

REVIEW ARTICLE

Biosimilars in psoriasis: Clinical practice and regulatory perspectives in Latin America

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ABSTRACT

Latin American countries view biosimilar agents as an effective approach to curtail health-care expenditures while maintaining the safety and efficacy profile of their branded innovator comparators. To understand the complexities of the regulatory landscape and key therapeutic issues for use of biosimilars to treat moderate to severe psoriasis in Latin America, the International Psoriasis Council convened dermatology experts from Argentina, Brazil, Chile, Colombia and Mexico in October 2015 to review the definition, approval, marketing and future of biosimilars in each country and develop a consensus statement. The regulatory framework for marketing approval of biosimilars in Latin America is currently a mosaic of disparate, country-specific, regulatory review processes, rules and standards, with considerable heterogeneity in clarity and specificity. Regulations in Argentina, Brazil, Chile and Mexico have undergone multiple refinements whereas Colombia is finalizing draft guidelines. Verification of the similarity in quality, safety and efficacy of biosimilars to the innovator biologic remains a key challenge for policy makers and regulatory authorities. Other key regulatory challenges include: naming of agents and traceability, pharmacovigilance, extrapolation of indications, and interchangeability and substitution. An urgent need exists for more Latin American countries to establish national psoriasis registries and to integrate their common components into a multinational psoriasis network, thereby enhancing their interpretative power and impact. A Latin American psoriasis network similar to PSonet in Europe would assist health-care providers, pharmaceutical companies, regulators and patients to fully comprehend specific products being prescribed and dispensed and to identify potential regional trends or differences in safety or outcomes.

Key words: biosimilars, Latin America, pharmacovigilance, psoriasis, regulation.

INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory condition with an immense impact on patients' lives.^{1–3} The disease is often associated with multiple comorbidities (in addition to psoriatic joint disease) and a substantial physical, emotional and psychosocial burden.^{1,2,4} According to the World Health Organization (WHO), the prevalence of psoriasis ranges from 0.09% in Tanzania to 11.4% in Norway.^{3,5}

In Latin American countries, treatment options for moderate to severe psoriasis vary but typically include ultraviolet B/psoralen-ultraviolet A, phototherapy, methotrexate, cyclosporin,

acitretin and, more recently, targeted biologic agents.⁶ Biotechnology-derived targeted biologic agents (e.g. infliximab) have ushered in a new treatment paradigm for immune-mediated inflammatory diseases, including psoriasis, but are cost prohibitive.

In many Latin America countries, the patents of some biologics have expired or will expire soon. This has generated impetus to develop safe and effective biosimilar agents at a lower cost. In turn, this is expected to provide greater access of biologics to patients and also help curtail burgeoning health-care expenditures. This is particularly important in Latin America where many countries have limited health-care resources and

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targeted biologic agents are suboptimally utilized due to cost and reimbursement issues.⁷

To understand the current regulatory landscape and key therapeutic issues for use of biosimilars to treat psoriasis in Latin America, the International Psoriasis Council (IPC) convened dermatology experts from Argentina, Brazil, Chile, Colombia and Mexico in Copenhagen, Denmark, on 7 October 2015. This article summarizes the material presented and discussed during the IPC Latin American biosimilar meeting with the goal of helping health-care providers in Latin America understand this rapidly evolving therapeutic area and how biosimilar agents could potentially impact their clinical practice.

EVALUATING BIOSIMILARS FOR PSORIASIS: WHAT HEALTH-CARE PRACTITIONERS SHOULD KNOW

Biosimilars are generated by recombinant DNA technology with the goal of producing a therapeutic entity that is highly similar to the previously approved reference or originator product with no clinically meaningful differences in purity, efficacy or safety. However, small differences among manufacturing processes may significantly impact the quality, purity, biologic characteristics and clinical activity of the final product. For example, while amino acid sequences of biosimilars and reference products may be identical, even minor variations in the manufacturing process can impact three-dimensional protein folding, glycosylation, molecular charge and presence of impurities.⁸ Thus, biosimilars present a new set of clinical developmental and regulatory challenges compared with conventional low molecular weight synthetic generics, and their marketing approval is correspondingly more complicated.

Verification of the similarity in quality, safety and efficacy of biosimilars to the innovator biologic remains a key challenge for policy makers and regulatory authorities in many countries. Furthermore, in order to make informed health-care decisions, physicians and patients must also feel confident that these products are as safe and effective as the reference product and that they have been rigorously vetted during the approval process. This is particularly germane in light of the fact that no long-term clinical efficacy and safety studies of biosimilars are typically performed prior to their marketing approval.

