, phase III clinical trial in adults with previously untreated, advanced stage follicular lymphoma [47]. Equivalence of the global response was observed in the group with GP2013 (87%) compared with reference rituximab (88%) [47]. Based on primary and secondary efficacy outcomes, the equivalence between GP2013 and the reference rituximab in terms of overall response rate for tumour assessment, and similar complete response, partial response, stable disease and progressive disease, in patients with untreated, advanced stage follicular lymphoma was demonstrated [47].

The overall frequencies of common adverse events and serious adverse events were comparable between both treatment groups in follicular NHL (Combination and Maintenance phases) and in rheumatoid arthritis. The safety profiles including immunogenicity of GP2013 in the pivotal populations are consistent with the known safety profile of the reference medicine reported in clinical trials and post-marketing surveillance. Additionally, no safety risks were detected in patients who switched from the reference medicine to GP2013 [47].

2.1.4 Truxima® (Celltrion)

CT-P10 (Truxima®) is a biosimilar of rituximab developed by Celltrion Healthcare in South Korea. CT-P10 is commercialized with the brand name

Truxima® by Celltrion in Brazil and Colombia and by Saval in Chile. Truxima® was approved for the treatment of NHL, CLL, rheumatoid arthritis and granulomatosis with polyangiitis and microscopic polyangiitis [48, 49].

CT-P10 has shown high similarity in its primary structure, higher-order structures, post-translational modifications and biological activities [50]. Biosimilarity of CT-P10 with the reference rituximab, was achieved with a 3-way similarity assessment conducted between CT-P10, EU-rituximab and US-rituximab, focusing on the physicochemical and biological quality attributes [50]. A multitude of analyses revealed that CT-P10 has identical primary and higher order structures compared to the original product. Purity/impurity profiles of CT-P10 measured by the levels of aggregates, fragments, non-glycosylated form and process-related impurities were also found to be comparable with those of reference medicinal product [50]. In terms of the post-translational modification, CT-P10 contains slightly less N-terminal pyro-glutamate variant, which has been known not to affect product efficacy or safety. Arrays of biological assays representative of known and putative mechanisms of action for rituximab have shown that biological activities of CT-P10 are within the quality range of reference rituximab [50].

A Phase I clinical trial was conducted to evaluate the pharmacokinetics of CT-P10 and reference rituximab. Results of the study demonstrated that CT-P10 and reference rituximab were statistically equivalent after a single course of treatment at week 24. The study also found that the efficacy, pharmacodynamics, immunogenicity and safety were similar up to two courses of treatments up to 72 weeks [51]. The results of another Phase I open-label extension clinical study demonstrated that switching to CT-P10 from reference rituximab was effective with comparable safety to continuing CT-P10 for two years [52].

Phase III comparative clinical trials on CT-P10 were carried out in patients with rheumatoid arthritis, advanced follicular lymphoma and low-tumour-burden follicular lymphoma (LTBFL) [52, 53]. The results showed that treatment with CT-P10 in rheumatoid arthritis patients resulted in highly similar efficacy, PK, PD, immunogenicity and safety profiles compared to those treated with reference rituximab [52]. CT-P10 also showed to be equivalent in terms of efficacy and safety in patients with LTBFL [53].

2.1.5 Zaytux® (AryoGen)

Zaytux®/Zytux® is a biosimilar of rituximab developed by AryoGen Biopharma in Irán and distributed in Peru by Perulab. It is used for treatment of adult patients with NHL, CLL, Rheumatoid Arthritis (RA) and Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

Comparability studies revealed similar physicochemical and biological properties between Zytux and reference rituximab [54]. Similar primary structure and post-translational modification were found. In addition, comparable secondary, tertiary and quaternary structures were obtained for the rituximab originator and biosimilar, analyzed by CD spectroscopy, NMR spectroscopy, FTIR and Ion mobility MS. Small differences in mass determination studies were found in biosimilar Zytux® with regard to reference rituximab; the most relevant are the incomplete truncation of the C-terminal lysine of heavy chains and a difference of 2 Da in light chains. Data has shown high similarity of N-glycan pattern and identity of the main glycoforms [54]. Batch-to-batch comparability assessment of released N-glycans from rituximab and its biosimilar showed that their N-glycan patterns are qualitatively similar, but quantitatively heterogeneous, although they are considered acceptable changes. Surface plasmon resonance-binding studies showed that the Fc binding of Zytux and rituximab to recombinant human Fc receptor and FcRn

receptor variants exhibit similar equilibrium constant (KD) values. Additionally, comparable results were obtained from binding assays to C1q and complement-dependent cytotoxicity (CDC) assays. Furthermore, binding assays between the antibodies and CD20 were performed and they showed similar affinities [54].

