

Review: Application of Bioequivalence Testing of Medicines in Peru

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ABSTRACT

This is a review of the current status of drug bioequivalence studies in Peru. A bibliographic search was conducted in PubMed (Medline database) for bioequivalence studies in Peru. Generic drugs constitute the basis of pharmacological requests in health care systems in Latin American countries. Peru has enacted laws and regulations that require bioequivalence studies of high health risk drugs and exemptions, based on international legislation, to be conducted in research centers accredited by the authority of Health. There is a list of 19 drugs that must demonstrate their therapeutic equivalence through in vivo or in vitro studies, of which 13 have shown bioequivalence in vivo, and 8 of those have shown bioequivalence in vitro. There is a challenge for health authorities to enforce the current legislation and an even greater challenge for pharmaceutical laboratories to demonstrate bioequivalence of multi-source drugs with the reference drug.

KEYWORDS: Bioequivalence, multi-source drug, reference drug, drug regulation, in vitro testing

INTRODUCTION

In 1984, the North American Congress approved the law of "patent protection and data exclusivity" for the pharmaceutical industry of generic drugs. This law was to initiate relative bioavailability studies to demonstrate therapeutic equivalence that would guarantee similarity in safety and efficacy of a generic (multi-source) drug with the innovative drug. This law also intended to provide accessibility to drugs that otherwise may be too expensive, therefore assuring an economic benefit (1, 2). Subsequently, the World Trade Organization (WTO) and the World Health Organization (WHO) recommended that the countries that are part of these organizations grant 20 years of exclusive sale to the innovative drug, which was extended to trade agreements with the countries where the innovative drugs originated (1). After the government grants the patent for the innovative drug, then the government grants licenses to similar and

generic drug manufacturers so they can produce and develop other formulations in compliance with Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP) (3, 4).

Innovator drugs are expensive, so they are not accessible to a large sector of the population in Peru. The use of generic drugs is usually cheaper compared to the innovator (5, 6). In Peru, bioequivalence studies have been mandated by the Law of Pharmaceutical Products, Medical Devices and Health Products, Supreme Decree, which regulates the interchangeability of drugs, and by the Ministerial Resolution on the list of generic essential drugs (7–10). To date, the implementation process of these studies has been very slow. In this review, we will highlight studies of bioequivalent generic drugs in Peru (5, 11).

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METHODS

A review of the published literature on bioequivalence studies was conducted and compiled through the PubMed/Medline database. The search terms used were "bioequivalence", "therapeutic equivalence," and "in vivo and in vitro bioequivalence in Peru." The selection criteria included articles published in English and Spanish. No filters referring to the year of publication were used, and November 15, 2021 was the cut-off date.

At the same time, the web portals of the General Directorate of Medicines, Supplies and Drugs (DIGEMID) and the Ministry of Public Health of Peru were searched for regulations that require application and implementation of bioequivalence studies in Peru. Based on the collected literature, this review article has been divided into concepts, regulatory aspects, current state of studies, and future perspectives.

CONCEPTS THAT SUPPORT BIOEQUIVALENCE STUDIES

Throughout the world, three types of drugs products exist - the innovator (brand name drug), the similar (medicines manufactured by different laboratories under the same commercial name), and the generic, all of which are prepared by the pharmaceutical industries according to quality standards and regulated and authorized for prescription by the health authorities of each country (2, 4).

An innovator drug is the pharmaceutical product that has been developed through scientific research, going through all phases (i.e., discovery, preclinical, and phase I, II, and III clinical trials) to demonstrate its quality, safety, and therapeutic efficacy. The product is registered for the first time for commercialization with a regulatory agency (2, 12, 13). For an innovative product, development and commercialization requires a large financial investment, which is typically undertaken by a multinational pharmaceutical industry for 7–15 years. Because of this effort, a patent is justified and obtained for the active drug and the manufacturing process. A patent usually lasts for 20 years (3). The "reference" or "comparator" is the innovator product with which the generic or similar product is intended to be interchangeable, as shown in a bioequivalence study. Normally the reference is the innovator product that was registered in the country of origin (i.e., where it was patented and produced), but if the product is no longer marketed in the country, a similar drug is sought from the pharmaceutical market (12, 13). A "similar" drug has the same commercial name, pharmaceutical form, active ingredient, and amount of

drug as the innovator drug, but no bioequivalence study has been done to establish interchangeability with the innovator drug (6, 12, 13).