Biosimilar agents depend, at least in part, on prior safety and efficacy data obtained with the reference products (rather than obtaining data from independent clinical studies) for licensing. The goal of biosimilar development is therefore demonstrating comparability across a wide range of analytical, preclinical and clinical studies, which include comparative assessments of pharmacokinetics, pharmacodynamics and immunogenicity (i.e. antidrug antibody response).^{9,10} The statistical issue of bioequivalence or non-inferiority is also an important consideration when considering comparative clinical studies.^{11,12} The US Food and Drug Administration (FDA) and European Medical Agency (EMA) require equivalence clinical trials to confirm comparability of efficacy and safety of biosimilars to their reference products, and in many cases end-points do not differ from that of the pivotal studies of the originator.

Some designs include a transition phase and an extended follow up to 52 weeks.

For novel biologic reference products, submission documentation for licensing focuses on phase 1–3 studies; for biosimilars, however, more attention is given to physiochemical, biologic and animal studies (Fig. 1).¹³ Preclinical analytical assessment to evaluate the comparability of biosimilars relative to the reference agent plays an important, but not exclusive, role in the regulatory approval process. In a prior publication, the International Psoriasis Council put forward suggestions for the preclinical assessment of biosimilars and proposed the use of a biosimilar index.⁸

As reviewed in detail elsewhere, other key regulatory challenges with respect to biosimilars include: naming of agents and traceability; extrapolation of approval to an indication in which the biosimilar has not been clinically evaluated; interchangeability and substitution; and pharmacovigilance (see later).^{14–17}

Naming and traceability

Accurate product identification is critical to trace the manufacture, distribution and prescription of targeted biologic agents including biosimilars along the entire supply chain as well as to accurately monitor safety signals after approval (pharmacovigilance). Thus, a key issue facing regulators is how to name biosimilars: should these agents use the same non-proprietary name as the branded reference product or a different name? It is impossible to attribute an adverse event to a specific biosimilar in the post-approval setting if the same WHO International Nonproprietary Name is used without some kind of distinguishing identifier. To permit traceability (and avoid inadvertent or haphazard switching at the pharmacy or institutional level), the name of each biosimilar needs to be easily distinguishable from its reference biologic counterpart and indeed other analogous biosimilars. The FDA has recently issued draft guidelines on biosimilar agent labeling and suggests using the proprietary name or product name specific to the biosimilar agent.¹⁰ It also recommends adding a statement in product labeling to indicate biosimilarity to the reference product.

Extrapolation of indications

Regulatory authorities may approve a biosimilar agent for one or more of the indications of the reference biologic product depending on the submitted preclinical and clinical evidence of comparability. In some countries, extrapolation of indications is allowed for biosimilar agents to include disease states for which the reference product was approved but for which the biosimilar was not specifically clinically evaluated.

This practice has been criticized because of marked potential differences among the disease states with respect to other concomitant therapies that may be administered as well as the mechanism of action, target organ, immunogenicity and pharmacokinetics of the therapeutic agent.¹⁷ As a result, some physicians may be reticent to prescribe a biosimilar that has not been as stringently evaluated in a specific disease state as the reference product.¹⁷ This may be particularly germane with respect to Crohn's disease and ulcerative colitis. Thus, in Canada, an infliximab biosimilar was not approved for these