Data from clinical trials in CLL and NHL patients showed comparable outcomes in terms of efficacy and safety for Zytux® and reference rituximab [55]. CLL patients were included in a double-blind, randomized study that showed non-inferior and comparable results in terms of efficacy (overall response rate and B-cell specific markers) and safety (infusion reactions, hematologic toxicity and non-hematologic toxicity). Another study carried out in 10 CLL and 10 NHL patients evaluated the safety and efficacy of Zytux® in comparison with reference rituximab [56], concluding that Zytux® was not inferior to reference rituximab, and was comparable and even better in terms of safety and efficacy.

2.2 Trastuzumab

Developed by Genentech in the United States, trastuzumab is marketed with the brand name Herceptin® and manufactured by Roche. Approved by the FDA in 1998, trastuzumab was the first humanized monoclonal antibody against cancer. It is a humanized IgG1 / κ monoclonal antibody that targets the extracellular domain of the human epidermal growth factor receptor 2 (HER2) and is used for the treatment of HER2-positive early or metastatic breast cancer [57]. In 2021, there are a total of four different trastuzumab biosimilars approved in Latin America, with seven different brand names marketed in Argentina, Brazil, Colombia and Peru (**Table 1**).

2.2.1 Kanjinti® (Amgen)

ABP 980 (Kanjinti®) is a trastuzumab biosimilar developed in the United States by Amgen. ABP 980 was approved by the FDA for all approved indications of the reference product, including the treatment of HER2-overexpressing adjuvant and metastatic breast cancer and HER2-overexpressing metastatic gastric or gastro-esophageal junction adenocarcinoma. It was registered in Argentina and Perú as Kanjinti® by Varifarma S.A.

ABP 980 was proved to have a similar physicochemical and functional properties to those of reference trastuzumab, physicochemical is similar to reference trastuzumab in terms of primary and higher order structure, carbohydrate structure, kinetic binding properties (vs. both US- and EU-sourced reference trastuzumab) and purity [58–60]. Minor differences between the two agents were not considered clinically meaningful.

In a single-dose clinical study, the pharmacokinetic similarity of ABP 980 to both US- and EU- trastuzumab was demonstrated. No differences in safety and tolerability between treatments were noted and no subject tested positive for binding antibodies [61]. Additionally, pharmacodynamic was proven to be of similar potency to that of EU-sourced reference trastuzumab in terms of proliferation inhibition and induction of ADCC [59].

In the phase III LILAC clinical study, ABP 980 demonstrated similar clinical efficacy and tolerability to that of reference trastuzumab in patients with HER2-positive early breast cancer [62, 63]. In addition, the immunogenicity and safety profiles of ABP 980 were similar to those of reference trastuzumab, and a single switch from reference trastuzumab to ABP 980 had no impact on the immunogenicity or safety of ABP 980 [62]. Switching from trastuzumab to ABP 980 had no significant impact on event-free survival and did not adversely affect its tolerability [63]. Sensitivity analyses were carried out based on central laboratory evaluation of

tumour samples; estimates for the two drugs were contained within the predefined equivalence margins, indicating similar efficacy [62]. ABP 980 and reference trastuzumab had similar safety outcomes in both the neoadjuvant and adjuvant phases of the study [62, 64].

2.2.2 Tuzepta® / Zedora®/ Ogivri®/ Bisinte ® (Biocon)

Known as MYL-1401O (Tuzepta®, Zedora®, Ogivri® and Bisintex®) this trastuzumab biosimilar was developed in India by Biocon / Mylan. It was approved by the FDA in 2017 and in the United States, it is marketed by Mylan with the brand name Ogivri®. MYL-1401O is indicated for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease. In Argentina, MYL-1401O was registered as Tuzepta® by Laboratorio Raffo; in Brazil it was registered as Zedora® by Libbs; in Colombia it was registered as Ogivri® and distributed by Mylan. In Bolivia, Chile, Paraguay and Perú is commercialized as Bisintex® and distributed by PharmaTech Boliviana in Bolivia, Recalcine in Chile, Pharma International in Paraguay and Abbott in Perú.

