



## Special Article

## Biosimilar Drugs in Mexico: Position of the Mexican College of Rheumatology, 2012

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## ABSTRACT

Biotechnological drugs (BTDs) are complex molecules whose manufacturing process precludes the ability to identically reproduce the structure of the original product, and therefore there cannot be an absolute equivalence between the original (innovative) medication and its biosimilar counterpart. BTDs have been proven useful in the treatment of several rheumatic diseases; however, their high cost has prevented their use in many patients. Several BTD patents have expired or are close to expire, triggering the development of structurally similar drugs with efficacy and safety profiles comparable to the innovative compound; however, these must be evaluated through evidence-based medicine. The Mexican General Health Law contemplates the registration of these biosimilar drugs for their use in our country. This document is a forethought from members of the Mexican College of Rheumatology, pharmacologists, and epidemiologists, in accordance with Mexican health authorities regarding the necessary scientific evidence required to evaluate the efficacy and safety of biosimilar drugs before and after their arrival to the Mexican market.

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### Medicamentos biocomparables en México: la postura del Colegio Mexicano de Reumatología, 2012

## RESUMEN

Los medicamentos biotecnológicos (MBT) son moléculas complejas cuyo proceso de elaboración impide replicar con gran exactitud la sustancia original, por lo que no existe una equivalencia absoluta entre la droga original (innovador) y el biocomparable. Los MBT han probado su eficacia en diversas patologías reumáticas, aunque su alto costo impide su utilización en muchos pacientes. Diversas patentes de medicamentos biotecnológicos han expirado o expirarán próximamente, detonando así el desarrollo de fármacos

## Palabras clave:

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estructuralmente similares y probablemente con eficacia y seguridad comparable a los medicamentos innovadores, aunque estas características deben ser probadas. La Ley General de Salud Mexicana actual contempla el registro de estos medicamentos para su utilización en nuestro país. Este documento, es una reflexión de miembros del Colegio Mexicano de Reumatología, farmacólogos e investigadores en epidemiología, en conjunción con nuestras autoridades sanitarias, sobre los estudios científicos necesarios de los biocomparables previos y posterior a su incursión en el mercado mexicano.

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## Introduction

With the expiration of patents on biotech drugs, the development of structurally similar substances with the therapeutic qualities of original molecules, in Mexico called biosimilar drugs (BSD) has started. Their presence can promote greater access for users based on their cost, but their use has not been without debate.

Unlike conventional medicines, also called “small molecules”, the biotechnology-derived drugs are complex molecules, so much so that there is no possibility of “absolute equivalence” between “original” and BSD. In this situation, the risks they face in the absence of a clear statement on the rules of conduct and practice among the synthesis and use of BSD are imminent. The *European Drug Agency* (EMA) and the *Food and Drug Administration* (FDA) have set the standard in the field; in Mexico, the Federal Commission for the Protection from Sanitary Risks (COFEPRIS) has initiated the necessary regulations for good clinical practice. The issue has also occupied various medical associations and specific groups of stakeholders around the world.

This paper discusses the *position of the Mexican College of Rheumatology* regarding BSD in this country. We expose the result of a profound reflection by various opinion leaders dealing with the use, research and regulation of biotech drugs.

## Context

### Biosimilar Drugs

#### Definitions

1. Biotech drug: substance produced through biotechnology with molecular effects either for prevention, treatment or rehabilitation of a disease, and presented in a pharmaceutical form. Identified as such given its pharmacological activity and physical, chemical and biological properties.<sup>1</sup>
2. Innovative biotech drug: this refers to drugs developed originally against a molecular target and has demonstrated efficacy and safety for clinical use.
3. Biotechnology biosimilar: not an innovative biotech drug, which proves to be biosimilar in terms of safety, quality and efficacy with the reference biotech drug.
4. Biotechnology reference: innovative biotech drug that is used as a reference for biotech drug registration.
5. The BSD is developed after the end of the patent of the originally approved biological drug (biological reference drug) and has a similar activity.
6. Biosimilarity tests: tests, assays and analysis which are required to demonstrate that a biosimilar biotech drug has the same quality, safety and efficacy as the biotech drug of reference.