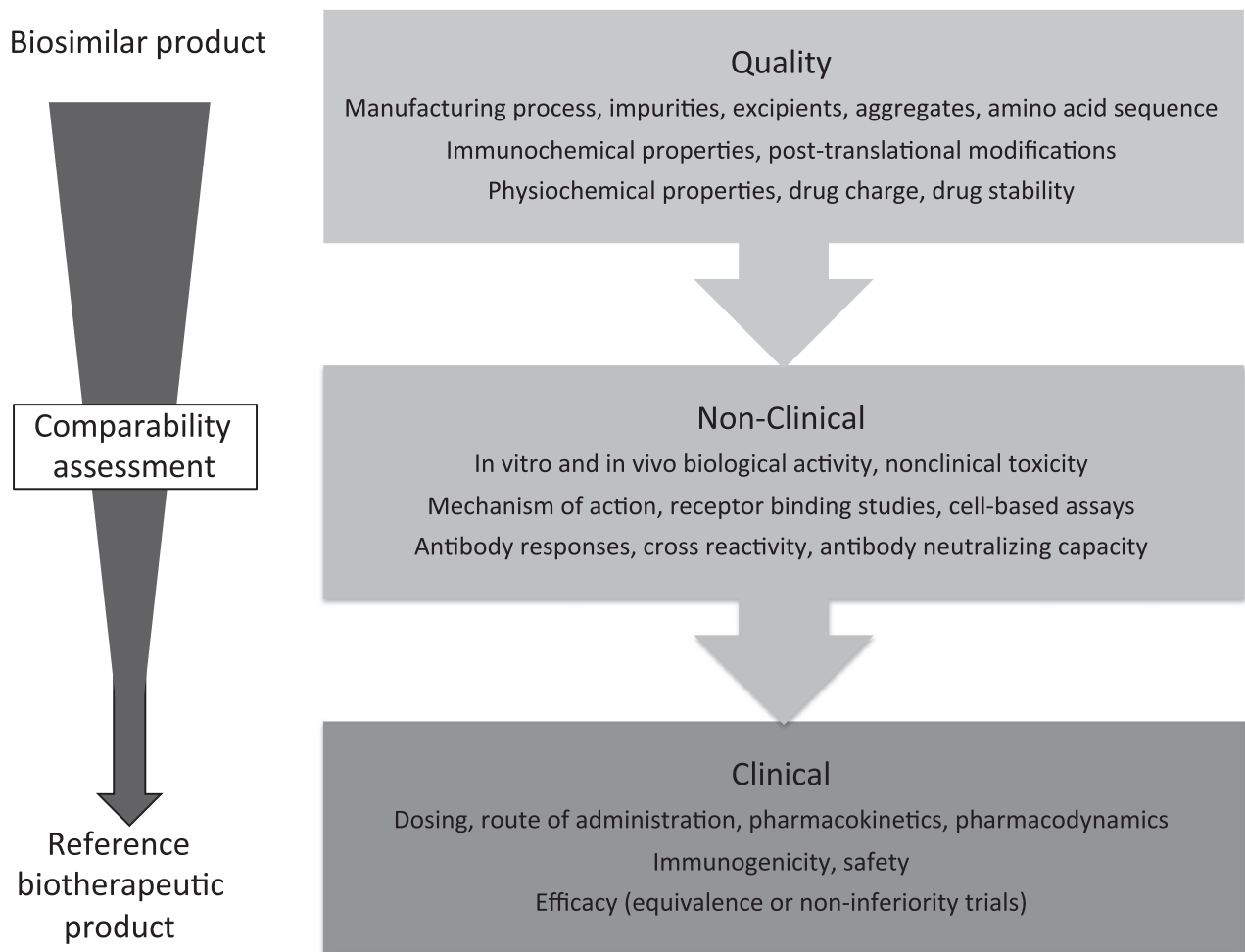


Figure 1. Quality, non-clinical and clinical assessments required to demonstrate comparability of biosimilar and reference, branded biotherapeutic products. The width of the arrow (left) indicates relative magnitude of data needed.

two indications.¹⁸ To ensure safe and effective clinical use of biosimilars, therefore, clinical trials in all indications are appropriate. However, taking adalimumab as an example where it is approved for nine indications, conducting clinical trials in all indications would be challenging and cost prohibitive.

Interchangeability and substitution

Interchangeability means that physicians can prescribe a therapeutically biosimilar agent rather than the reference biologic agent with the expectation of: (i) a comparable clinical result in any given patient; and (ii) the safety risks and efficacy after alternating or switching are no different from those after continuous use of the reference product.¹⁹ Substitution refers to the practice whereby a hospital or pharmacy can legally switch a prescribed reference product to a biosimilar agent without the approval of the prescribing physician and/or knowledge of the patient.

Latin American countries have different perspectives on substitution, but clearly haphazardly switching targeted biologic agents impairs the ability of prescribers to assess

accurately response to treatment and outcomes and complicates pharmacovigilance. Ideally, physicians should always be notified prior to any biosimilar substitutions being made, and they should always be given explicit authority to consider overriding any suggested substitutions.

CURRENT LANDSCAPE OF BIOSIMILARS IN SEVERAL LATIN AMERICAN COUNTRIES

Currently, regulatory agencies in Argentina (ANMAT: Administración Nacional de Medicamentos, Alimentos y Tecnología Médica),²⁰ Brazil (ANVISA: Agência Nacional de Vigilância Sanitária),²¹ Chile (ANAMED: Instituto de Salud Pública de Chile, Agencia Nacional de Medicamentos)²² and Mexico (COFEPRIS: Comisión Federal para la Protección contra Riesgos Sanitarios)²³ have all issued country-specific final guidelines to regulate licensing of biosimilars. The agency in Colombia (INVIMA: Instituto Nacional de Vigilancia de Medicamentos y Alimentos), however, has not progressed beyond

issuing a draft decree, which is awaiting final approval.^{24,25} Comparing the regulatory landscape among countries worldwide is obfuscated by the plethora of names given to biosimilars, including biocomparables, intended copies, copy biologics, biologic products, follow-on biologics, follow-on protein product or subsequent entry biologics.²⁶ For consistency, the term biosimilar agent is used wherever possible in this article although different country-specific terms are included and explained for completeness when necessary.

The current regulatory landscape with respect to the approval, marketing and future of biosimilar agents to treat psoriasis and the potential impact of these agents on the daily practice of medicine has rapidly evolved over the past decade. The following sections present a contemporary review of regulatory perspectives, approved biosimilar agents and clinical practice in five Latin American countries, namely, Argentina, Brazil, Chile, Colombia and Mexico (Table 1, Fig. 2).

