Chilean legislation on bioequivalence and biosimilarity and current controversies related to drug interchangeability

Jana Stojanova[a], Mariane Lutz[a], Gabriel Lazcano[b], Marcelo Arancibia[a]

[a] Centro Interdisciplinario de Estudios en Salud (CIESAL), Escuela de Medicina, Universidad de Valparaíso, Viña del Mar, Chile
[b] Escuela de Medicina, Universidad de Valparaíso, Viña del Mar, Chile

* **Corresponding author** marcelo.arancibiame@uv.cl

Citation Stojanova J, Lutz M, Lazcano G, Arancibia M. Chilean legislation on bioequivalence and biosimilarity and current controversies related to drug interchangeability. *Medwave* 2020;20(2):e7825

Doi 10.5867/medwave.2020.01.7825

Submission date 26/11/2019
Acceptance date 28/1/2020
Publication date 25/02/2020

Origin Not commissioned

Type of review Externally peer-reviewed by four reviewers, double-blind

Keywords pharmaceutical preparations, generic drugs, biological products, biosimilar pharmaceuticals, public health

Abstract

Medicines are an economic good and a fundamental component of public and private health spending and decision-making. Assurance of their quality, efficiency, and safety is essential. In Chile, the wide variety of available drugs, including innovator products, and generics—some of which are certified as bioequivalent, while others are not—creates a potentially confusing scenario for both consumers and health providers. In this review, we intend to shed light on the concepts of bioequivalency (the standard permitting interchangeability for small-molecule drugs) and biosimilarity (the standard permitting interchangeability for biological compounds of greater molecular complexity). In both cases, how the active substance interacts with the host organism must be demonstrated by studies designed and carried out for this purpose. Interchangeability is defined as the possibility of using a product of the same active principle, as long as the pharmaceutical form and dosage scheme are the same. Regulations related to bioequivalence and biosimilarity must not only guarantee safety and efficacy when products are interchanged but also facilitate cost savings and access to medicines. Implementation of evidence-based guidelines that standardize concepts of interchangeability could lead to more educated usage and reduced information asymmetry between patients (users) and industry. Drug interchangeability is particularly relevant in two government health initiatives in Chile: the Explicit Guarantees in Health Care (GES) plan, and the Law on Financial Protection for High-Cost Diagnostics and Treatment in Health Care (also known as the "Ricarte Soto Law"). Nonetheless, it is not possible to guarantee that all alternative drug products on the Chilean market are bioequivalents of the reference product. Synthesis of the available knowledge on bioequivalent and biosimilar pharmaceutical products in Chile could facilitate and contribute to stakeholder decision-making and the development of better health policies.

Main messages

- Bioequivalence and biosimilarity are fundamental for interchangeability of small-molecule drugs and biopharmaceuticals.
- Legislation regulating access to drugs and drug interchangeability is currently under discussion in Chile.
- Pharmacologic legislation could be served by including evidence-based criteria for bioequivalence and biosimilarity to guarantee drug interchangeability, and regulatory agencies should have an active role in educating consumers of biosimilar and bioequivalent drugs.

Introduction

Medicines are not only economic goods but also "credence goods"—products whose value is difficult for consumers and non-experts to ascertain. This leaves most decision-making to doctors and/or pharmacists as well as, potentially, pharmacy staff[1]. The trend toward increased global spending on pharmaceuticals is largely explained by aging populations and the growing prevalence of noncommunicable diseases.

In Chile, consumers face high out-of-pocket costs for pharmaceutical products[2]. Various measures have been taken to improve access to medications, including the Law on Financial Protection for High-Cost Diagnostics and Treatment in Health Care (the "Ricarte Soto Law"). Others measures associated with decentralized initiatives (for example, "Popular Pharmacies") and legislative initiatives (such as the Law on Drugs I, and the Law on Drugs II, which is currently under discussion) have also been carried out[3].