The totality of evidence for MYL-1401O supports its biosimilarity to reference trastuzumab based on a comparability exercise, including structural and functional analytic similarity assessments and a confirmatory clinical study [65, 66]. The comparability studies conducted for MYL-1401O and reference trastuzumab included a physicochemical stability study, where all storage conditions were tested. The results showed that there was no change in the tertiary structure of MYL-1401O as assessed by second-derivative ultraviolet and fluorescence-derived spectral analysis, and no evidence of oligomer formation or fragmentation was observed as assessed by gel exclusion chromatography and dynamic light scattering. Ion-exchange chromatography showed no significant changes in the distribution of ionic variants [67].

MYL-1401O was well tolerated and demonstrated pharmacokinetic and safety profiles similar to reference trastuzumab in healthy volunteers [68]. This was proved with a single-centre, randomized, double-blind, three-arm, parallel-group, phase I study conducted in healthy adult male volunteers who received MYL-1401O or reference trastuzumab as a 90-min intravenous infusion. The clinical study demonstrated that among women with HER2-positive metastatic breast cancer receiving taxanes, the use of MYL-1401O compared with reference trastuzumab resulted in an equivalent overall response rate at 24 weeks [66].

2.2.3 Trazimera® (Pfizer)

PF-05280014 (Trazimera®) is a trastuzumab biosimilar developed in the United States by Pfizer and approved in the European Union in 2018 [69]. It is indicated for the treatment of adult patients with HER2 positive metastatic breast and gastric cancer [70]. Trazimera® was registered in Argentina by Pfizer and in Brazil by Wyeth.

Physicochemical characterization was proved to be similar to reference trastuzumab (both EU and US sourced) in terms of primary, secondary and tertiary structures, post-translational modifications, charge variants, purity and stability [71]. No clinically significant differences between PF-05280014 and EU- and US-sourced reference trastuzumab were found following formulation changes (i.e., slight shift in total a fucosylation, terminal galactosylation and G0 species). Minor structural and functional differences between PF-05280014 and reference trastuzumab were not considered clinically relevant [71].

Pharmacodynamic properties of PF-05280014 were found to be similar to those of reference trastuzumab (both EU- and US-sourced) in terms of biological activity, including binding and functional characteristics (e.g., HER2 binding, C1q binding,

Fab- and Fc-based functions, ADCC and ADCP activities). Equivalent efficacy and similar tolerability to reference trastuzumab in metastatic HER2-positive breast cancer, and similar efficacy and tolerability to reference trastuzumab in women with early HER2-positive breast cancer were proven [69].

Several pharmacokinetic studies were carried out that proved the similarity between PF-05280014 and trastuzumab-EU in terms of pharmacokinetic activity. One of these studies was performed in a multinational, double-blind, randomized, comparative clinical trial testing of PF-05280014 versus trastuzumab-EU, where overall 702 metastatic breast cancer patients were treated with PF-05280014 and trastuzumab-EU. PF-05280014 and trastuzumab-EU had similar pharmacokinetic parameters and influential pharmacokinetic covariates in patients with HER2-positive metastatic breast cancer [72]. Finally, another randomized, double-blind study [71], compared pharmacokinetics, efficacy, safety and immunogenicity of PF-05280014 and trastuzumab reference product as neoadjuvant treatment for operable HER2-positive breast cancer. PF-05280014 demonstrated non-inferior pharmacokinetics and comparable efficacy, safety and immunogenicity to trastuzumab-EU in patients with operable HER2-positive breast cancer receiving neoadjuvant chemotherapy [71].

Further results on safety, efficacy, immunogenicity and overall survival of HER2-positive metastatic breast cancer patients were reported in a randomized, double-blind study comparing PF-05280014 with reference trastuzumab when each patient was given paclitaxel as first-line treatment [73]. The study showed no notable differences between both groups in progression-free survival or overall survival. Safety outcomes and immunogenicity were similar between the treatment groups. Additionally, when given as first-line treatment for HER2-positive metastatic breast cancer, PF-05280014 plus paclitaxel equivalence was demonstrated to trastuzumab-EU plus paclitaxel in terms of objective response rate.

