

REVIEW

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Biosimilars in oncology and inflammatory diseases: current and future considerations for clinicians in Latin America

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ABSTRACT

Biological therapies have revolutionized the treatment of several cancers and systemic immune-mediated inflammatory conditions. Expiry of patents protecting a number of biologics has provided the opportunity to commercialize highly similar versions, known as biosimilars. Biosimilars are approved by regulatory agencies via an independent pathway that requires extensive head-to-head comparison with the originator product. Biosimilars have the potential to provide savings to healthcare systems and expand patient access to biologics. In Latin American countries, regulatory frameworks for biosimilar approval have been introduced in recent years, and biosimilars of monoclonal antibody and fusion protein therapies are now emerging. However, the situation in this region is complicated by the presence of “non-comparable biotherapeutics” (also known as “intended copies”), which have not been rigorously compared with the originator product. We review the considerations for clinicians in Latin American countries, focusing on monoclonal antibody biosimilars relevant to oncology, rheumatology, gastroenterology, and dermatology.

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Introduction

Biotherapeutics, or biologics, are therapeutic products manufactured using living systems. Their production typically involves genetically engineered animal, plant, or bacterial cells. Since their introduction, biologics have had a substantial impact on the clinical management of various cancers and systemic inflammatory conditions such as rheumatoid arthritis (RA), inflammatory bowel diseases (IBD), psoriasis, and psoriatic arthritis.^{1–4} However, patient access to such biologics can be limited or subject to inequity, and improving access to these highly effective treatments remains an unmet need in many countries.^{5–8} Barriers to access include treatment protocols or guidelines not permitting use; drug availability or supply chain problems; prohibitively high patient out-of-pocket expense; logistical challenges related to attending medical appointments; concerns over the safety and cost-effectiveness of treatment; reimbursement or insurance coverage issues; and, finally, time-consuming paperwork for physicians.^{5–15} As a result of access limitations, patients may be unable to benefit from potentially disease-modifying or life-prolonging treatment.

On a global level, the expiry of patents or exclusivity for a number of biologics has provided the opportunity for other manufacturers to develop highly similar follow-on products, known as “biosimilars,” “similar biotherapeutic products,” or “biocomparables,” among other terms. In recent years,

biosimilar versions of complex fusion protein and monoclonal antibody (mAb) products have been authorized, and many others are in development.¹⁶ The introduction of high-quality biosimilars has the potential to provide savings for healthcare systems and to expand access to biologics.^{5–7} Indeed, greater treatment utilization and price reductions are already evident in areas where biosimilars have been introduced.¹⁷

Biosimilars are expected to have a particularly important role in regions where healthcare resources are limited, such as Latin American and Caribbean countries.^{5–7,18–20} Latin America and the Caribbean accounts for 9% of the global population and 8.5% of global expenditure on health, whereas Europe, Canada, and the United States (US) collectively represent approximately 18% of the world’s population but account for about 75% of world health expenditures.²¹ Healthcare systems across Latin America are heterogeneous, fragmented, and segregated, with diverse, independent health-coverage schemes.^{18,22} Many of the aforementioned barriers to accessing biologics are relevant in the region.^{5–7,23} In Brazil, for example, the use of trastuzumab for the treatment of metastatic breast cancer was not reimbursed within the public health system until as recently as 2017.^{24,25} Similarly, in one survey of 212 rheumatologists from Latin America, approximately half of respondents reported that coverage for

Table 1. Examples of comparative physicochemical and biological studies conducted during the development of biosimilar infliximab CT-P13.^{34–37}

Type of analysis	Attribute assessed*	Example(s) of experimental techniques*
Physicochemical characterization	Primary structure	Amino acid analysis Peptide mapping by high-performance liquid chromatography Peptide mapping by liquid chromatography–mass spectroscopy
	Higher order structure	Fourier transform infrared spectroscopy Circular dichroism Disulfide bond structure Antibody conformational array
	Purity	Size-exclusion chromatography with high-performance liquid chromatography Size-exclusion chromatography with multi-angle static light scattering
	Glycosylation	Oligosaccharide profile analysis N-linked glycan analysis Monosaccharide analysis
	Charge isoforms	Isoelectric focusing
Biological characterization	Binding to soluble TNF	In vitro TNF-neutralization assay ELISA
	Binding to transmembrane TNF	Cell-based binding affinity assay Induction of apoptosis by reverse signaling assay
	Binding to FcRn	Surface plasmon resonance
	Binding to C1q	ELISA
	CDC activity	Cell-based assay
	Binding to various Fcγ receptors	Surface plasmon resonance
	ADCC activity	Various cell-based assays

*Listing not exhaustive.

ADCC, antibody-dependent cell-mediated cytotoxicity; C1q, complement component 1q; CDC, complement-dependent cytotoxicity; ELISA, enzyme-linked immunosorbent assay; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; TNF, tumor necrosis factor.

biologics is available for only very few (< 10%) patients within the public health system.⁸ With health a constitutional right across much of the region, patients without private health insurance may have to resort to legal action against the government in order to access standard therapies.^{20,24–26} Additionally, several biologics are reported to have higher prices in some Latin American countries than in the European Union (EU).²⁷ The availability of biosimilars of the most widely utilized biologics could play an important part in addressing such challenges.

There is, however, an unmet educational need regarding biosimilars among prescribers in the region, particularly in relation to global standards concerning the development and authorization pathways of these therapies. In a recent survey of physicians in Argentina, Brazil, Colombia, and Mexico, 88% of whom reported prescribing biologics, more than one-third of respondents did not consider themselves familiar with biosimilars.²⁸ This review thus provides an overview of the biosimilar concept, the biosimilar landscape in Latin America, and the key biosimilar mAbs and fusion proteins that are in development or have been approved globally. These biosimilars, which are likely to reach the Latin American market in the near future, are relevant to clinicians specializing in either oncology or the treatment of immune-mediated inflammatory diseases.