The terms "generic" or "multi-source" have been used since 1967 to describe drugs that are pharmaceutical equivalents that may or may not be therapeutic equivalents (6, 12, 14). These drugs may differ in the quality of the excipients (binders, disintegrants, glidants, stabilizers, flavorings, etc.) and the manufacturing process. Generic products are manufactured by different pharmaceutical laboratories with the name of the international non-proprietary designation (INN) of the drug after the patent has expired (6, 14). These generic drugs will comply with international quality standards (3). Ideally, these drugs should be therapeutically equivalent to the innovative product and interchangeable (12, 13).

An interchangeable drug product is a generic or similar product that has demonstrated therapeutic equivalence with the reference or innovator by an in vivo or in vitro bioequivalence study. These studies are used to compare similar and generic/multi-source products with the innovator to show that they have the same safety and efficacy profile, thereby establishing interchangeability in clinical practice (2, 12).

REGULATORY ASPECTS OF BIOEQUIVALENCE

The enactment of the National Drug Policy in 2004 in Peru encouraged bioavailability studies be conducted for high-risk drugs (15). In 2009, Law no. 29459 (articles 4, 10, and 20) mandated that drugs must have bioequivalence studies (7). In 2011, Supreme Decree 016-2011-SA indicated that for the registration and re-registration of category 1 and 2 drugs, therapeutic equivalence studies should be included (16). On the basis of these legal antecedents, in 2015 the drug interchangeability regulation was published, the purpose of which was to receive technical and regulatory suggestions (17). The regulation was approved by Supreme Decree No. 024-2018-SA and was enacted on March 16, 2019 (8). This regulation is inspired, conceptualized, and elaborated on the basis of guidelines of the WHO, United States Food and Drug Administration (FDA), European Medicines Agency (EMA), and Canada's General Directorate for Health Products and Foods (Health Canada). In this decree, health risk criteria have been taken into account; there are instructions to carry out studies gradually over time and to use the specified method to demonstrate therapeutic equivalence. In vivo bioequivalence studies are conducted in research centers that must be certified, accredited, and meet

criteria of the Regulation of Clinical Trials of the National Institute of Health (INS). These research centers also have the supervision and technical opinion of the DIGEMID. Initially, the studies are conducted in the laboratory of the National Quality Control Center (CNCC) of the INS (8).

For relative bioavailability studies of a multi-source drug, DIGEMID is responsible for certifying and publishing on its website a list of reference or comparator drugs, including those with a health requirement and those from voluntary applications (18, 19). The preferred choice is the innovator (or reference) product manufactured and marketed in Peru. Alternative choices are, in order of priority, the innovator product from another country; the reference drug described in the WHO list; the innovator product from a country that is a member of the International Council for Harmonization (ICH); or lastly, the leading drug in the pharmaceutical market (8, 20).

Article 14 provides a long list of certain drugs that require in vivo therapeutic equivalence studies in Peru (8). These products include immediate-release drugs administered orally with a systemic effect, drugs with a narrow therapeutic margin and critical use, drugs where there is scientific evidence of bioavailability or bioequivalence problems related to the active pharmaceutical ingredient (API) or its formulations (not related to dissolution problems). In vivo studies are needed when there is scientific evidence that polymorphism of the API, the excipients, and/or the pharmaceutical processes used in manufacturing influence bioavailability. In vivo studies are also required to establish equivalence through comparative clinical, pharmacodynamic, dermatopharmacokinetic studies, and/or in vitro studies for drugs designed for systemic absorption (non-oral and non-parenteral); these include transdermal patches, suppositories, testosterone gel, contraceptives inserted into the skin, and others; modified-release drugs that act by systemic absorption; fixed-dose combination drugs with systemic action where at least one of the APIs require studies in vivo; products other than solutions for non-systemic use (oral, nasal, ocular, dermal, rectal, vaginal application) designed to act without systemic absorption. Article 27 mentions drugs that do not require bioequivalence studies (parenteral [intravenous, subcutaneous or intramuscular] as an aqueous solution, elixirs, syrups, tinctures, powders for reconstitution as a solution, aqueous solutions for inhalation through nebulizers and nasal drops, aqueous solutions for optic or ophthalmic use, and pharmaceutical forms in gases), but these drugs must meet specifications of the corresponding pharmacopoeia or manufacturing laboratory's own

technique when appropriate (8). DS No 024-2018-SA-MINSA requires in vitro bioequivalence studies of lamivudine (150 and 300 mg tablets), zidovudine (100 capsules and 300 mg tablets), lamivudine and zidovudine combination therapy (150 and 300 mg tablets), and diazepam (10 mg tablets) (8). Subsequently, Ministerial Resolution No. 404-2021 (March 19, 2021) expanded the list of drugs for which therapeutic equivalence must be demonstrated through in vivo or in vitro studies (Table 1) (8, 19, 21, 22).