## Worldwide Experience With Non-rheumatic Biosimilar Drugs: An Overview

Since 2004, interferon alfa, recombinant insulin and growth hormone lost their worldwide patent, so it became necessary to regulate all emerging biotech. Regulatory agencies such as EMA and the FDA, and the World Health Organization have begun

developing guidelines to regulate these drugs; among the elements that stand out are: physicochemical characterization, clinical efficacy, safety, immunogenicity, and pharmacovigilance.

Regarding clinical use, BSD are not interchangeable, at least in the European Union, and their clinical action cannot be extrapolated from those produced by innovative medicines.<sup>2</sup> Only in the European Union, from 2006 to 2010 14 BSD were registered and approved.<sup>3</sup>

## Regulatory Framework for Biocomparables in Mexico

Different laws and regulations have been established:

1. Health Law: Article 222 (7 May 1997).
2. Regulation of Health Products: Articles 87 and 167 (4 February 1998).
3. Addendum to the General Health Law: Article 222 Bis (June 11, 2009).
4. Reform to the General Health Law (general framework for biotech and biosimilar drugs, October 19, 2011).
5. Regulation of new molecules (February 2012).
6. Emergency Standard NOM-EM-001-SSA1-2012.

It is noteworthy that, on the basis of the latest Mexican legislation, the regulatory authority has not given any recognition to innovative biotech drugs (see [Annex 1](#)).

## Biosimilar Drugs Through Evidence-based Medicine: Fundamentals, Classification and Practice

Evidence-based medicine is a strategy used by physicians to make the best decisions and must be based on three pillars: the best available information in the international literature, physician's experience and the opinions and preferences of the patient.<sup>4</sup>

As part of this strategy, it has been suggested that classifying the data analysis according to the quality of the studies from which it derives and thereafter generate a recommendation is a good strategy. This is particularly relevant when implementing medical treatment. Highest rating should be assigned to the comparative trials with randomization, while those with a lesser score are case series and expert opinions.<sup>5</sup>

In Mexico, only one drug with registration is marketed, for veterinary use, Kikuzubam<sup>®</sup> (rituximab; Probiomed), as an innovative biotech drug and strictly not considered a BSD. We reviewed the world literature through *PubMed* and *EMBASE* search engines, there are no published phase III clinical studies with this BSD, and it was based on the comparison of data on efficacy and safety of MabThera<sup>®</sup> (rituximab, Roche) that it obtained its approval. In the only study available, mentioned in the prescribing information in its large and small versions, an open-label, randomized, crossover trial involving 54 patients with NHL is mentioned. It showed that there were no differences between the treatments studied. However, there is no clear assessment of adverse effects nor does it specify the reasons for the losses or deaths in each group, there is no clear evidence on the effectiveness and safety of this drug and it is questionable whether it can be used in other diseases.<sup>6</sup> With the information available it is not possible to issue a recommendation

based on the evidence about the biotech drug Kikuzubam® and the claim made by the manufacturer on interchangeability is incorrect.

Other BSD employed in Latin America (Etanar® and Reditux®) only have abstracts presented at rheumatology congresses based on observational studies and funded by the manufacturer, without comparison with other treatments.<sup>7</sup>

### Posture of the Mexican College of Rheumatology

Therapeutic advances in rheumatology include biotechnological drugs produced from living cells and that may include monoclonal antibodies, soluble receptors and receptor antagonists, which modify various functions.