Table 1. Summary of regulatory and clinical issues relating to use of biosimilars for psoriasis in Latin American Countries

	Argentina	Brazil	Chile	Colombia	Mexico
Directives by country health authorities/ MOH	Published	Published	Published	Draft published	Published
Extrapolation to psoriasis	No	Allowed	Allowed	Pending	Allowed
Extrapolation to pediatric psoriasis	No	Pending	Allowed	Pending	Allowed (if reference product has indication)
Interchangeability at the pharmacy level	Pending	Pending	Allowed with physician/patient approval	Pending	Allowed
Interchangeability at the institution/hospital level	Pending	Pending	Not allowed (but occurring)	Pending	Allowed
Interchangeability at the physician level (medical substitution)	Pending	Pending	Allowed	Pending	Allowed
Registered biosimilars Drug [manufacturer]	Novex (rituximab) [Elea]	No Remsima (infliximab) [Hospira] approved but not yet marketed	Remsima (infliximab) [Celltrion] Reditux (rituximab) [Dr Reddy's Labs]	Etanar (etanercept) [Shanghai CP Goujian]; biomimic not biosimilar	Infinitam (etanercept) [Probiomed] Remsima (infliximab) [Hospira] Estart (etanercept) [Shanghai CP Goujian] biomimic
Implementation of biosimilar use	Allowed (biologic product)	Allowed (biologic product)	Allowed (biologic product)	Pending	Allowed (biocomparables)
Pharmacovigilance	Physician spontaneous report, industry registries	Mandatory by the manufacturer	Performed by MOH (physicians must report any adverse events)	Irregular	Mandatory by manufacturer
Existing registries in psoriasis	Yes	No	No	No	No
Planned registries in psoriasis	No	In progress (Brazilian Society of Dermatology)	No	No	No
Differential naming of biosimilars	No	No	No (trademark only)	No	No
Traceability of biosimilars	Yes	No	Yes (by trademark)	No	Yes
Estimated cost reduction	30%	Not defined	20%	Not defined	Not defined
Actual cost reduction	10%	Not defined	20%	Same price as innovator	35% vs reference product

MOH, Ministry of Health.

[Correction added on 3 November 2016, after first online publication: "Extrapolation to psoriasis" and "Extrapolation to pediatric psoriasis" under Argentina have been changed to No.]

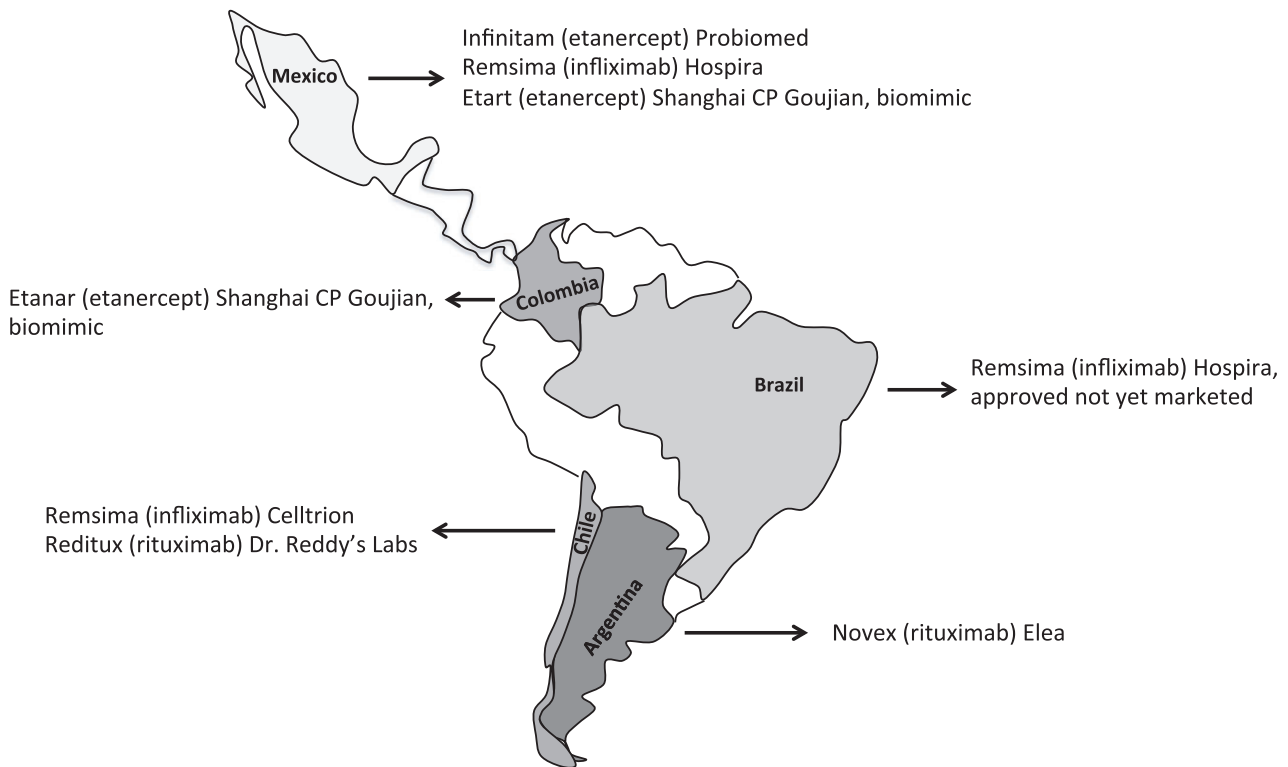


Figure 2. Biosimilars for immune-related inflammatory diseases in Latin American countries.