Regarding the legislation on relative bioavailability studies in Latin American countries (Argentina ANMAT3185/99; Brazil ANVISA 987/99; Colombia INVIMA 1400/2001; Costa Rica SINALVI N° MS-CTI-001-2021; Chile MINSAL 500/12; Ecuador R. ARCSA -DE- 015-2018JCGO; Mexico NOM-177-SSA1-2013; Paraguay R.N° 077/18; Uruguay Decree N° 12/007; Venezuela R.N° 212-2006), all include drugs with a narrow therapeutic margin (they have very close therapeutic and toxic concentrations). Also included are drugs indicated for serious conditions (antibiotics, anticonvulsants, antineoplastics, antiretrovirals, antiarrhythmics, digitalis, immunosuppressants, among others), drugs with incomplete absorption, low solubility, instability, and those with evidence of bioavailability problems.

CURRENT STATUS OF BIOEQUIVALENCE STUDIES

Relative bioavailability studies demonstrate the bioequivalence of a generic drug (multi-source) in comparison with the reference, and therapeutic interchangeability is established in clinical practice. However, for a certain group of drugs, therapeutic equivalence is established through in vitro bioequivalence studies, based on the criteria of the Biopharmaceutical Classification System (BCS). Solid oral immediate-release medications must meet one of the following BCS criteria (8, 10, 22–24).

- Class I (high solubility and high membrane permeability): very fast or rapid dissolution with release of more than 85.0% of drug in 15 or 30 min, respectively. Excipients criterion: the drugs should not contain excipients that affect the absorption of the drug.
- Class III (high solubility and low membrane permeability): very fast dissolution with release of more than 85.0% of drug in 15 min. Excipients criterion: the test drugs must contain the same excipients in similar amounts as the reference product.

Table 1. Medicines that Require In Vivo and/or In Vitro Bioequivalence Studies in Peru (8, 19, 21, 22)

Category	API	Dosage Form	Dose	Type of study
Anticonvulsants	Valproic acid, semisodium valproate, and sodium divalproate	Extended-release tablet	250 and 500 mg	In vivo
	Valproic acid, semisodium valproate, sodium divalproate, and sodium valproate	Delayed release tablet, coated gastro-resistant tablet, and enteric-coated tablet	250 and 500 mg	In vivo
	Carbamazepine	Tablet	200 mg	In vivo
	Sodium phenytoin	Capsule	100 mg	In vivo
	Lamotrigine	Compressed tablet	50 and 100 mg	In vivo
	Lamotrigine	Dispersible or chewable tablet	50, 100, and 200 mg	In vivo
	Levetiracetam	Extended-release tablet	500 mg	In vivo
	Oxcarbazepine	Tablet	300 and 600 mg	In vivo
Antiarrhythmics and Digitalis	Verapamil hydrochloride	Coated tablet	80 mg	In vivo
	Digoxin	Tablet	0.25 mg	In vivo
Anticoagulants	Warfarin sodium	Tablet	5 mg	In vivo
Bronchodilator	Theophylline	Sustained-release tablet	250 mg	In vivo
Hormones (thyroid)	Levothyroxine sodium	Tablet	25, 50, 75, 100, 125, and 150 mcg	In vivo
Immunosuppressants	Azathioprine	Coated tablet	50 mg	In vivo
	Mycophenolate mofetil	Capsule and coated tablet	250, 250, and 500 mg	In vivo
	Tacrolimus	Capsule	0.5, 1, and 5 mg	In vivo
Psychopharmaceutical	Lithium carbonate	Tablet	300 mg	In vivo
Other	Topiramate	Coated tablet	25, 50, and 100 mg	in vitro
	Levetiracetam	Coated tablet	500 and 1000 mg	in vitro
	Levodopa + carbidopa	Tablet	25 and 250 mg	in vitro

API: active pharmaceutical ingredient.

Table 2 lists the relative bioavailability studies that demonstrate bioequivalence, conducted by pharmaceutical laboratories in accordance with regulations and laws. Table 3 lists in vitro bioequivalence studies conducted by researchers from various Peruvian universities (5, 10, 23–28).

FUTURE PERSPECTIVES

Despite the efforts and dedication of regulators to implement bioequivalence studies in Peru, progress has been slow. Health authorities and university researchers encourage and promote the performance of bioequivalence studies, and laboratory pharmacists comply with regulations for registration and re-registration of their pharmaceutical products. All this effort makes it possible to have a greater number of bioequivalent generic drugs that fulfill their social good, that is, to be accessible and available to the population with fewer economic resources (3, 14). By having bioequivalent multi-source drugs, Peruvian medical specialists can prescribe them in clinical practice to demonstrate interchangeability with the innovative drug for a specific disease (15). Bioequivalence and pharmacogenomic studies are essential in the Peruvian

population, who have tricontinental (European, African, Asian) and Latin American ancestry (*CYP2D6*, *CYP2C9*, *CYP3A4* genes, and others). Bioavailability may vary according to genetics, leading to personalized doses to optimize pharmacological therapy (29, 30).