The increased use of these drugs has caused health expenditures to increase significantly. The expiration of several patents for biotech drugs has led to the production of new options that force both doctors and the government, through its regulatory agencies, to seek legal elements that ensure the quality, efficacy and safety, and accessibility of these drugs.<sup>8</sup>

Mexico was the first country in Latin America to have a regulatory standard on BSD (2006) that led to the publication in 2009 of a decree that is added to Article 222 Bis of the General Law of Health.<sup>9</sup>

Under existing Mexican law, the Mexican College of Rheumatology expresses its position on the BSD:

1. It must also be understood that an innovative biotech drug is one that has been developed and registered worldwide for the first time for one or more indications. A BSD is one which through molecular biology techniques achieves a comparable structure and function, similar to the innovative product.
2. The obtention of biotechnology products requires a complex process that does not guarantee that BSD are equal to innovative products. Therefore, BSD efficacy cannot be extrapolated or its safety *be considered interchangeable*.
3. The safety information for long-term monitoring cannot be adequately assessed if patients change an innovative drug for a BSD or *vice versa*. The substitution of the drug cannot be an accepted practice.
4. Approval of a BSD must meet the preclinical and clinical trials identified by Mexican law (Regulation on New Molecules Committee).<sup>10</sup> We recommend the inclusion of Mexican clinicians with expertise in the field to interact with the new molecules Subcommittee of COFEPRIS ([www.cofepris.gob.mx](http://www.cofepris.gob.mx)), to establish the respective report.
5. The label of each product should clearly emphasize that this is an innovative biotechnological (MB) or biosimilar (BSD) drug.<sup>9</sup>
6. The biotech drug maker is obliged to exercise pharmacovigilance for long term side effects and these should be reported to COFEPRIS ([www.cofepris.gob.mx](http://www.cofepris.gob.mx)). We recommend a greater commitment to this responsibility by all health professionals involved with BSD use.
7. The appropriate use of biotech drugs requires the interaction of physicians, pharmacologists and regulatory entities. This can benefit the right to health of patients as long as they count on quality products, effective and safe.
8. This position should be updated in light of new evidence, at least every two years.

Finally, we show that this working group is in favor of BSD and biotech drug development, both in Mexico and in other parts of the world and their approval by regulatory agencies, provided they are subject to the highest standards of quality in terms of production and development, the evaluation of efficacy and safety with adequate phases III and IV, studies followed by a strict

pharmacovigilance program. The goal for the development of BSD must include substantial savings for public health institutions, patients who can afford these medicines with pocket payments and improve access for the wider population to these drugs; however, ensuring maximum therapeutic efficacy and optimal patient safety should take precedence.

### Ethical Responsibilities

**Protection of People and Animals.** The authors state that no experiments were performed on humans or animals.

**Data Confidentiality.** The authors state that no patient data appear in this article.

**Right to Privacy and Informed Consent.** The authors state that no patient data appear in this article.

### Conflict of Interest

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Cardiel, Mario H.: Roche, Pfizer, Bristol-Myers Squibb, Amgen, Lilly, Abbott, MSD.

Espinosa, Rolando: Lilly, Sanofi. He is currently president of the Mexican College of Rheumatology, and is closely related to laboratories that produce drugs with therapeutic applications in rheumatology. He does not receive financial compensation for this honorary position.

Valerio Esquivel, Jorge A.: Merck, Sanofi, Roche, Novartis, Aventis, Merck, Schering Plough, Bristol, Abbott, Centocor.

Barreira-Mercado, Eduardo: MSD, Roche, Novartis, Sanofi.

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### Annex 1. The Relevance of Bioequivalence Studies Based on Biosimilar Drugs

Unlike small molecules, biosimilarity tests should assess the quality, consistency, manufacturing process, safety and efficacy, including tests to determine the structure and physicochemical, biological and immunological properties of the molecule.

The preclinical study protocol comprises:

1. Studies of *in vitro* pharmacodynamics.
2. Comparative studies of pharmacodynamics *in vivo* in relevant animal models if there is a relevant species.
3. Comparative preclinical toxicity studies in relevant species.
4. Comparison and immunogenicity toxicokinetics in animal.
5. Local tolerance, if applicable.

The Mexican Official Standard establishes the performance of Phase I studies (single-dose clinical safety growing), phase II

studies (clinical safety of pharmacokinetics/pharmacodynamics) and phase III studies (clinical therapeutic efficacy and safety); in all these case studies should be comparative to the reference product.

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