There is currently a wide range of pharmaceutical products available in the Chilean market, divided into two categories: innovator (patented) products, and alternative products (drugs that contain the same active ingredient). Not all alternative pharmaceuticals on the Chilean market have undergone tests to demonstrate similar pharmaceutical characteristics to the innovator product. Alternative products that have demonstrated similarity according to set criteria are referred to as "bioequivalents" (for small-molecule drugs) and "biosimilars" (for biological products). This scenario is confusing for both users and providers.

The objective of this review is to describe the concepts of "bioequivalence" and "biosimilarity," and related regulatory issues, and to analyze various controversies associated with these types of drugs currently under discussion in Chile.

Accessibility of medicines in Chile

In its report on Latin America, the United Nations Development Program (UNDP) highlights Chile's guarantee of equitable access to health benefits across different levels of income[4]. However, this access does not extend to pharmaceutical products[5]. In Chile, 90% of spending on drugs is private and only 10% is public, unlike other Organization for Economic Cooperation and Development (OECD) countries, where an average of 43% of spending is private and 57% is public[6]. As a proportion of total health expenditure, this spending breakdown differs by socioeconomic quintile, with those in the lower income tier spending 68% and those with higher income spending 47%[7]. This indicates a lack of protection for people with reduced economic resources, a gap that increases for higher-cost drugs. The eighth Family Budget Survey showed an increase in health spending as a proportion of total household expenditure from 5.2% in 2012 to 6.2% in 2016, with a greater increase in lower-income households and people with higher-than-average age[8,9].

Two governmental initiatives have been implemented to improve access to benefits and treatments: the Explicit Guarantees in Health Care (GES) plan, Law 19,966, which covers highly prevalent pathologies, and the Law on Financial Protection for High-Cost Diagnostics and Treatment in Health Care (the "Ricarte Soto Law," named after a public figure), Law 20,850. Pharmacological treatment is a key aspect of both laws and the products offered to the population as part of the schemes are required to exhibit "proven quality." The economic sustainability of these initiatives depends on access to products with competitive costs, so biosimilar and bioequivalent medicines play a central role.

Interchangeability, bioequivalence, and biosimilarity

Pharmaceutical products marketed in Chile are classified as either innovator products (drugs with a patent for invention) or generics (drugs that are marketed once the license granted to the innovator product expires). Generics must match the quality of the innovator product and constitute a lower-cost alternative for consumers[10]. Generics that are shown to be bioequivalent through standardized testing are considered "interchangeable" and constitute a pharmaceutical equivalent that can be used as an alternative treatment in clinical practice. Under these circumstances it is assumed that the therapeutic effect will be identical to the original product, however the possibility exists that it differs due to a patient's characteristics.

The U.S. Food and Drug Administration (FDA) considers a drug bioequivalent if the area under the plasma concentration versus time curve (area under the curve; AUC) of the active ingredient, over a dosage interval, is not less than 80% and not more than 125% of the AUC exhibited by the innovator drug[11]. For drugs with a narrow therapeutic margin, such as antiepileptics, a lower range has been proposed (between 90% and 111%)[12]. Similar criteria are applied in regulation from Australia[13], Europe[14], and the World Health Organization, constituting a general framework at the population level that might not accommodate drugs that exhibit large inter-individual differences in pharmacokinetics under certain circumstances.

Drug bioequivalence is based on a certification process that guarantees that the alternative products have the same quality, efficacy and safety in their clinical behavior as the reference product, even if they have a different manufacturing origin, ensuring that the amount absorbed and the speed of absorption of the active ingredient are comparable and the bioavailability is similar to that of the innovative product[15].

Bioequivalence in solid pharmaceutical forms that are administered orally (tablets, capsules, or coated tablets) is mainly demonstrated in *in vivo* studies, which allow for evaluation of drug behavior through the measurement of plasma levels over time within a dosing interval. Aqueous solutions, gases or powders are exempt from *in vivo* evaluation and can thus be declared bioequivalent based on abbreviated studies[16].