Argentina

In many respects, Argentina has been at the forefront of biopharmaceutical product development in Latin America. The country has a rich history of encouraging growth of the pharmaceutical industry, and local companies now supply more than half of the country's pharmaceutical needs. Argentinean companies have manufactured biotechnology-related products for two decades and regulatory authorities have permitted the introduction of biosimilar agents into the market place for many years. Indeed, the Pan American Health Organization has declared ANMAT to be a leading agency in the region.

Argentina has established a well-delineated regulatory pathway for biosimilar agents and has spearheaded the requirement for rigorous standards for approval in Latin America.²⁰ Note, however, that for registration purposes, biopharmaceutical is the term used for new biologic products or new originator products and biologic product is used for biologic intended copy drugs (i.e. biosimilars).²⁶ In 2011 and 2012, Argentina introduced several regulations impacting the licensing of biologic products in general in 2011 and 2012. The initial regulation (Disposition 7075) introduced in October 2011 delineated the general framework for the registration of new biologic products and emphasized the need for clinical studies for approval. This legislation also established the requirement of a pharmacovigilance program for the post-commercialization stage.

The second regulation (Disposition 7729), introduced in November 2011, defined the registration requirements for

biosimilar agents. The innovator drug, called reference or comparator drug, must be approved by ANMAT or other agencies with similar standards, and must be widely commercialized and have an adequate benefit-risk profile. Applications for approval must prove that the biosimilar agent has the same pharmaceutical formulation identity, potency and purity as well as comparable efficacy and safety profiles as the reference product. However, the magnitude of documentation needed to demonstrate similarity of a biosimilar agent with the reference product was not clearly specified, and applications are evaluated on a case-by-case basis.

The final regulation (Disposition 3379), introduced in June 2012, specifically relates to biopharmaceutical agents manufactured using recombinant DNA technology including monoclonal antibodies, and defines additional information essential for marketing approval. This includes, for example, detailed elaboration on the actual manufacturing process and quality control, the source and production of raw materials, as well as details on the actual immunological production techniques.

Despite the well-established pathway for licensing, only one biosimilar, rituximab (Novex®; Laboratorio Elea, Sanabria, Argentina), has been approved in Argentina to date.²⁷ Rituximab was approved by ANMAT in 2013 based on clinical data for a non-dermatological condition (non-Hodgkin lymphoma), and extrapolated to only rheumatoid arthritis. [Correction added on 3 November 2016, after first online publication: This sentence has been corrected to exclude psoriasis and

pediatric psoriasis which haven't been granted approval.] No comparative phase 3 studies establishing safety and efficacy were necessary for approval. Hitherto, there have been no alerts about safety or immunogenicity of this agent in the post-marketing setting, and there is no provision at present to permit interchangeability by physicians or substitution at the pharmacy or institutional/hospital levels.

Important educational opportunities with respect to prescribers' knowledge of and prescribing practices for biosimilar agents exist in Latin America, particularly in Argentina. A recent 2015 survey in Latin America, conducted by the Alliance for Safe Biologic Medicines, showed that Argentinean prescribers were the least familiar with biosimilar agents, with approximately four out of 10 respondents reporting they had never heard of biosimilars or were unable to define them.²⁸ On the other hand, health-care payers (e.g. benefits directors at insurance companies) in Argentina had a greater comfort level with biosimilar agents compared with several other Latin American countries according to a small survey published in 2015.²⁹ This enhanced level of comfort in terms of providing access to biosimilar agents appeared to stem from the belief that ANMAT would rigorously review data on safety and efficacy of biosimilars prior to approval.

Brazil

In Brazil, a staggering 40% of the Ministry of Health's budget for pharmaceuticals is attributed to biotherapeutics, and yet these agents account for no more than 3% of medication prescriptions written.³⁰ Because clinical use of biotherapeutic agents represents such a sizeable segment of the country's health-care total budget, the introduction of affordable biosimilar agents is of enormous interest in Brazil. In order for a biologic product (including biosimilars) to be marketed and distributed in Brazil, it must be registered with ANVISA and its manufacture or importation has to be authorized by the federal government and licensed by the appropriate state government.