Biosimilarity: overview of fundamental principles

Unlike chemically derived, small-molecule generic medicines, biologics are usually large, difficult-to-characterize molecular entities that display a certain degree of microheterogeneity from batch to batch.²⁹ Given that even small differences in the manufacturing process may affect the performance of a biologic, it has been agreed that the regulatory pathway for generic medicines, which is based on bioequivalence data alone, is not appropriate for biosimilars. Importantly,

“biosimilarity” is a regulatory designation; it does not have a scientific definition. In guidance from the World Health Organization (WHO), for example, a biosimilar is defined as “a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.”³⁰ Reflecting the complexity of these products, it is crucial that the biosimilar approval processes and regulatory standards adopted by national regulatory agencies are sufficiently stringent to ensure that biosimilars meet acceptable levels of quality, safety, and efficacy.³⁰

A core principle of the regulatory frameworks for biosimilar authorization set out by the WHO and authorities such as the European Medicines Agency (EMA), Health Canada, and the US Food and Drug Administration (FDA) is that similarity between a biosimilar and its originator product must be based on a rigorous, stepwise, head-to-head comparison exercise.^{30–33} This comparison exercise is founded on an initial analytical phase to determine physicochemical and biological similarity (Table 1); the results of these studies will determine the nature and extent of the non-clinical and clinical data required, which are reduced relative to the data package required for licensing a novel biologic. Clinical studies typically include a comparative pharmacokinetics (PK) and pharmacodynamics (PD) assessment, usually followed by at least one confirmatory efficacy and safety comparison. Given that the aim of the clinical efficacy study is to confirm biosimilarity between a potential biosimilar and its originator product, these trials should be conducted in sufficiently homogeneous and sensitive populations using the most sensitive clinical endpoint to detect product-related differences.^{30,38} Reflecting the importance of the initial structural and functional assessments, licensing of a biosimilar is based on a consideration of the totality of the evidence from all stages of the comparison process.³⁰ Importantly, the dosage form and route of administration of a biosimilar must be the same as those of the originator product.³⁰

In principle, the approval of a biosimilar for indications held by the originator product but not studied during the

biosimilarity exercise, known as extrapolation, is acceptable within most biosimilar regulatory frameworks with appropriate scientific justification. Pertinent considerations include the mechanism of action of the active substance and the target receptors involved in each indication, and any differences in the safety and immunogenicity profile of the originator between indications.³⁹ Furthermore, as mentioned above, it is crucial that biosimilarity has been confirmed in a clinical test model that is deemed sensitive for detecting product-related differences; important factors include the patient population (which will determine effect size), endpoint, dosage, and time point used in the efficacy and safety comparison.⁴⁰

The regulatory framework concerning biosimilars is continuing to evolve, with regulatory authorities issuing additional guidelines or updates to existing guidance. In December 2016, for example, the FDA published additional guidance for industry on designing clinical pharmacology programs to support a determination of biosimilarity.⁴¹ This guidance covers issues such as the design, population, and dose selection for comparative PK and PD studies, and it is one of a series of guidance documents issued by the FDA as it implements the Biologics Price Competition and Innovation Act of 2009, under which the abbreviated pathway for biosimilar approval was established. The clinical pharmacology document supplements previous guidance on scientific and quality considerations in demonstrating biosimilarity to an originator product.^{31,42}

In the remainder of this review, we consider true biosimilars as biologics that have been found to be highly similar to their respective originator products based on a comprehensive, head-to-head comparison exercise aligned with that described in the WHO guidelines (Table 2).³⁰ This is important because non-originator biologics that have not met such criteria for biosimilarity are marketed in some regions, including Latin America, and are often incorrectly referred to as “biosimilars.” The International Federation of Pharmaceutical Manufacturers and Associations has proposed the term “non-comparable biotherapeutic products” to describe those biologics that are intended as “copies” of a licensed originator, have been developed without a complete comparison exercise, and have not been approved via a regulatory pathway consistent with the WHO recommendations.⁴³ Non-comparable biotherapeutics have also been referred to as “biomimics” and

“intended copies” (the term we use hereafter).⁴⁴ In some cases, these products have been licensed prior to the implementation of biosimilar guidelines, via regulatory pathways not appropriate for biologics, such as those used for generic drugs.^{43,44} Unlike biosimilars, intended copies lack clear evidence of similarity in quality, safety, and efficacy to the corresponding originator biologic.⁴³

Biosimilars in Latin America: current situation

Regulatory landscape

Manufacturers in Argentina, Cuba, and Mexico have produced biotherapeutics since the 1980s.⁴⁵ Because few Latin American countries had patent laws at that time, many of these therapies were intended copies of other biologics and were registered as generics. It has been reported that around 100 such intended copies existed at the turn of the millennium.⁴⁵ Since that time, however, countries in Latin America have begun to develop and implement regulation specific to biosimilars.

A detailed summary of the regulatory scenario concerning biosimilars in each country is outside the scope of this review and has been provided recently elsewhere.^{46,47} In brief, regulatory guidance for the evaluation of biosimilars is now in place in several Latin American countries, including Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Guatemala, Mexico, Panama, Peru, and Venezuela.^{46,48} The term “biosimilar” is not necessarily used in each case; in Mexico, for example, “biocomparables” is the official term.⁴⁹ Other countries, such as Bolivia and Paraguay, are in the process of developing or finalizing legislation.^{46–48} In general, the region is moving toward increasing standards of regulation, and the WHO guidelines have been adopted or used as a basis for guidance in several instances.^{45,50}

Despite such progress, harmonization of biosimilar regulations across the region remains a somewhat distant objective.⁴⁵ The Pan American Network for Drug Regulatory Harmonization’s Biotechnological Products Working Group, formed in 2010, recommended that the region follows WHO guidance,⁴⁵ but regulatory pathways currently remain inconsistent from country to country. Furthermore, requirements are not aligned with the WHO pathway in all cases. For example, in addition to a “complete dossier” pathway and a comparative pathway similar to the respective approval routes for novel biologics and biosimilars in other countries, regulations in Colombia describe a third, “abbreviated” comparative pathway via which a biologic can be evaluated.^{46,49,51} The abbreviated pathway has attracted substantial criticism that it deviates markedly from international norms and does not provide certainty that a product approved by this route would have an acceptable benefit–risk profile,^{46,49,52,53} although such claims have been refuted by authors in Colombia.^{54,55} In another example, although Brazilian biologic approval guidelines from the Agência Nacional de Vigilância Sanitária (ANVISA) describe a comparative pathway for the approval of biosimilars akin to that in the WHO guidance, there is a lack of clarity regarding the nature of the clinical studies that are needed.^{46,56} In a similar manner, Mexican guidance from the Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS) states that the