2.2.4 Herzuma (Celltrion)

CT-P6 (Herzuma®) is a trastuzumab biosimilar developed in South Korea by Celltrion. CT-P6 is a HER2 receptor antagonist approved in the European Union for the treatment of HER2-overexpressing breast cancer. It was registered in Brazil by Celltrion with the brand name Herzuma®.

Comparability studies evaluating analytical similarities between CT-P6 and reference trastuzumab demonstrated that it exhibits highly similar structural and physicochemical properties, as well as ADCC and anti-proliferative activities, compared with the reference trastuzumab [74]. Regarding the glycosylation, galactosylated glycans, sialic acid and glycations, comparison between CT-P6 and the reference products trastuzumab showed that, although significant variabilities were detected in CT-P6, they were in the same range of those observed in the reference product [74].

The clinical comparability between CT-P6 and reference trastuzumab was tested in a randomized, double-blind, two-group, parallel-group, single-dose study to evaluate the pharmacokinetics, safety and immunogenicity of CT-P6 compared to reference trastuzumab in healthy subjects [75]. In this study, equivalence between conditions, with similar serum concentration in the period tested, similar safety profiles, no serious adverse events or deaths, and no subject tested positive for anti-drug antibodies was observed [75].

Further studies included a phase III, double-blind, randomized, parallel group study with active, multicentric, international and prospective control to compare the effectiveness and safety of CT-P6 and reference trastuzumab as neoadjuvant and adjuvant treatment in patients with early-stage breast cancer HER2-positive. This trial demonstrated that neoadjuvant CT-P6 had comparable efficacy to

reference trastuzumab and confirmed the similarity in safety, including comparable risk of cardiotoxicity. When used as adjuvant therapy following neoadjuvant treatment, CT-P6 demonstrated comparability to reference trastuzumab in terms of preventing progressive disease in patients with HER2-positive early-stage breast cancer [76].

Currently, CT-P6 is indicated for the treatment of patients with metastatic breast cancer who have overexpressing tumours with HER2, for the treatment of patients who have already received chemotherapy treatments for their metastatic diseases, in combination with paclitaxel or docetaxel for the treatment of patients who have not yet received chemotherapy. CT-P6 in combination with intravenous capecitabine or 5-fluorouracil (5-FU) and a platinum agent is indicated for the treatment of patients with inoperable, locally advanced, recurrent or metastatic HER2-positive adenocarcinoma of the stomach or gastroesophageal junction, who have not received prior treatment for metastatic cancer [77].

2.3 Infliximab

Infliximab was developed in the United States by Janssen Biotech, approved by the FDA in 1998 and marketed under the brand name Remicade®. It is a chimeric recombinant monoclonal antibody with IgG1 / κ isotype that targets TNFα and was the first TNFα inhibitors used to treat chronic inflammation [78]. It is used for the treatment of several conditions, including inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis and Behçet's disease. There are two infliximab biosimilars approved in Latin America, with broad distribution in the region, marketed under four different brand names in Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, Paraguay and Peru (**Table 1**).

2.3.1 Remsima® /Flixceli® (Celltrion)

CT-P13 (Remsima®/Flixceli®) is an infliximab biosimilar developed in South Korea by Celltrion. It was the first biosimilar monoclonal antibody approved by the European Union [12]. CT-P13 is indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis with clinical trials, and by extrapolation for the treatment of psoriatic arthritis and psoriasis. It is also indicated by extrapolation for adults and children older than 6 years for Crohn's disease and ulcerative colitis. In Argentina, CT-P13 was registered by Gobbi-Novag with the brand name Remsima®. In Brazil, Colombia, México and Paraguay CT-P13 was registered by Celltrion as Remsima®. In Chile, CT-P13 was registered by Saval as Remsima®. In Ecuador, CT-P13 was registered by Oxialfarm also as Remsima®. In Peru, CT-P13 is commercialized as Flixceli® and was registered by AC Pharma.

The physicochemical and biological properties of CT-P13 have been extensively characterized compared with those of the reference infliximab, demonstrating high similarity in its physicochemical properties compared to the originator [79]. Among the properties that were evaluated are primary structure and major orders of structure, type, and distribution of glycans, purities/impurities, number and distribution of charged variants, binding to the molecular target and biological potency. A similar activity has also been demonstrated in pharmacodynamics [80], where it has been shown that both have equivalent binding affinities to TNFα, and lack of binding to TNFβ and TNFα from other species. *In vitro* studies demonstrated equivalent apoptotic effects and antibody-dependent cell mediated cytotoxicity (ADCC) and CDC, as well as similar cross-reactivity in human tissue [81].