Patient access to targeted biologic agents to treat psoriasis is complicated by the fact that the Brazilian Ministry of Health treatment protocol (Clinical Protocol and Therapeutic Algorithm [PCDT] 1.229) for psoriasis excludes these drugs.⁶ As a result, there is no reimbursement for biologics to treat moderate to severe psoriasis; furthermore, reimbursement by private health-care insurance companies is not mandatory even for moderate to severe psoriasis.⁶ If targeted biologic agents are deemed medically necessary and the most cost-effective medicine, however, individual patients can sue the government and receive the drug after a judicial ruling.^{31,32} Such a legal process not only creates unnecessary stress for patients but also fosters inequities in health care by preferentially benefiting wealthier individuals with a socioeconomic status sufficient to pay legal representatives.

Like Argentina and Chile, Brazil is also considered at the vanguard of a movement to introduce legislation to regulate biosimilar agents in Latin America. Prior to 2010, the regulatory pathway in Brazil was similar for new biologic products and biologic products (i.e. biosimilars). This situation changed in 2010 when ANVISA introduced Resolution 55/2010³³ that

delineated two pathways for the licensing of comparative biologic products (biosimilars).³⁴ One pathway relates to licensing of monoclonal antibodies and other complex molecules (comparative pathway) and a less rigorous route for simpler molecules such as pegylated interferon and low molecular weight heparin (individual pathway).³⁵

- 1 Individualized development pathway: The license application requires a complete dossier with respect to the development, manufacturing, quality control, non-clinical and clinical data but comparative data are needed only to demonstrate therapeutic effect. Extrapolation of indications is not permitted.
- 2 Comparative pathway: This more rigorous approval pathway, which closely mirrors the WHO guidelines set forth for Similar Biotherapeutic Products,³⁶ necessitates preclinical and clinical studies demonstrating comparability with a product previously approved in Brazil. Although the application is more comprehensive, approval may be expedited if an international affiliated regulatory agency (like the EMA or FDA) has already approved the biosimilar agent. This requires that the other agency adopts similar technical scientific criteria to ANVISA's criteria and there is access to the registration information. Importantly, this regulatory pathway does allow extrapolation to other indications.

According to RDC 55/2010, extrapolation of indications should respect the following:

- 1 Comparability in terms of safety and efficacy between the biosimilar agent and reference products must be demonstrated.
- 2 The patient population and study design used to compare the safety and efficacy should be able to detect potential differences, if any, between the biosimilar agent and reference products.
- 3 The mechanism of action and receptor involved in the different indications must be the same.
- 4 The safety and immunogenicity of the biologic product (biosimilar agent) should be sufficiently characterized.
- 5 Biologic products registered by the individualized development pathway will not be able to extrapolate safety and efficacy data to other therapeutic indications of the biologic reference product.

In 2015, an infliximab biosimilar (CT-P13; trade name Remsima™, marketed by Hospira in Brazil [Pfizer, New York, NY, USA]) was approved for rheumatoid arthritis. Part of the submission material involved a phase 3 study demonstrating similarity between Remsima and the reference biologic product, Remicade™ (infliximab; Janssen Biotech, Horsham, PA, USA).³⁷ The strength of the comparative data involving Remsima and Remicade was sufficient for ANVISA to approve use of Remsima in all indications of the reference product without additional specific clinical studies. Thus, Remsima was extrapolated to the treatment of psoriasis and psoriatic arthritis. Nevertheless, at present, no biosimilar agent is actually available for clinical use in Brazil. Indeed, anecdotally, Brazilian

physicians are expressing great consternation regarding the introduction of biosimilar agents into clinical practice, particularly when it comes to using a product for a clinical indication in which specific safety and efficacy data are absent.

Based on previous experience, drug costs will likely drive the discussion and approval of biosimilars in Brazil. It is also likely that all biosimilars, regardless of the robustness of their clinical data, will be approved through the faster comparative pathway. Finally, ANVISA is likely to approve and coordinate mandatory interchangeability of biosimilar agents with the reference products.

Chile

In response to financial pressures to permit utilization of biosimilar agents, Chile began cautiously drafting guidelines for the evaluation of biosimilars in 2011 and employed EMA and WHO guidelines as valuable starting points.³⁸ Subsequently, the Instituto de Salud Pública (ISP) passed Resolution 170 in August 2014 and established regulations for all biologic drugs, including biosimilar agents. This resolution defines the term biosimilar and requires manufacturers to conduct preclinical and clinical studies with a reference product in order to adequately characterize the biosimilar agent and to demonstrate safety, efficacy and immunogenicity comparable with the reference biologic. Extrapolation of indications is permitted provided the diseases in question have similar pathophysiologies and receptor involvement, and the agents have an analogous mechanism of action as well as similar efficacy, safety and immunogenicity.

This resolution also allows substitution of the biosimilar agent for the reference biologic but only with physician approval and informed consent of the patient. The medical community has strongly rejected the practices of some hospitals purchasing biosimilars and substituting these drugs for use in non-approved indications without patient or physician consent.