Table 2. Key principles outlined in World Health Organization guidelines on evaluation of biosimilars.³⁰

1. Development of a biosimilar involves a stepwise comparison exercise, beginning with a comparison of the biosimilar and originator product in terms of quality attributes
2. Licensing a product as a biosimilar is dependent on demonstrating similarity to the originator product in terms of quality, non-clinical, and clinical properties
3. The product is unlikely to qualify as a biosimilar if relevant differences are identified during the comparison exercise
4. The final product should not be referred to as a biosimilar if comparison studies with the originator product are not conducted throughout the development process
5. Biosimilars are distinct from “generic medicines”
6. Like other biotherapeutics, biosimilars require effective regulatory oversight in order to maximize their benefits and manage potential risks

Table content adapted from the WHO guidelines; see source document for full details. Note: the WHO uses the term “similar biotherapeutic products” to describe biosimilars.

assessments required will be determined on a case-by-case basis.^{46,56} Such “loopholes” could provide the potential for the approval of products that would not necessarily meet the standards for biosimilars established in other global regulatory regions.

Non-comparable biotherapeutics (intended copies)

Against this evolving regulatory background, several mAb and fusion protein products marketed in Latin America have been described as intended copies (Table 3).^{2,16,44,57} A 2016 systematic literature review found that most comparative studies reported for such intended copies were either analytical, non-clinical, or observational in nature; as such, there remains a significant dearth of published data demonstrating the safety and efficacy of these agents.¹⁶

In several cases, commentators have raised concerns or questions about the similarity of intended copies with the corresponding originator products. Tout et al, for example, highlighted that a PK analysis of the rituximab product Reditux™ yielded markedly different results than those reported separately for originator rituximab.⁵⁹ Scheinberg, meanwhile, noted that the efficacy results in an observational study of the etanercept product Etanar® were significantly different from those reported previously in the literature for the originator product.⁶⁰ Furthermore, a recent analytical assessment of seven intended copies of etanercept (among them Etanar® and Infinitam®) found that, although each copy exhibited a degree of similarity to the originator in structure and binding activity, a number of significant structural and biochemical differences were apparent.⁶¹ None of the seven products met release-specification criteria typically applied to originator etanercept across all test assays. The study’s authors noted that the potential for unanticipated clinical consequences resulting from such differences should not be overlooked.⁶¹

Studies such as these illustrate the key point that intended copies should not be considered biosimilars and that a high degree of similarity to an originator product cannot be guaranteed without a rigorous comparison exercise. The importance of this distinction is underscored by the withdrawal of the rituximab intended copy Kikuzubam® from the market in 2014, following reports of anaphylactic reactions in patients who were switched to the product from originator rituximab, or vice versa.⁵⁷ Thus far, no unexpected or significant safety concerns have been identified in association with true biosimilars approved according to robust regulatory requirements.⁶²

There have been calls for intended copy products to be re-evaluated against current regulatory criteria specific to biosimilars, and this is a significant issue facing regulators in Latin America.^{44,45} In Mexico, for example, there were 23 intended

copies, or “biolimbos,” on the market before the country’s bio-similar guidelines came into effect, and the regulator COFEPRIS has requested that the manufacturers conduct assessments to demonstrate the biosimilarity of these agents and the corresponding originator products.⁶³ The WHO has issued guidance recommending a stepwise approach to reviewing all authorized biologics and identifying those licensed on the basis of data that do not meet current regulatory expectations.⁶⁴ Further developments on this issue are awaited with interest.

Additional non-originator mAbs

We are aware of three non-originator mAb products relevant to oncology or inflammatory diseases that have been authorized in Latin American countries since 2014, without prior appraisal in a region known to have stringent biosimilar regulations. These products (BCD-020, BEVZ92, and RTX83) were considered “proposed biosimilars” in the aforementioned systematic literature review, and for each mAb there is evidence of one or more comparative clinical studies with the originator.^{16,65} However, we have not identified detailed information in the public domain concerning the basis for regulatory approval in Latin America, and gaps have been highlighted in the published literature regarding these biologics.^{16,65} Therefore, independent evaluation of these products is challenging. For example, in 2014, the rituximab product RTX83 (marketed as Novex® by Laboratorio Elea) was approved in Argentina seemingly before the primary completion of a comparative, non-inferiority, efficacy and safety trial with the originator product in diffuse large B-cell lymphoma (NCT02268045).^{46,48,66} The apparent absence of comparative clinical data at the time of marketing authorization led other authors, in a 2016 publication, to conclude that the product could not be considered a true biosimilar.⁴⁸ Efficacy, safety, PK/PD, and immunogenicity data from the clinical study were subsequently presented at a congress in December 2017⁶⁷ and were followed by the publication of a population PK analysis from the same trial.⁶⁸ Additionally, published comparative analytical, non-clinical, and PK/safety data have been identified.^{16,65}

In 2016, the same company gained authorization for a bevacizumab product (Bevax®; assumed by the current authors to have been developed under the identifier BEVZ92¹⁶) in Argentina.⁶⁹ We are unclear what supportive evidence was assessed by the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT) when granting its approval.⁷⁰ No publications on BEVZ92 were identified in the above-mentioned systematic review^{16,65}; however, the results of a comparative PK trial in patients with metastatic colorectal cancer (NCT02069704) have been published subsequently in abstract form.⁷¹ In 2017, the manufacturer of Bevax® registered a comparative PK study

Table 3. Examples of intended copy monoclonal antibody and fusion protein therapies authorized in Latin America.^{2,16,44,57,58}

Originator product	Intended copy (company)	Countries in Latin America where authorized
Etanercept	Etanar®/Etart (Shanghai CP Goujian)	Colombia/Mexico
	Infinitam® (Probiomed)	Mexico
Rituximab	Kikuzubam® (Probiomed)	Bolivia, Chile, Mexico, Peru (withdrawn in 2014)
	Reditux™ (Dr Reddy’s Laboratories)	Bolivia, Chile, Ecuador, Jamaica, Paraguay, Peru

Intended copies included are those identified in the systematic literature review by Jacobs et al.¹⁶

(NCT03293654) and a comparative efficacy and safety study (NCT03296163) for a potential bevacizumab biosimilar identified as MB02; we presume these trials are being conducted to support regulatory submissions in other localities.