Clinical studies were carried out to demonstrate the equivalence between CT-P13 and reference infliximab in terms of PK/PD, safety and efficacy in patients with rheumatoid arthritis and active ankylosing spondylitis [80, 82]. Furthermore, clinical studies were conducted in patients with ulcerative colitis and Crohn's disease, where comparability with reference infliximab has also been seen in terms of efficacy and safety, thereby also providing evidence of interchangeability between the both [79, 83]. Further evidence of interchangeability has been seen after the change of treatment from reference infliximab to CT-P13 in patients with rheumatoid arthritis and ankylosing spondylitis, since it is well tolerated and the results are comparable in terms of efficacy, immunogenicity and safety [80, 82–84].

2.3.2 Ixifi®/Xilfya® (Pfizer)

Another infliximab biosimilar is PF-06438179/GP1111 (Ixifi® / Xilfya®), which was developed in the United States by Pfizer. PF-06438179 was approved by the FDA in 2017 as a treatment for patients with rheumatoid arthritis, Crohn's disease, paediatric Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. PF-06438179 was registered in Argentina with the brand name Ixifi® by Pfizer. In Brazil, it was registered as Xilfya® by Wieth.

Non-clinical comparability studies between PF-06438179 and reference infliximab have shown similar protein structure, with peptide map profiles superimposable and the same peptide masses, indicating identical amino acid sequences. In addition, data on post-translational modifications, biochemical properties, and biological function provided strong support for non-clinical similarity of PF-06438179 [85].

Clinical studies that compared the PK, safety and immunogenicity of PF-06438179 and reference infliximab included a single-dose intravenous administration in healthy adult patients, three-arm, double-blind, randomized (1:1:1) study with parallel groups. The PK results obtained in studies with healthy patients showed similar serum concentrations-time profiles across the treatment groups. Adverse events were similar among PF-06438179 and reference infliximab and the neutralizing and anti-drug antibody profiles were similar between groups [86].

The clinical comparability of PF-06438179 with reference infliximab was tested also in a controlled study in patients with rheumatoid arthritis with an inadequate response to methotrexate. Results show no clinically significant differences in efficacy, pharmacodynamics, immunogenicity and safety among patients receiving PF-06438179 and reference infliximab and in patients who made the transition (single exchange) from reference infliximab to PF-06438179 [87].

2.4 Adalimumab

Developed in the United States by Abbott (today AbbVie), Adalimumab (Humira®) was the first fully human monoclonal antibody approved by the FDA in 2002. Adalimumab was approved in 2003 in the European Union with the brand names Humira® and Trudexa®. It is a fully human IgG1/κ anti-tumour necrosis factor α (anti-TNFα) monoclonal antibody that prevents the interaction of TNFα with its receptors, thereby interfering with the inflammatory signalling central to chronic autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, paediatric Crohn's disease, moderate to severe chronic psoriasis and juvenile idiopathic arthritis [88]. Currently there are three adalimumab biosimilars approved in Latin America, marketed under three brand names in Argentina, Brazil and Peru (**Table 1**).

2.4.1 Amgevita® (Amgen)

ABP 501 (Amgevita®/ Amjevita®) is a biosimilar of adalimumab developed in the United States by Amgen. It was the first adalimumab biosimilar to be approved by FDA in 2016 and by EMA in 2017 [69]. It is authorized for the treatment of inflammatory diseases in adults, including moderate-to-severe rheumatoid arthritis; psoriatic arthritis; severe active ankylosing spondylitis; severe axial spondyloarthritis; chronic plaque psoriasis; hidradenitis suppurativa; non-infectious intermediate, posterior and panuveitis; Crohn's disease and ulcerative colitis. ABP 501 was registered in Argentina, Brazil and Colombia by Amgen with the brand name Amgevita®. In Peru, ABP 501 was registered by TecnoFarma also with the brand name Amgevita®.