While several biosimilar agents are available in Chile, none are approved for use in psoriasis. The infliximab biosimilar Remsima® (CT-P13; Celltrion Laboratories, Korea) has been available for clinical use since December 2013. The dossier submitted to Chilean authorities included studies for rheumatoid arthritis and ankylosing spondylitis. While the manufacturer attempted to gain approval for extrapolation to all indications, including Crohn's disease, Remsima was eventually approved only for rheumatoid arthritis and ankylosing spondylitis in adults. The medical community has generally opposed attempts to use this product in other disease states despite a 20% reduction in price relative to the originator agent Remicade.

As noted previously for Argentina, a biosimilar of rituximab, Reditux® (Dr Reddy's Laboratories, Hyderabad, India), was also approved in April 2010 and is priced approximately 25% less than the reference product. This biosimilar agent was submitted for licensing before the regulatory update in 2014 and was approved for rheumatoid arthritis and non-Hodgkin's lymphoma without bioequivalence clinical trials for any indications. To date, ISP has not reconsidered approval of this agent under

the new regulations. More recently in 2012, introduction of a biosimilar of etanercept, Etanar® (Shanghai CP Guojian Pharmaceutical, Shanghai, China) was contemplated but after pre-marketing consultation with physicians, no formal application was presented to ANAMED.

Colombia

The social security system in Colombia is based on fundamental principles of efficiency, universality and solidarity. While this framework should guarantee access of the entire population to any type of medication, government agencies and the structure of the health system in general create conditions making it particularly challenging to meet these objectives with respect to targeted biologic therapies. As in many other Latin American countries, use of targeted biologic therapies in Colombia consumes a substantial portion of the health-care budget. Therefore, economic pressures to introduce biosimilar agents into the market place are intense, and the possibility of drugs of dubious origin and questionable quality has created a concern among physicians and patients alike.³⁹

The Colombian Biotechnology Decree 1782 from INVIMA was proposed in 2014 and is awaiting final approval.²⁵ The decree describes the standards and procedure to evaluate the quality, safety and efficiency of biologic medications for marketing approval and pharmacovigilance. The goal of the proposed decree is to allow the licensing of biosimilar agents in Colombia in order to lower treatment costs. Note, however, terms such as biosimilar or follow-in biologics and biogenerics are not explicitly stated. According to the proposed guidelines, INVIMA could potentially review biologic medicines applications according to three routes:

- 1 Full application pathway for original innovator biotherapeutic agents: preclinical *in vivo* or *in vitro* analysis and clinical trials of the biologic medicinal product.
- 2 Comparable route: preclinical pharmacological evaluation and clinical safety and efficacy must demonstrate similarity between the biosimilar agent and reference biotherapeutic medicine.
- 3 Abbreviated route: laboratory studies of bioequivalence (e.g. pharmacokinetic data) of the active component only are required without clinical trials confirming its efficacy and safety. This pathway is for pharmaceutical products that have been approved in another country, for example.

The ability to decide which of the routes is the most appropriate or define whether the route chosen by the pharmaceutical company is ideal rests on a specialized chamber group. While members of this chamber have the power to approve or request additional information as appropriate, the actual structure and method of selecting are not specified in the decree.

While the full application pathway (for original innovator biotherapeutics) and comparable pathway are consistent with the regulations for approval of biosimilars in other countries, the inclusion of an abbreviated pathway for approval in Colombia is unique in the world. This pathway would be inconsistent with the guidelines issued by the WHO and creates gaps in the review process to ensure the quality, safety and efficacy of

approved drugs. The decree opens the possibility of regulatory decisions based on the experience of countries whose health standards are lower than those historically acceptable in Colombia, and this could adversely affect the quality of biotechnological and biologic products that Colombians receive.⁴⁰ Indeed, Vice President Joe Biden of the USA has urged the President of Colombia, Juan Manuel Santos Calderón, to introduce stringent legislation on the introduction of biosimilar agents to safeguard the health and safety of Colombians.⁴¹

It should be noted that there are serious concerns about critical issues missing from Decree 1782. For example, an important omission relates to interchangeability and the extrapolation of medical indications. This is of great concern to both physicians and patients when switching from an innovative medicine to a biosimilar agent and merits detailed clarification. In addition, pharmacovigilance and immunogenicity are only briefly addressed in the proposed standards, and this lack of clarity compromises early identification of potential adverse effects potentially impacting the health of individuals who receive biosimilar agents.

The identification of therapeutic targets and the development of biologic and biosimilar agents in dermatology are encouraging, and the socioeconomic benefits of biosimilars are fully recognized in Colombia. Currently, there are no biosimilar agents, *per se*, licensed in Colombia although the non-originator biologic Etaner (etanercept; Shanghai CP Goujian Pharmaceutical), referred to as a biomimic, is approved for marketing. Biomimics (also known as intended copies) are agents approved prior to introduction of regulations for biosimilar agents but have not demonstrated equivalence in terms of safety and efficacy with the reference biologic.