Lastly, in June 2017, it was announced that the rituximab product BCD-020 had been authorized in Bolivia and Honduras under the name Usmal.⁷² To the best of our knowledge, neither Bolivia nor Honduras has yet finalized an approval pathway specific to biosimilars.^{46,50} The development program for BCD-020 encompassed comparative clinical studies in RA and lymphoma, from which data are available.^{16,65,73} According to the manufacturer, multiple physicochemical and biological studies conducted in line with EMA guidelines have also been carried out,⁷² although we are not aware that they have been published.^{16,65} Prior to its approval in Latin America, BCD-020 was authorized in a number of other markets, including Russia (as AcellBia®), Kazakhstan, Sri Lanka, and Vietnam.^{72,74}

In short, it is unclear whether regulators with well-established, stringent requirements for demonstrating biosimilarity, such as the EMA and FDA, will approve these products as biosimilars in the future.

“True” biosimilars

Reflecting the regulatory shortcomings described earlier, a 2016 position statement from representatives of the multi-stakeholder Latin American Forum on Biosimilars concluded that the only mAb marketed in the region that could, at that time, be considered a true biosimilar was CT-P13.⁴⁸ CT-P13 is an infliximab biosimilar developed by Celltrion and marketed as Remsima® and Inflectra® in 80 countries worldwide, including Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Peru, and Venezuela, among other Latin American nations.^{46,75,76} The approval of CT-P13 was based on a full comparison exercise with originator infliximab, which included head-to-head clinical trials in patients with ankylosing spondylitis and RA.^{77,78} Authorization of CT-P13 in Brazil represented the first approval of a mAb biosimilar via ANVISA’s comparative pathway.⁷⁹ Since that time, ANVISA has approved an etanercept biosimilar (SB4; Brenzys™) and a trastuzumab biosimilar (MYL-1401O; Zedora).^{80,81} As described in later sections, these products were previously authorized as biosimilars in highly regulated markets including the EU (SB4) and US (MYL-1401O), having each demonstrated biosimilarity to the respective originator product through an extensive comparison exercise.^{82,83}

Pharmacovigilance

Another key issue facing regulators in Latin America is that, although most authorities consider it essential to implement a pharmacovigilance plan following commercialization of a biosimilar,⁴⁸ few countries in the region have adequate infrastructure in place to capture the relevant information.⁸⁴ The need to improve pharmacovigilance activities, for example by training more regulatory staff and implementing better systems of data collection and analysis, has been highlighted.⁴⁵

Indeed, suboptimal surveillance processes and systems reportedly contributed to delays in the withdrawal of Kikuzubam®.²

In summary, although regulation specific to biosimilars has increased in Latin American countries in recent years, much progress remains to be made if standards, transparency, and licensing decisions are to be comparable with those in other major regulatory regions, such as Europe, Canada, Japan, and the US. In addition, pharmacovigilance programs for biosimilars represent an urgent and unmet need for most Latin American nations.

Biosimilar monoclonal antibody therapies relevant to oncology: global scenario

Among the first wave of biosimilars licensed worldwide were drugs used in supportive care in cancer, with the authorization of epoetin and filgrastim biosimilars in Europe in 2007 and 2008, respectively.⁸⁵ Similarly, the first biosimilar authorized in the US, in 2015, was a version of filgrastim.⁸⁶ However, the recent or imminent expiry of patents and exclusivity for several anti-cancer mAbs has instigated the global development of numerous biosimilars of these therapies, principally bevacizumab, rituximab, and trastuzumab.¹ Bevacizumab is an inhibitor of vascular endothelial growth factor and is indicated for the treatment of an array of tumor types, including metastatic colorectal cancer, metastatic breast cancer, non-small-cell lung cancer, and metastatic renal cell carcinoma. Rituximab targets CD20 and is used in the treatment of non-Hodgkin’s lymphoma (NHL), chronic lymphocytic leukemia, as well as RA and other conditions. Finally, trastuzumab is a mAb directed against human epidermal growth factor receptor 2 (HER2) and is licensed most notably for the treatment of HER2-overexpressing breast cancers. As shown in Table 4, numerous potential biosimilars of these agents have progressed to clinical studies and, in some cases, regulatory approval in markets known to have robust biosimilar pathways aligned with the WHO guidelines (considered for the purposes of this review as Australia, Canada, the EU, Japan, the Republic of Korea, and the US). Hence, a number of these products may reach the Latin American market in the next several years.

As noted earlier, the aim of comparative clinical studies is to detect any potentially clinically relevant differences between a potential biosimilar and the corresponding originator product.³⁰ Regulators prefer that comparative efficacy and safety studies of biosimilars are conducted using a patient population and clinical endpoint that will most sensitively detect such product-related differences. Although survival-based endpoints are preferred for demonstrating benefit in trials of new anti-cancer agents, for trials of potential anti-cancer biosimilars these endpoints are unlikely to be sufficiently sensitive for demonstrating biosimilarity with an originator product.³⁸ These factors are considered in the design of appropriate clinical trials, alongside clinician input, practical issues, and historical trials of the originator product.⁸⁸

In the case of potential biosimilars referencing bevacizumab, such considerations explain why most comparative clinical trials are being conducted in a population with previously untreated advanced non-small-cell lung cancer, a setting within which bevacizumab has a well-characterized safety and efficacy profile used in combination with paclitaxel and

Table 4. Examples of potential and authorized biosimilar monoclonal antibodies relevant to oncology.