CONCLUSIONS

Legislation has been enacted to mandate in vitro and in vivo bioequivalence studies in Peru; however, there is still a challenge for health authorities to enforce current legislation and an even greater challenge for pharmaceutical laboratories to demonstrate bioequivalence of multi-source drugs with reference drugs. Having bioequivalent (quality, efficacy, and safety) medications (multi-source and similar commercial brand) guarantees interchangeability in clinical practice with the reference medication (efficiency).

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Table 2. In Vivo Bioequivalent Drugs Approved by DIGEMID in Peru (8, 17)

In Vivo Bioequivalent	Dosage Forms (Dose)	Brand Name, Manufacturer (Certificate Number)	Indication
Cyclosporine	Soft capsule (100 mg)	Supramunn, Teva Peru SA (EE03968)	Immunosuppressive drug
Carbidopa+ Levodopa	Tablet (25 and 250 mg)	Trade Name, Sanofi Aventis Del Peru SA (EE1466)	Parkinson's disease
Cilostazol	Tablet (25 and 250 mg)	Cilosvitae, Galenicum Health Peru SAC (EE01870)	Phosphodiesterase 3 inhibitor, vasodilator, and antiplatelet agent
Dutasteride + Tamsulosin	Prolonged-release capsule, hard (0.5 and 0.4 mg)	Bripost-TD, QM Pharma Quality Medicine SAC (EE09137).	Benign prostatic hyperplasia
Escitalopram	Coated tablet (20 mg)	Etalpram, Eurofarma Peru SAC (EE04274)	Antidepressant (selective serotonin reuptake inhibitor)
Etoricoxib	Coated tablet (90 and 120 mg)	Movicoxib, Deutsche Pharma SAC (EE09486 and EE09380)	Non-steroidal anti-inflammatory drug (selective COX-2 inhibitor)
Ibrutinib	Hard capsule (140 mg)	Binap, Varifarma SA (EE07537)	Bruton's tyrosine kinase inhibitor (BTK), antineoplastic
Lamivudine + Zidovudine	Coated tablet (150 and 300 mg)	Trade Name, Seven Pharma SAC (EE02372)	Trade Name, Seven Pharma SAC (EE02372)
Olanzapine	Coated tablet (10 mg)	Olazanvitae, Galenicum Health Peru SAC (EE01928)	Atypical antipsychotic drug
Quetiapine	Coated tablet (25 mg)	Trade Name, Sanofi Aventis Del Peru SA (EE00899)	Atypical antipsychotic drug
Rosuvastatin	Coated tablet (20 mg)	Xuniro, Sanofi Aventis Del Peru SA (EE00507 and EE00027)	Statin inhibitor of HMG-CoA reductase
Sitagliptin	Coated tablet (100 mg)	Sitavitae, Galenicum Health Peru SAC (EE09486)	Antihyperglycemic drug that belongs to the class of dipeptidyl-peptidase 4 inhibitors (DPP-4 inhibitor)
Ceftriaxone	Iny (1 g)	Betasporina, Medifarma*; Cefalogen, Eurofarma Peru SAC* (EE04413 and EE05383)	Antibiotic

DIGEMID: General Directorate of Medicines, Supplies and Drugs.

*These laboratories have voluntarily accepted bioequivalence studies, since powders for solution for injection do not require bioequivalence studies

Table 3. In Vitro Bioequivalent Generic Drug Comparison Studies from Peru

API	Results and Conclusions	Reference
Amlodipine	Amlodipine generics are in vitro equivalent to the reference drug.	24
Amoxicillin, Doxycycline, Fluconazole	The generics doxycycline and amoxicillin are equivalent. Fluconazole was not equivalent.	2
Carbamazepine	Generics of carbamazepine are equivalent.	10
Diazepam	Generic diazepam not equivalent.	26
Phenytoin	Phenytoin generics are not equivalent.	23
Glibenclamide	Generics of glibenclamide are equivalent.	5
Ibuprofen	Generic of ibuprofen are equivalent.	27
Paracetamol, Chlorphenamine, Phenylephrine	The three types of generics are not equivalent.	28

API: active pharmaceutical ingredient.

CONFLICTS OF INTEREST

The authors disclosed no conflicts of interest related to this article.

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