ABP 501 is a fully human recombinant monoclonal antibody with the same amino acid sequence, pharmaceutical form, and dosage strength as reference adalimumab. It is, however, not formulated with the same excipients as adalimumab and includes different buffer components and stabilizers; because of these, several similarity studies between them had been conducted. ABP 501 has been proved to be both analytically and functionally similar to reference adalimumab [89, 90]. Results from analytical studies that evaluated identity, general properties, primary and higher-order structure, carbohydrate structure, isoelectric profile, purity and impurities, and thermal-forced degradation profiles have confirmed ABP 501 to be structurally similar to reference adalimumab [89]. In addition, results from functional characterization studies have demonstrated that ABP 501 and reference adalimumab have similar binding affinity to TNFα and comparable inhibition of TNFα activities *in vitro*. Furthermore, ABP 501 and reference adalimumab have shown comparable induction of effector functions and have also been shown to be similar to adalimumab with respect to binding to a panel of Fc receptors, including FcγRIa, FcγRIIa, FcγRIIIa (158V), FcγRIIIa (158F) and FcRn [90].

In terms of pharmacokinetics, a clinical study was conducted in healthy adults who received ABP 501 or reference adalimumab [91]. The results of the study showed that there were no meaningful differences between ABP 501 and reference adalimumab in terms of safety, efficacy and immunogenicity under the conditions of use approved for adalimumab and in accordance with the regulations and guidance for biosimilars development [91]. Phase III clinical studies have shown that ABP 501 and reference adalimumab have similar clinical efficacy, safety and immunogenicity profiles over 52 weeks of treatment in a sensitive population of immunocompetent patients with psoriasis [92]. Additionally, data from a different randomised, double-blind, phase III equivalence study in patients with moderate-to-severe rheumatoid arthritis has indicated that the clinical efficacy, safety and immunogenicity of ABP 501 is similar to that of reference adalimumab [93].

2.4.2 Hyrimoz® (Sandoz)

The adalimumab biosimilar GP2017 (Hyrimoz®) was developed in Germany by Sandoz and in 2018 was authorized in the European Union for use in patients with rheumatoid arthritis, plaque psoriasis, Crohn's disease, uveitis and ulcerative colitis and all indications for which reference adalimumab is approved [94]. GP2017 was registered in Brazil by Sandoz with the brand name Hyrimoz®.

GP2017 has been shown to exhibit similarity to reference adalimumab with respect to primary, secondary, and tertiary structures, carbohydrate structure, molecular size, charges, and impurities. Differences between GP2017 and reference adalimumab in glycosylation variants were not clinically relevant [94]. Similarity was also determined in functional activity determinations of binding to TNFα, to the human Fcγ receptor subtypes, and to FcRn. Other functional comparative

studies include CDC, ADCC, C1q, apoptosis inhibition and apoptosis induction/reverse signalling [95].

A comparability clinical study of GP2017 with reference adalimumab was performed to evaluate similarity in pharmacokinetics, safety and immunogenicity over 72 days post injection [96]. In the study, maximum serum concentration and AUC from the time of dosing extrapolated to infinity were observed within the predetermined margin of similarity between GP2017 and reference adalimumab. Most treatment emergent adverse events were mild or moderate in intensity and the determination of anti-drug antibodies was similar between groups, with 57.9% GP2017, 69.8% for EU-adalimumab and 69.5% for US-adalimumab [96].

In addition, the clinical efficacy of GP2017 compared to that of reference adalimumab was tested in a phase III randomized study in psoriasis in patients with moderate-to-severe plaque psoriasis or rheumatoid arthritis. In this study, it was shown that the tolerability, safety and immunogenicity profiles of the two agents were similar. The efficacy between groups was shown, where multiple switching between GP2017 and reference adalimumab (up to four times) had no impact on efficacy, tolerability, or immunogenicity. The role of reference adalimumab in the management of autoimmune inflammatory conditions is well established and this study provides evidence that GP2017 is an effective biosimilar alternative for patients requiring adalimumab therapy [97].

2.4.3 Xilbrilada® (Pfizer)

PF-06410293 (Abrilada®/Xilbrilada®) is a biosimilar of adalimumab developed in the United States by Pfizer and approved by the FDA in 2019, where it is marketed with the brand name Abrilada®. PF-06410293 is indicated for the treatment of patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, plaque psoriasis and juvenile idiopathic arthritis. PF-06410293 was registered in Brazil by Wyeth, where it is marketed as Xilbrilada®.