Originator product	Biosimilar (company)	Patient population(s)* in comparative clinical studies	Primary outcome measure [†]	Authorization status
Bevacizumab	ABP 215 (Amgen)	Advanced non-squamous NSCLC	ORR	Approved in EU and US
	BCD-021 (Biocad)	Advanced non-squamous NSCLC	ORR (with PK substudy)	Approved in Russia and Sri Lanka [‡]
	BEVZ92/MB02 (mAbxience)	mCRC	PK	Approved in Argentina [‡]
		Advanced non-squamous NSCLC	ORR	
	PF-06439535 (Pfizer)	Advanced non-squamous NSCLC	ORR	
	SB8 (Samsung Bioepis)	Advanced non-squamous NSCLC	ORR	
Rituximab	BCD-020 (Biocad)	RA	ACR20	Approved in countries including Bolivia, Honduras, Kazakhstan, Russia, Sri Lanka, and Vietnam; recommended for approval in India [‡]
		CD20+ indolent NHL	CD20+ cell count, ORR	
	CT-P10 (Celltrion)	RA	PK (2 × studies)	Approved in Australia, EU and Republic of Korea; under review in US
		Advanced CD20+ FL CD20+ LTB FL	PK, ORR	
	GP2013 (Sandoz)	RA	ORR	Approved in Australia and EU; under review in US
		Advanced CD20+ FL RA	PK	
	PF-05280586 (Pfizer)	RA	AEs (switch study)	
	RTXM83 (mAbxience)	CD20+ LTB FL DLBCL	PK	Approved in Argentina [‡]
Trastuzumab	SAIT101 (Archigen Biotech)	RA	PK	
		CD20+ LTB FL HER2+ EBC	ORR	
	ABP 980 (Amgen)	HER2+ EBC	pCR	Recommended for approval in EU; under review in US
	BCD-022 (Biocad)	HER2+ MBC	ORR (with PK substudy)	Approved in Russia and Sri Lanka [‡]
	CT-P6 (Celltrion)	HER2+ MBC	PK	Approved in EU, Japan, and Republic of Korea; under review in US
		HER2+ EBC	pCR	
	MYL-14010 (Mylan)	HER2+ MBC	ORR ⁸⁷	Approved in Brazil, India, and US; under review in Australia, Canada, and EU
	PF-05280014 (Pfizer)	HER2+ MBC	ORR	
	HER2+ EBC	PK	Under review in EU and US	
	HER2+ MBC	ORR		
SB3 (Samsung Bioepis)	HER2+ EBC	pCR	Approved in EU and Republic of Korea; under review in US	

Table last updated in April 2018. Products included are those discussed in the body text or identified in the systematic literature review by Jacobs et al¹⁶ with comparative trials in patients; the products described as intended copies in Table 3 are excluded. Other biosimilars are also in development. Tabulated trials compare the biosimilar with the originator product and may be completed, ongoing, or planned (terminated trials and extension studies not included). Trial information from ClinicalTrials.gov unless noted. Authorization details predominantly from company websites.

*Biosimilars may also have undergone comparative PK studies in healthy volunteers.

[†]Note that some PK trials include efficacy endpoints as secondary outcome measures.

[‡]Yet to be evaluated in a region known to have a stringent regulatory pathway for biosimilar approval that is aligned with WHO recommendations (defined for the purposes of this review as Australia, Canada, the EU, Japan, the Republic of Korea, and the US). It is not known whether regulatory agencies in such markets will authorize these products as biosimilars.

ACR, American College of Rheumatology; AE, adverse event; DLBCL, diffuse large B-cell lymphoma; EBC, early breast cancer; EU, European Union; FL, follicular lymphoma; HER2+, human epidermal growth factor receptor 2-positive; LTB, low tumor burden; MBC, metastatic breast cancer; mCRC, metastatic colorectal cancer; NHL, non-Hodgkin's lymphoma; NSCLC, non-small-cell lung cancer; ORR, overall/objective response rate; pCR, pathological complete response; PK, pharmacokinetics; RA, rheumatoid arthritis; WHO, World Health Organization.

carboplatin. Overall/objective response rate has been chosen as the primary endpoint in most instances (Table 4), although survival outcomes are being measured as secondary endpoints in several of the trials. In September 2017, ABP 215 was licensed by the US FDA as bevacizumab-awwb, and became the first bevacizumab biosimilar to be authorized in a region with stringent biosimilarity criteria and the first US-licensed anti-cancer biosimilar.⁸⁹ The product was authorized for all

eligible indications of the originator product; hence, appropriate scientific justification was made for extrapolation. ABP 215 has since been authorized in the EU.⁹⁰

For potential rituximab biosimilars, several different approaches are evident across the clinical development programs. For example, although most manufacturers have designed clinical efficacy and safety comparisons in the setting of follicular lymphoma, diffuse large B-cell lymphoma has

also been used as a clinical test model (Table 4).⁹¹ This perhaps reflects the fact that identifying a homogenous, sensitive study population in lymphoma is not straightforward.⁹¹ Presumably in the interests of maximizing sensitivity, most of the comparative studies in follicular lymphoma are being conducted in previously untreated patients and are assessing rituximab as monotherapy, rather than in combination with chemotherapy. Although in most countries rituximab is not licensed as a single-agent therapy in the initial treatment of follicular lymphoma, a recent Phase 3 trial in this setting revealed that monotherapy with originator rituximab was effective in deferring disease progression and the introduction of chemotherapy or radiotherapy compared with watchful waiting.⁹²

Comparative PK trials of biosimilars are often conducted in healthy volunteers, but this approach is unsuitable in the case of rituximab given the potential health risks associated with B-cell depletion. PK assessments for many potential rituximab biosimilars are being carried out in patients with RA, who may represent a more homogeneous population for PK determinations than those with cancer.⁹³ Furthermore, because rituximab has multiple mechanisms of action whose relative contributions may differ between indications, and because the dose–response relationship for rituximab also varies between disease states,⁹¹ comparative data collected in both NHL and RA populations may prove helpful in scientifically justifying extrapolation across indications.

CT-P10 was the first rituximab biosimilar to be approved in a region with a strict biosimilar approval pathway, with authorizations in the EU, Republic of Korea, and Australia.^{76,94} The European Commission authorized the product for all indications of the originator product.⁹⁵ In addition to comprehensive structural and functional analyses to establish similarity between CT-P10 and the originator, the European submission included clinical data from trials conducted in both RA and advanced follicular lymphoma populations.^{96–98} It has been reported that the manufacturer aims to launch this product in various Latin American countries, including Colombia, Costa Rica, the Dominican Republic, Guatemala, and Nicaragua, during 2018.⁹⁹ A second rituximab biosimilar, GP2013, has also been approved in the EU, as well as in Australia.^{100,101}