A "biowaiver" is applied to generics that demonstrate high gastrointestinal solubility and permeability in simple *in vitro* studies, according to the Biopharmaceutical Classification System[17], and is used to register many drugs classified as bioequivalents in Chile. Forgoing the requirement for *in vivo* bioequivalence studies has led to an increase in the number of drugs registered as bioequivalents.

In Chile, all bioequivalent drugs are clearly identified by a yellow stripe on the label and a bioequivalence certification seal. However, as stated, not all generic drugs in Chile are bioequivalent. While internationally the term is used to refer to all bioequivalent products, in Chile it refers principally to those marketed under the name of the active ingredient, regardless of whether bioequivalence is certified. "Generic bioequivalents" are marketed using the chemical name of their active ingredient, whereas "branded bioequivalents" are marketed using a distinct trade name. In addition, there are "branded generics," which may or may not be bioequivalent. Some pharmaceutical laboratories offer versions of each of these three alternatives, but with very different prices, causing confusion among consumers and, often, among health professionals.

Unlike bioequivalent pharmaceuticals that have a small molecular size and reproducible chemical synthesis, biological drugs are obtained or extracted from biological systems such as cell lines, tissues and microorganisms, and are therefore more complex, making them difficult to analyze and characterize using physicochemical methods and bioassays[18,19].

Examples of biopharmaceuticals include monoclonal antibodies, cytokines and hormones, many of which originate as metabolites from living organisms. They are very sensitive to changes associated with the numerous steps involved in the manufacturing process, which are difficult to reproduce, making it impossible to obtain structurally identical molecules and raising reasonable doubt about comparable efficacy[19]. These products are highly relevant in the therapeutic arsenal of chronic inflammatory diseases, such as lupus, rheumatoid arthritis, and ulcerative colitis, in addition to being effective in the treatment of multiple neoplasms. Therefore, they have shown the highest growth in the pharmaceutical industry, comprising 20% of the global market in 2017[20].

In biological drugs, "biosimilarity" is the regulatory term for comparability with the reference product and the criterion for naming the generic versions. Biosimilar drugs are also known as "follow-on" biological agents[19], referring to the expiration of the patents of the innovator drugs, which began in 2001.

Biosimilars and innovator drugs have the same dosage schemes and routes of administration but may have different characteristics related to their complexity and/or production methods (e.g., a similar amino acid sequence but with differences in glycosylation or deamination[19]). Biosimilars must, however, undergo analytical studies to show comparability to the reference agent, including toxicology (primarily through *in vivo* animal models), pharmacokinetic and immunogenetic tests, as well as pharmacodynamic evaluations. In some cases, comparative clinical trials are also requested. Biosimilars should be approved only when they are shown to be comparable to the innovator drug in terms of their physicochemical properties and biologic activity as well as their safety profile and clinical efficacy. Based on data extrapolation, biosimilars may also be authorized for other indications for which the reference agent has been approved[21,22]. However, it should be noted that biopharmaceuticals are heterogeneous molecules that may exhibit complex pharmacodynamics relationships as well as a less predictable clinical effect[18].

A critical aspect in the analysis of biopharmaceuticals is their immunogenicity, given that activation of the immune response is the most severe adverse event associated with their use. This might involve anything from allergic responses to the emergence of autoimmune disorders. These effects are difficult to study, and cannot be predicted, as they are multivariate and depend on factors associated with the drug molecule (pattern of glycosylation, composition of impurities and mechanism of action) and/or the patient, mainly related to the genetic profile, resulting in reactions that are idiosyncratic and not very predictable. For this reason, pharmacovigilance is key in biological drug therapy[23].

"Interchangeability" allows for the replacement of one medicine with another bioequivalent or biosimilar product, using the same pharmaceutical form and dosage, guaranteeing the quality as well as the effectiveness and safety of drug therapy. However, due to the difficulties described above, automatic substitution is not allowed for biological products, as the evidence supporting this practice is scarce and is only available for specific products, such as tumor necrosis factor inhibitors and growth hormone[24,25].