Mexico

Although specific regulations pertaining to biologic products in general have been lacking for many years, Mexico has spearheaded the manufacture of biosimilar agents in Latin America and has more recently been vigorously refining legislation pertaining to the licensing of biologic products, including biosimilars.⁴² Biocomparables is the official term for biosimilar agents in Mexico and is separate from similares (small molecular size generics with no bioequivalence evaluations). In June 2009, reformation of The General Health Law addressed the issue of biologics by the inclusion of Article 222 Bis.²³ This amendment allows reference to originator drugs but did not clearly delineate the scope and nature of the required studies for regulatory review. However, it would appear that biosimilar agents must demonstrate biocomparability versus reference product as well as present phase 2 and 3 studies specifically in the Mexican population. The regulatory body for approval of medicines in Mexico (COFEPRIS) subsequently issued guidelines for biocomparables and these were enacted in 2012.²³ Since that time, COFEPRIS has also formulated detailed regulations pertaining to drug interchangeability, biocomparability, safety, efficacy and quality requirements pertaining to older non-originator biologic agents (biolimbos) that were registered in Mexico prior to the 2011 regulations.⁴³ As many as 23 biolimbos registered

as generics in the years preceding this regulation did not undergo review for marketing authorization consistent with generally acknowledged standards for biosimilars and must now renew licensing every 5 years.^{43,44}

Currently, there are two biosimilar agents approved for clinical use in Mexico: Infinitam (Probiomed, Mexico City, Mexico), a biosimilar of etanercept, and Remsima (Hospira/Pfizer), a biosimilar of infliximab. These products can be used to treat psoriasis because Mexican regulators allow extrapolation from the main therapeutic indication (rheumatoid arthritis) for a biosimilar provided that the agent has demonstrated biocomparability in terms of safety, quality and effectiveness. Infinitam may also be used for pediatric psoriasis in children aged 4 years or older. Interchangeability of biosimilars for reference agents is allowed provided, of course, the biosimilar is in the National Health System database. Promotion of substitution of biosimilars for branded reference products as well as governmental contracts that include large discounts for biosimilars are expected to garner large cost savings (~32% in public institutions and 45% in private sales) for the Mexican health-care system.

Intensive pharmacovigilance is required for all biotech products, whether or not they are biosimilars, and each public institution must provide patient reports. This system provides health authorities with comprehensive monitoring of potential adverse events and also permits efficacy evaluation in Mexican patients. Each manufacturer must submit a regular report of intensive pharmacovigilance.

NEED FOR NATIONAL PSORIASIS REGISTRIES AND A MULTINATIONAL NETWORK IN LATIN AMERICA

National psoriasis registries have been introduced in many countries throughout the world to collect safety and efficacy data of different treatments to help improve disease management. The registries can also provide invaluable data to help understand the etiology of psoriasis, the spectrum of common comorbidities and the impact of psoriasis on everyday living. Currently, national psoriasis registries in Latin America are uncommon, limiting the ability of patients, physicians, policy makers and approval agencies to fully comprehend specific products being prescribed and dispensed and to identify potential regional trends or differences in safety or outcomes.

A critical component of any national registry is to collect, monitor and evaluate post-licensing safety data (pharmacovigilance) to detect differences in adverse effect profiles between a biosimilar, its reference product and other biosimilars.¹⁵ This is especially challenging in most Latin American countries because no single national pharmacovigilance database captures all of the adverse event reports for a licensed product.¹⁵ The case of kikuzubam (rituximab biomimic; Probiomed) in Mexico illustrates the importance and value of effective pharmacovigilance. Anaphylactic reactions in some patients who were switched from rituximab innovator product (MabThera; Genentech [South San Francisco, CA, USA]/Biogen [Cambridge, MA, USA]) to kikuzubam led regulatory authorities to withdraw marketing approval of kikuzubam in 2014.¹²

This example emphasizes the need for more Latin American countries to establish national psoriasis registries, and furthermore to integrate their common components into a multinational psoriasis network, thereby enhancing their interpretative power and impact. An international surveillance network of national psoriasis registries has been established in Europe (PSOINET) to monitor long-term safety and efficacy of psoriasis therapies.^{45,46} A similar Latin American network could ultimately be modeled along these lines.

SUMMARY AND CONCLUSIONS

Many Latin American countries have adopted the WHO³⁶ and EMA⁴⁷ development and licensing procedures for biosimilar agents but considerable heterogeneity exists in clarity and specificity of regulations from country to country.⁴⁸ Verification of the similarity in quality, safety and efficacy of biosimilars to the innovator biologic remains a key challenge for policy makers and regulatory authorities. In the post-approval setting, pharmacovigilance is critical to monitor safety including immunogenicity between a biosimilar agent, reference product and other biosimilars. A multinational psoriasis network would be invaluable to integrate post-marketing safety and efficacy data of biosimilars among existing national psoriasis registries in Latin American countries and would help to identify potential regional trends or differences in safety or outcomes.

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