Considering potential trastuzumab biosimilars, there are again differences in the clinical test models utilized by different manufacturers (Table 4). Some comparative efficacy and safety trials have been designed in early breast cancer, while others are being conducted in metastatic breast cancer. Approval of a trastuzumab biosimilar for use in the adjuvant setting following a trial in the metastatic setting may be scientifically justifiable, and vice versa, depending on the totality of the evidence regarding similarity and if it can be established that the mechanism of action is the same in these indications.¹⁰² At the time of writing, three trastuzumab biosimilars have been approved in markets with stringent biosimilarity requirements, and extrapolation was permitted for each product. CT-P6, which has been studied in both early and metastatic breast cancer populations, was launched in the Republic of Korea in 2017, and authorized in the EU and Japan in 2018.^{76,87,103–105} Additionally, SB3 has been approved in both the EU and the Republic of Korea.¹⁰⁶ In

December 2017, MYL-14010 became the first trastuzumab biosimilar to be licensed by the US FDA, as trastuzumab-dkst¹⁰⁷; the evidence supporting biosimilarity included a comparative study carried out in the metastatic breast cancer setting.¹⁰⁸ Later that month, MYL-14010 was approved in Brazil, where it will be commercialized by local pharmaceutical company Libbs Farmaceutica.¹⁰⁹ Although the product will initially be supplied to Libbs by the manufacturer Biocon, over time the technology will be transferred to Libbs and public partner Butantan, enabling domestic production.¹⁰⁹ Two further potential trastuzumab biosimilars, ABP 980 and PF-05280014, have been submitted for assessment by the EMA and US FDA,^{110,111} with ABP 980 recommended for approval in the EU.¹¹²

Biosimilars relevant to inflammatory conditions: global scenario

In a similar manner to the mAb biosimilars relevant to oncology, there are numerous mAb and fusion protein biosimilars pertinent to the treatment of inflammatory conditions either in late-stage development or that have been recently authorized in regions with stringent biosimilarity criteria. The anti-tumor necrosis factor (anti-TNF) drugs adalimumab, etanercept, and infliximab, and the anti-CD20 mAb rituximab, comprise the principal originator products (potential rituximab biosimilars are discussed in the previous section). All of these agents are licensed in the treatment of RA. The anti-TNF therapies are additionally indicated for the treatment of several other immune-mediated inflammatory conditions, including psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, juvenile idiopathic arthritis (adalimumab and etanercept), certain forms of non-infectious uveitis (adalimumab), Crohn's disease (adalimumab and infliximab), and ulcerative colitis (adalimumab and infliximab). Table 5 lists examples of potential or approved biosimilars that have progressed to clinical trials in patients, in many cases following comparative trials in healthy volunteers to establish PK similarity.¹⁶

Comparative clinical efficacy and safety trials for most of the potential or authorized adalimumab, etanercept, and infliximab biosimilars have been designed in the setting of RA, utilizing the primary efficacy measure of 20% response according to American College of Rheumatology criteria (Table 5). Comparative studies in plaque psoriasis employing efficacy endpoints based on the Psoriasis Area Severity Index (PASI) have also been used in several cases. The different indications have different strengths and weaknesses as clinical test models. For example, psoriasis represents a condition in which an anti-TNF drug may be administered as monotherapy, and, given that concomitant immunosuppression may reduce the likelihood of anti-drug antibodies, this setting is likely sensitive for detecting potential immunogenicity differences between a biosimilar and the originator product.¹¹⁶ In contrast, RA may be an attractive indication for a comparative trial because it represents the largest patient population for anti-TNF agents¹¹⁶; this may aid patient recruitment, but it also ensures the availability of a wealth of robust data concerning the originator that may be helpful when assessing a

Table 5. Examples of potential and authorized biosimilars relevant to inflammatory diseases.

Originator product	Biosimilar (company)	Patient population(s)* in comparative clinical studies	Primary outcome measure [†]	Authorization status
Adalimumab	ABP 501 (Amgen)	RA	ACR20	Approved in Australia, EU and US
		PsO	Change in PASI	
		PsO	PASI75	Approved in EU and US
	BCD-057 (Biocad)	RA	ACR20	
	BI 695501 (Boehringer Ingelheim)			
			PsO	Under review in EU and US
			CD	
			PsO	
			PK (interchangeability study)	
		CHS-1420 (Coherus Biosciences)	PsO	PASI75
	GP2017 (Sandoz)	PsO	PASI75	
		RA	DAS28-CRP	
	LBAL (LG Life Sciences)	RA	DAS28-ESR	
	PF-06410293 (Pfizer)	RA	ACR20	
	SB5 (Samsung Bioepis)	RA	ACR20	Approved in Australia, EU, Republic of Korea
	ZRC-3197 (Cadila Healthcare)	RA ¹¹³	ACR20 ¹¹³	Approved in India [‡]
Etanercept	CHS-0214 (Coherus Biosciences)	RA	ACR20	Approved in Australia, Canada, EU, and US
		PsO	PASI75	
		RA	DAS28-CRP	Approved in Republic of Korea; withdrawn in 2015 because manufacturing facility sold ¹¹⁴
	GP2015 (Sandoz)	PsO	PASI75	
	HD203 (Hanwha Chemical)	RA	ACR20	
		LBEC0101 (LG Life Sciences)	RA	DAS28
	SB4 (Samsung Bioepis)	RA	ACR20	Approved in Australia, Brazil, Canada, EU, Republic of Korea; under review in Switzerland
Infliximab	BCD-055 (Biocad)	AS	PK	Approved in Russia [‡]
		AS	ASAS20	
		RA	ACR20	Approved in India [‡]
	BOW015 (Reliance Life Sciences)	RA ¹¹⁵	ACR20 ¹¹⁵	
	CT-P13 (Celltrion)	RA	ACR20 ⁷⁷	
		AS	PK	Approved in 80 countries (including several in Latin America)
		RA	ACR20-CRP, PK, long-term safety	
		NI-071 (Nichi-Iko Pharmaceutical)	RA	DAS28-ESR
		RA	Safety	
		RA	ACR20	
	PF-06438179/GP1111 (Pfizer/Sandoz)	RA	ACR20	Approved in US; recommended for approval in EU
	SB2 (Samsung Bioepis)	RA	ACR20	Approved in Australia, Canada, EU, Republic of Korea, US
Rituximab	See Table 4			

Table last updated in April 2018. Products included are those identified in the systematic literature review by Jacobs et al¹⁶ with comparative trials in patients; the products described as intended copies in Table 3 are excluded. Other biosimilars are also in development. Tabulated trials compare the biosimilar with the originator product and may be completed, ongoing, or planned (terminated trials, extension studies, and studies conducted after authorization not included). Trial information from ClinicalTrials.gov unless noted. Authorization details predominantly from company websites.