Regulatory aspects

Any alternative to the innovator drug should either be tested for bioequivalence before entering the market or be required to go through an abbreviated certification process requiring approval from a nationally recognized foreign agency. This is the case in some countries of the European Union, Canada, the United States, and Australia, where pharmaceutical products must meet various regulations with regard to quality and pricing in order to be considered interchangeable[26]. In Latin America, certification of bioequivalence of a product is heterogeneous, with countries allowing *in vitro* tests as a feasible alternative to certification from agencies[27]. There are several ways to regulate bioequivalence, including case-by-case studies (e.g. assessing the need for bioequivalence studies according to the clinical risk of the drug), compliance with criteria established by technical advisory committees and the application of guidelines developed by each country[27].

Several other regulations are being considered, such as the restriction of the number of pharmacies per geographic area, the prohibition of advertising of drugs that require a medical prescription and incentives of any kind from pharmaceutical laboratories to health professionals and employees of pharmacy establishments, as well as strict regulation of profit margins of pharmacies. These measures differ from the current situation observed in Chile, where there are multiple incentives to vendors and prescribers, contributing to further confusion regarding conceptual aspects, contributing to practices that are not based on evidence or in the patient's best interest.

In Chile, the bioequivalence policy came into effect through the Law on Drugs I (2014), in which 329 bioequivalent products were registered, increasing to 1,216 in 2017[28]. As of October 2019, 1,555 products are registered with Chile's National Institute of Public

Health (Instituto de Salud Pública; ISP) (http://www.ispch.cl) and a total of 3,000 is expected by the end of 2020.

As observed in the recent report of the National Economic Prosecutor's Office (Drug Market Study EM03-2018), the ISP does not adequately inform users about each drug in the market with regard to aspects such as product availability, scientific studies that support new uses, and potential adverse effects identified though pharmacovigilance, among others[1]. As the availability of medicines labeled as bioequivalents increases, it is necessary to ensure that all alternatives to the innovator drug actually comply with the criteria for this designation[29]. In this context, it would be desirable that the entity in charge, the ISP, play a more active educational role, enabling the user to understand the basis for interchangeability and thus have greater confidence in selecting drugs.

Draft legislation known as the "Law on Drugs II" is currently before Congress. This bill originally consisted of a single article aimed at regulating generic bioequivalent drugs, promoting greater availability and accessibility, and avoiding vertical integration of laboratories and pharmacies[30]. The legislation stipulates changes to Article 101 of the Health Code, proposing that medicines be prescribed under their international nonproprietary name, which would allow consumers to exercise their right to compare medicines with the same active ingredient(s) and choose the product with the most convenient cost. The legislation defines interchangeability as the act of replacing one drug with another that has certified bioequivalence and thus the same international nonproprietary name. In addition, it proposes that each health establishment be required to stock a minimum number of bioequivalent options for a given drug. This creates the potential for "indiscriminate interchangeability" because, as mentioned above, the measure does not ensure that products available in pharmacies have been certified as bioequivalent and are thus truly interchangeable, as the bill does not stipulate bioequivalence studies for certification. The regulatory framework for biosimilar products is relatively recent, as reflected in the history of regulations carried out by external agencies. For example, the first European Medicines Agency (EMA) regulation was published in 2005[31] and updated in 2014[32]. The EMA serves as an advisory body but ultimately member countries regulate the terms for interchangeability internally[21]. The FDA began approving biosimilars in 2010[33].

The Chilean ISP only accepts the results of bioequivalence studies that are carried out in research centers previously accredited or certified—by them, for national centers, or by a high-level foreign health regulatory agency, such as the FDA and the EMA, among others.