Comparative non-clinical studies between PF-06410293 and reference adalimumab were conducted and they confirmed similarity [98]. Structural analysis evaluating peptide mapping showed similar chromatographic profiles, confirming that the amino acid sequences PF-06410293 and reference adalimumab are identical. Data on post-translational modifications, biochemical properties, and biological function provided strong support for analytical similarity. Binding to TNFα was similar for PF-06410293 and reference adalimumab. In addition, *in vivo* studies in rats showed that intravenous application of PF-06410293 and reference adalimumab were well tolerated, and exhibited similar pharmacokinetics, with equivalent maximum drug concentration and AUC [98].

The clinical similarity between PF-06410293 and reference adalimumab was tested in a clinical study, double-blind, randomized, comparative, efficacy of individuals with severely active rheumatoid arthritis and with inadequate response to methotrexate. The study demonstrated therapeutic equivalence (similarity) and similar responses between treatments with PF-06410293 and reference adalimumab. The study shows the absence of clinically significant differences in efficacy, pharmacodynamics, immunogenicity and safety between individuals who received PF-06410293 or reference adalimumab. Moreover, equivalent response was observed in patients who transitioned from PF-06410293 to reference adalimumab, and those who transitioned from reference adalimumab to PF-06410293. The comparative results obtained in this study in individuals with rheumatoid arthritis on background methotrexate provide further evidence of high similarity between reference adalimumab and PF-06410293 [99].

2.5 Bevacizumab

Bevacizumab (Avastin®) is a humanized monoclonal antibody with IgG1 / κ isotype that targets the vascular-endothelial growth factor (VEGF), which in turn prevents endothelial proliferation and inhibits angiogenesis. It was developed by Genentech, receiving its first approval in the United States in 2004 by the FDA, and currently is marketed by Roche. Originally indicated in combination use with standard chemotherapy against metastatic colon cancer, it has since been approved for use in certain lung cancers, renal cancers, ovarian cancers and glioblastoma multiforme of the brain. Two biosimilars of bevacizumab are commercialized in Latin America by 2021. They are approved in Argentina, Brazil, Colombia, Ecuador and Paraguay, and traded under two brand names (**Table 1**).

2.5.1 Bevax® (mAbxience)

BEVZ92 (Bevax®) is an antibody biosimilar of bevacizumab developed in Argentina by PharmaADN (today mAbxience) and marketed by Laboratorios Elea in Argentina. It is indicated in combination with other chemotherapy and biologic agents for metastatic cancer from colon [100], and by extrapolation to adults with metastatic cancer from rectum, breast, kidney, glioblastoma, ovary, peritoneum, uterus, and non-small cell lung cancer. BEVZ92 is distributed by Grünenthal in Ecuador and distributed by Laoratorios Bioéticos in Paraguay with the brand name Bevax®.

The clinical comparability of BEVZ92 and reference bevacizumab was performed in the clinical trial NCT02069704, which was completed in June 2017. This was a multi-centre, open-label, bioequivalence study of BEVZ92 and reference bevacizumab, randomized with 2 parallel arms to compare efficacy, safety, immunogenicity and the pharmacokinetic profile of BEVZ92 and reference bevacizumab in combination with chemotherapy for metastatic colorectal cancer [100]. Patients have shown similarity in pharmacokinetics comparing the geometric mean ratio of AUC in patients treated with BEVZ92 and with reference bevacizumab [100]. In addition, the objective response, clinical benefit and progression-free survival were similar for BEVZ92 and reference bevacizumab groups. The safety profile did not show relevant differences between both study arms, with similar levels of grade 3 or 4 adverse events and serious adverse [100]. The immunogenicity assessed as the incidence of anti-drug antibodies was similar and low for both study arms. The reported results show that, when used in the same way, BEVZ92 and reference bevacizumab are highly similar in terms of PK, immunogenicity, safety and efficacy for the treatment of metastatic colorectal cancer. Romera et al. also reported that BEVZ92 was similar to reference bevacizumab in an extensive physicochemical and functional characterization, including primary structure, higher order structure, biological activity, and binding affinity to VEGF, although the data was not shown [100].

In 2016 a Treatment Registry for the pharmacovigilance of BEVZ92 was established to collect adverse drug reactions (ADRs) from patients treated with this biosimilar. Physicians have sent information to this registry from 818 patients treated with BEVZ92 between 2016 and 2018 for metastatic colorectal cancer, epithelial ovarian cancer, recurrent, metastatic or persistent cervical cancer, metastatic breast cancer, advanced non-small cell lung cancer, glioblastoma, advanced or metastatic renal cell carcinoma, and off-label clinical cancer indications [101]. Of those, 416 patients that had at least one follow-up point were included for analysis, with 44 reports filed involving 51 ADRs (23 serious). The comparison of the list of ADRs in cancer patients for BEVZ92 with those for reference bevacizumab in post-marketing surveillance studies show similarity to the reference antibody, but the relative low

number of reports emphasize the need to continue with this pharmacovigilance program to better establish the safety profile of BEVZ92 in cancer patients [101].