*Biosimilars may also have undergone comparative PK studies in healthy volunteers.

[†]Note that some PK trials include efficacy endpoints as secondary outcome measures.

[‡]Yet to be evaluated in a region known to have a stringent regulatory pathway for biosimilar approval that is aligned with WHO recommendations (defined for the purposes of this review as Australia, Canada, the EU, Japan, the Republic of Korea, and the US). It is not known whether regulatory agencies in such markets will authorize these products as biosimilars.

ACR, American College of Rheumatology; AS, ankylosing spondylitis; ASAS, Ankylosing Spondylitis Assessment Score; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; EU, European Union; PASI, Psoriasis Area Severity Index; PK, pharmacokinetics; PsO, psoriasis; RA, rheumatoid arthritis; WHO, World Health Organization.

potential biosimilar.⁴⁰ As it may be challenging to combine all desired design elements in a single comparative trial, some manufacturers have chosen to assess their candidate biosimilar in multiple indications (Table 5).

The first adalimumab biosimilar to be approved in a market with strict biosimilar authorization requirements was ABP 501, which was licensed by the US FDA in September 2016 as

adalimumab-atto¹¹⁷ but has yet to be launched. This biosimilar has also been authorized in the EU and Australia.^{101,118} In all territories, eligible indications held by the originator product were authorized based on a submission package including data from trials in both psoriasis and RA.^{101,117,118} Two other adalimumab biosimilars have been approved recently, with BI 695501 obtaining licensure in the EU and US, and

SB5 gaining authorization in Australia, the EU, and the Republic of Korea.^{106,119} Another potential biosimilar, GP2017, has also been accepted for regulatory review by the EMA.¹²⁰

Four etanercept biosimilars have been authorized in areas with rigorous biosimilarity standards (Table 5). SB4 was approved in regions including Australia, Canada, and the EU based on a submission containing data from a comparative trial in patients with RA,^{106,121} while GP2015 has been approved in various markets, including the US, following an application encompassing the results of a trial in psoriasis.^{101,122–125} In both cases, approval was granted for other eligible indications of the originator.^{125,126} In early 2018, a third etanercept biosimilar, LBEC0101, gained approval in both Japan and the Republic of Korea.^{127,128} As described above, one etanercept biosimilar, SB4, is known to be approved in Latin America, having been authorized by ANVISA in Brazil in December 2017^{80,106}; the other follow-on etanercept products marketed in the region are best described as intended copies.

Lastly, four infliximab biosimilars, CT-P13, NI-071, PF-06438179/GP1111, and SB2, have been approved in markets with robust biosimilar pathways (Table 5).^{129–132} As mentioned, the submission package for the first of these, CT-P13, included data from initial comparative trials in RA and ankylosing spondylitis,^{77,78} and in most cases regulatory authorities allowed extrapolation to other eligible indications, including Crohn's disease and ulcerative colitis.¹³³ There was much debate on the issue of approval for extrapolated IBD indications.^{39,134} Therefore, real-world experience with CT-P13 used in IBD has been of particular interest to gastroenterologists. The significant body of post-authorization data published has not revealed any unexpected concerns in this population,¹³⁵ validating the regulatory decision to grant approval in the extrapolated indications. Indeed, in 2017, the European Crohn's and Colitis Organisation issued a position statement that supports extrapolation, which supersedes its previous position that authorization of anti-TNF biosimilars in IBD should be based on studies in this population.^{136,137} In Latin America, extrapolation to all indications has been permitted in Brazil⁴⁶ and Mexico, for example. In Brazil, CT-P13 is presently available only to patients with private health insurance. It is not currently known whether the product will become available to patients within the public health system, as the manufacturer has not established a development partnership with a local pharmaceutical company¹³⁸; current policy from Brazil's Ministry of Health is to encourage the formation of such partnerships as a means of fostering development of the country's domestic biopharmaceutical industry and to protect against drug supply shortages.¹³⁹

Patients with inflammatory diseases may be treated with biologics on a long-term basis. In the interests of reducing costs to patients and healthcare systems, there is substantial interest in establishing the role of biosimilars in therapeutic switches in patients with inflammatory diseases. Data on switching from the originator product to its biosimilar have been provided in the extension phases of comparative clinical studies and in the randomized NOR-SWITCH study, and have not identified any significant safety or efficacy concerns.^{122,140–142}

Budget impact models published to date have assessed the effect of anti-TNF biosimilars in various European countries.¹⁴³ These models have suggested that the biosimilars will likely offer cost savings and improved patient access to treatment; however, the true extent of economic gains is difficult to predict owing to the wide range of variables and market forces at play.

Implications and considerations for clinicians in Latin America

It is clear that true biosimilars have the potential to play an important part in improving access to biologics and reducing healthcare costs in Latin American countries, and numerous mAb and fusion protein biosimilars may soon become available in this region. The introduction of biosimilars has been supported by learned societies in Latin America^{144–146}; however, on the basis of the discussion above, we believe that several key aspects of biosimilars should be considered by healthcare professionals in these countries.

First, clinicians in Latin America should be cognizant of the rigorous standards for biosimilar approval specified in guidance from the WHO and in other highly regulated regions of the world, such as the EU and US. Biosimilar approval pathways in these markets have been created with the understanding that biosimilars may have a disease-modifying role in serious and life-threatening illnesses,³⁹ and thus far no significant concerns have arisen in terms of the safety, efficacy, or immunogenicity of biosimilars authorized according to these regulations.⁶² The same cannot be said for intended copy biologics approved according to less rigorous standards, and these agents cannot be considered true biosimilars, regardless of the level of clinical experience accrued with them.⁴⁵ Because intended copies co-exist with biosimilars in the Latin American market, to ensure informed therapeutic decision-making, clinicians should carefully consider the basis for the regulatory approval of the non-originator mAb and fusion protein products available in their country.