The draft legislation known as the "Law on Drugs II" mandates that drug registration be overseen by the ISP. Among other measures aimed at improving patients' accessibility to drugs, the Chilean government has recently (October 7, 2019) simplified the drug approval and registration process, reducing it to a maximum of 3 months, and approved the bioequivalence of products certified by a top-level agency such as the FDA. Likewise, it has delegated responsibility for inspecting and certifying foreign-based production plants for compliance with Good Manufacturing Practices (GMP) to ANAMED (the National Agency of Medicines, part of the ISP). Oversight of production plant compliance with GMP is a difficult task, as it requires a large budget to provide all of the required human and material resources.

In Chile, the revisions to the drug law currently in process should include the development of one comprehensive guide with standardized definitions of concepts relevant to interchangeability and the criteria that define it, stipulating scenarios in which it is acceptable to apply criteria obtained from analytical studies and/or recognized by foreign agencies.

Conclusions

Policies governing drug interchangeability differ between countries, with different requirements. In Chile, health policies related to access and prescribing are undergoing major revisions to promote greater access to less costly but equally effective drugs, such as bioequivalents and biosimilars.

Clarity on this subject can impact and contribute to decision-making by prescribers and users, as well as to the development of public policies on bioequivalent and biosimilar pharmaceutical products in Chile.

Notes

Author roles and contributions

All authors contributed to the conceptualization, methodology, investigation, writing of original draft, and review and editing of final draft.

Funding

The authors declare that there were no external sources of funding.

Conflicts of interests

The authors declare that they have no conflicts of interest involving this work.

Ethics

This study did not require evaluation by an ethical–scientific committee because it is based on secondary sources.

From the editors

The original version of this manuscript was submitted in Spanish. The English translation was copyedited by the journal.