2.5.2 Mvasi® (Amgen)

ABP 215 (Mvasi®) is a bevacizumab biosimilar developed by Amgen in the US. It was the first biosimilar of this originator monoclonal antibody to be approved by the FDA in 2017 and by the EMA in 2018 [69]. ABP 215 is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum, metastatic breast cancer, metastatic or recurrent non-small cell lung cancer, advanced and/or metastatic renal cell cancer and epithelial ovarian, fallopian tube, primary peritoneal or cervix cancer. ABP 215 is commercialized by Amgen in Argentina, Brazil and Colombia with the brand name Mvasi®.

Analytical tests to evaluate the similarity between ABP 215 and originator bevacizumab demonstrated that both products have the same peptide sequence, and that the glycosylation profile was similar. The biological and functional activities of ABP 215 and reference bevacizumab shown similar binding and inhibition of VEGFR-2 signalling among groups. More than 20 batches of original bevacizumab and 13 batches of ABP 215 were assessed for similarity and showed that structural and purity attributes, and biological properties are highly similar between them [102].

To assess the pharmacokinetics, safety, tolerability and immunogenicity equivalence of the biosimilar ABP 215 and reference bevacizumab, a randomized, single-blind, single-dose, phase I clinical study was performed. In this trial, the maximum observed serum concentration and AUC was similar between ABP 215 and reference bevacizumab. Furthermore, the safety profiles showed no difference, with no deaths or adverse events leading to study discontinuation, and no subject was positive for binding anti-drug antibodies [61].

The clinical equivalence in terms of safety, immunogenicity and efficacy between ABP 215 and original bevacizumab was evaluated in a phase III clinical trial in patients with advanced non-squamous non-small cell lung cancer. The frequency, type, and severity of adverse events were comparable between ABP 215 and reference bevacizumab, and no patient tested positive for anti-drug neutralizing antibodies. Moreover, the clinical efficacy of ABP 215 and reference bevacizumab was similar, with 39.0 and 41.7% patient overall response respectively. The data in this clinical trial supports a clinical equivalence ABP 215 and original bevacizumab [103].

3. Conclusion

In the last decade, progress made in the regulatory pathways to register biologic medicines with very high-quality standards allowed the approval of the first generation of biosimilar monoclonal antibodies in Latin America that showed robust evidence of safety and efficacy. This process occurred in parallel with the expiration of the patents of the earlier therapeutic monoclonal antibodies. By the end of 2021, biosimilar antibodies of rituximab, trastuzumab, infliximab, adalimumab and bevacizumab are expected to be commercialized in the region with 25 different brand names. This trend is stronger in countries like Brazil and Argentina, which have more than ten different biosimilar monoclonal antibodies approved and, as is the case for trastuzumab, three different biosimilars approved competing with Herceptin®, the antibody of reference. It is expected that more approvals of highly controlled biosimilars will increase the market competition and result in a significant reduction of prices compared to the reference monoclonal antibodies, without a compromise in quality and safety.

Acknowledgements

FONCYT-IP-COVID 19 N° 929, FONCYT- PICT2018-3954, Fundación Bunge y Born, INC 2018-2020, PID 2015-0034, Fundación Williams, and Fundación René Barón funded G.H., who is a member of Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET). P.K., M.G. and S.F. were funded by CONICET Doctoral Fellowships. Varifarma S.A. has partially funded the Grant PID 2015-0034 directed by Dr. Gustavo Helguera.

Conflict of interests

Varifarma S.A. has partially funded the Grant PID 2015-0034 directed by Dr. Gustavo Helguera.

Author details

Paola Karp, Matías Gatto, María Victoria Batto, Sol Ferrero and Gustavo Helguera*
Laboratory of Pharmaceutical Biotechnology, Instituto de Biología y Medicina Experimental (IBYME-CONICET), Buenos Aires, Argentina

*Address all correspondence to: gustavoh@ibyme.conicet.gov.ar

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