Second, an understanding of the concept of indication extrapolation will be needed both by clinicians specializing in oncology and those involved in the treatment of inflammatory diseases, considering the current number of biosimilars in clinical development. Experts from Latin America have indicated their support for the extrapolation of indications if it is soundly and scientifically justified,^{84,144} for example by demonstrating that the active substance has the same mode of action and target receptors from indication to indication. Indeed, a 2018 position statement on biosimilars from the Brazilian Society of Clinical Oncology emphasizes that decisions regarding extrapolation “should be made on a case-by-case basis,” rather than automatically.¹⁴⁵ Thus far, the concept of extrapolation has been validated by the post-authorization clinical experience with approved biosimilars in regions such as the EU.⁶²

Third, an appreciation of the importance of biosimilar pharmacovigilance is required and should be widely communicated among the healthcare professional community. Pharmacovigilance is important for all medicines and, for biosimilars, rare adverse events (AEs) may not be identified

within the abbreviated clinical trial program.³⁰ Because pharmacovigilance efforts are suboptimal in many Latin American countries, healthcare professionals in the region have a key part to play in post-marketing surveillance by reporting AEs and attributing them accurately.^{45,84,144} In a survey of prescribers in Argentina, Brazil, Colombia, and Mexico, approximately half of respondents claimed that they either reported AEs for biologics rarely (25%) or reported only some AEs (28%); 9% stated that they never reported AEs.²⁸ As such, a cultural shift may be required in the medical community towards giving greater importance to reporting AEs.¹⁴⁵

Fourth, related to pharmacovigilance, clinicians should consider traceability when prescribing biosimilars; it should be possible to distinguish originator products and their biosimilars accurately.¹⁴⁴ This is particularly important in countries such as Argentina, Colombia, Mexico, and Brazil, where the use of brand names is not permitted when prescribing within the public health system; distinct non-proprietary names for biosimilars would be needed to solve this problem.⁸⁴ Indeed, Brazilian medical societies have expressed their support for a distinctive nomenclature system for biosimilars and originator products.^{144,145} One suggestion has been to use the manufacturer's name as a unique identifier.⁸⁴ As biosimilar guidelines in Latin America do not consider the naming of these agents,⁴⁶ this remains an area for clarification. In other regions, this issue has been addressed in different ways. Biosimilars authorized in the EU use the same non-proprietary name as the originator product, but brand names and batch numbers must be used when reporting adverse reactions to aid identification.^{32,62} In the US, the FDA has assigned unique four-letter suffixes to the biosimilars it has licensed to date. Of note, in 2015, the WHO proposed the assignment of a unique "biological qualifier" code to all biological therapies with an International Non-proprietary Name, for the purposes of aiding in "the prescription and dispensing of medicines, pharmacovigilance and the global transfer of prescriptions."¹⁴⁷ However, in 2017, the WHO announced that, owing to a lack of consensus, it was not proceeding with the initiative.¹⁴⁸ With traceability in mind, in the short term, we suggest that physicians in Latin America make every effort to be specific when prescribing biologics and reporting AEs. In the aforementioned survey of Latin American prescribers, for example, more than a quarter (28%) of the respondents stated that they identify a biologic by its non-proprietary or generic name when reporting AEs.²⁸ Furthermore, only approximately half of respondents (51%) claimed that they consistently use batch numbers when reporting AEs.²⁸ In the longer term, it is conceivable that supply chain enhancements designed to track legitimate medicines from manufacturer to patient, thus defending against the infiltration of counterfeit products, could also aid pharmacovigilance for biologics, by benefiting batch-level traceability.¹⁴⁹ Argentina has already implemented a drug traceability program,¹⁵⁰ and a pilot involving barcoded medicine packs is due to take place in Brazil during 2018.¹⁵¹

Finally, healthcare professionals should be aware that in many Latin American countries, clear guidance is lacking in two crucial and related areas: interchangeability and substitution.^{46,49} In the US, an interchangeable biosimilar is defined as one that, in addition to meeting criteria for

biosimilarity, will also provide "the same clinical result as the reference product in any given patient" and "for a product administered to a patient more than once, there is no additional risk or reduced efficacy if a patient switches back and forth between an interchangeable product and a reference product, compared to using the reference product without switching."¹⁵² Interchangeable designation by the FDA may permit pharmacy-level substitution of a biosimilar for the corresponding originator product without the intervention of the prescriber, although substitution policies are to be determined according to state-level legislation. None of the biosimilars licensed to date in the US are designated as interchangeable because the FDA has yet to finalize the standards by which it will assess interchangeability. In most other regions with a known policy, pharmacy-level substitution is either not permitted or permitted only in certain circumstances, such as for treatment-naïve patients.¹⁵³ As a result, switches from an originator product to a biosimilar are typically authorized by the prescribing healthcare professional, subject to patient consent. In Latin America, medical societies have expressed concern about pharmacy-level substitution of biosimilars,^{145,146} given its potential implications for pharmacovigilance and safety.¹⁴⁴ The product provided to the patient may be unknown to the recipient and the prescriber in many cases,¹⁵⁴ and substitution is a particular concern in countries where intended copies are in use.^{2,84} Information on pharmacy-mediated substitution of biosimilars was collected for 13 Latin American countries in a 2017 global survey; Peru was the only country in the region for which it was indicated that substitution could occur.¹⁵⁵ Although substitution was reported not to occur in the other 12 countries, in all but one case, this appeared to be based on respondents' knowledge of normal pharmacy practices, rather than any regulation or guidance to prevent it.¹⁵⁵ Further clarification on these issues is eagerly awaited.

Conclusions

High-quality biosimilars of the most commonly used mAb and fusion protein therapies are expected to have a key role in addressing the increasing burden of non-communicable and chronic diseases in Latin American countries. However, because biologics are highly complex molecular entities and there is no scientific definition of "biosimilarity," establishing appropriately stringent regulatory standards and processes for biosimilar approval is crucial to ensuring that authorized products have an acceptable efficacy and safety profile. In our view, regulatory standards aligned with those from the WHO should be used to evaluate potential biosimilars in Latin America. Healthcare professionals have an important part to play in the adoption and widespread use of biosimilars and should not, in our opinion, prescribe products that do not meet such criteria. We believe that the safety of our patients must not be jeopardized in the interests of expanding access to treatment or minimizing costs.

Disclosure of potential conflicts of interest

Morton Scheinberg has been a consultant and speaker for Pfizer, GSK, Janssen, Roche, Samsung Bioepis, Boehringer Ingelheim, and Novartis.


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