References

1. Fiscalía Nacional Económica. Estudio sobre el mercado de medicamentos (EM03-2018). Santiago; 2018. [On line]. | Link |
2. Benítez A, Hernando A, Velasco C. Gasto de bolsillo en salud: una mirada al gasto en medicamentos. Puntos Ref. 2019;(502):1–23. [On line]. | Link |
3. Silva-Illanes N, Cuadrado C, Mendoza C, Guerrero C. Resumen de evidencia para política de regulación de precios de medicamentos para apoyar la toma de decisiones en Políticas de Salud. Santiago; 2017. [On line]. | Link |
4. Infante A, Paraje G. La Reforma de Salud en Chile. Santiago; 2010. [On line]. | Link |
5. Palacios Escobar Á. El Informe de Desarrollo Humano 2013: análisis internacional de los indicadores del progreso humano. Econ Inf. 2013;382:36–54. | CrossRef |
6. Diario Constitucional. Publican "Proyecto de Ley Fármacos II: introduciendo más competencia en el mercado". 2018. [On line]. | Link |
7. Ministerio de Salud de Chile. Encuesta Nacional de Salud 2009-2010. 2010. [On line]. | Link |
8. Instituto Nacional de Estadísticas. VIII Encuesta de Presupuestos Familiares. Santiago; 2018. [On line]. | Link |
9. Benítez A, Hernando A, Velasco C. Radiografía del gasto de bolsillo en salud en Chile: análisis del cambio en el gasto entre 2012 y 2016. Puntos Ref. 2018;(491):1–22. [On line]. | Link |
10. Cameron A, Mantel-Teeuwisse A, Leufkens H, Laing R. Switching from originator brand medicines to generic equivalents in selected developing countries: how much could be saved? Value Heal J Int Soc Pharmacoeconomics Outcomes Res. 2012;15(5):664–73. | CrossRef |
11. Raines, KW. A Primer on Generic Drugs and Bioequivalence: an overview of the generic drug approval process. [On line]. | Link |
12. Yu LX, Jiang W, Zhang X, Lionberger R, Makhlouf F, Schuirmann DJ, et al. Novel bioequivalence approach for narrow therapeutic index drugs. Clin Pharmacol Ther. 2015 Mar;97(3):286-91. | CrossRef | PubMed |
13. Mastan S, Bhavya Latha T, Ajay S. The basic regulatory considerations and prospects for conducting bioavailability/bioequivalence (BA/BE) studies – an overview. Comp Eff Res. 2011;1:1–25. | CrossRef |
14. Hema Nagadurga D. Bioavailability and Bioequivalence Studies. Pharmaceutical Formulation Design - Recent Practices. IntechOpen; 2019. | CrossRef |
15. Chow SC. Bioavailability and bioequivalence in drug development. Wiley Interdiscip Rev Comput Stat. 2014;6(4):304–12. | CrossRef |
16. Biblioteca del Congreso Nacional de Chile. Decreto 122 Exento. Modifica decreto No27 Exento, de 2012, que aprobó la "Norma que define los criterios destinados a establecer la equivalencia terapéutica en productos farmacéuticos en Chile." Santiago; 2014. [On line]. | Link |
17. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995 Mar;12(3):413-20. | CrossRef | PubMed |
18. Saavedra I, Quiñones L. Intercambiabilidad de medicamentos de origen biológico (biofármacos): consideraciones acerca de la aprobación de formulaciones biosimilares (biogenéricos) en Chile. Rev Méd Chile. 2006;134:1583–8. | CrossRef |
19. Martos-Rosa A, Martínez-de la Plata J, Morales-Molina J, Fayet-Pérez A, Acosta-Robles P. Biosimilares, el camino ha comenzado. Farm Hosp. 2015;39(2):114–7. | CrossRef |
20. Rickwood S, Kleinrock M, Núñez-Gaviria M. The Global Use of Medicines: Outlook through 2017. New Jersey; 2013. [On line]. | Link |
21. Rodríguez D, Asensio C. Fármacos biológicos y biosimilares: aclarando conceptos. Aten Prim. 2018;50(6):323–4. | CrossRef |
22. de Mora F. Biosimilar: what it is not. Br J Clin Pharmacol. 2015;80(5):949–56. | CrossRef |
23. European Medicines Agency (EMA). Guideline on similar medicinal products containing monoclonal antibodies, non-clinical and clinical issues. 2010. [On line]. | Link |
24. Ebbers HC, Muenzberg M, Schellekens H. The safety of switching between therapeutic proteins. Expert Opin Biol Ther. 2012;12(11):1473–85. | CrossRef |
25. Weise M, Kurki P, Wolff-Holz E, Bielsky MC, Schneider CK. Biosimilars: the science of extrapolation. Blood. 2014;124(22):3191–6. | CrossRef |
26. Galgatte UC, Jamdade VR, Aute PP, Chaudhari PD. Study on requirements of bioequivalence for registration of pharmaceutical products in USA, Europe and Canada. Saudi Pharm J. 2014 Nov;22(5):391-402. | CrossRef | PubMed |
27. Vacca-González C, Fitzgerald J, Bermúdez J. Definición de medicamento genérico ¿un fin o un medio? Análisis de la regulación en 14 países de la Región de las Américas. Rev Panam Salud Publica. 2006;20(5):314–23. | CrossRef |
28. Departamento de Estudio e Inteligencia. Disponibilidad de medicamentos bioequivalentes en el mercado farmacéutico metropolitano y sus ventajas económicas para los consumidores. Santiago; 2017. [On line]. | Link |
29. Holman A. Is Bioequivalence a Sufficient Measure of Equivalence? J Leg Med. 2019 Jul-Sep;39(3):247-261. | CrossRef | PubMed |
30. Senado de la República. Modifica el Código Sanitario para regular los medicamentos bioequivalentes genéricos y evitar la integración vertical de laboratorios y farmacias (Boletín 9914-11). Valparaíso; 2015. [On line]. | Link |
31. Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products. London; 2005. [On line]. | Link |
32. Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. London; 2014. [On line]. | Link |
33. Zhai MZ, Sarpatwari A, Kesselheim AS. Why Are Biosimilars Not Living up to Their Promise in the US? AMA J Ethics. 2019 Aug 1;21(8):E668-678. | CrossRef | PubMed |

Correspondencia a
Oficina 1107, Edificio R2
Angamos 655
Reñaca
Viña del Mar
Chile