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ORIGINAL RESEARCH

Policy of Multisource Drug Products in Latin America: Opportunities and Challenges on the Application of Bioequivalence In Vitro Assays

Claudia Miranda-Pérez de Alejo[1] · Alexis Aceituno Álvarez[2] · Gustavo Mendes Lima Santos[3] · Mirna Fernández Cervera[4] · Helgi Jung-Cook[5] · Miguel Ángel Cabrera-Pérez[1]

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Abstract

Background The replacement of traditional in vivo bioequivalence studies by in vitro dissolution assays, based on the biopharmaceutical classification system (BCS), has emerged as an important tool for demonstrating the interchangeability of multisource products. This paper summarizes the current implementation of the BCS-based biowaiver for the development of multisource products in Latin America, and identifies several challenges and opportunities for greater convergence and application of BCS regulatory requirements.

Methods Differences and similarities between the current BCS-based biowaivers' guidelines proposed by two relevant regulatory agencies for the Latin American region (FDA and WHO) and the new ICH harmonization guideline were identified and compared. An update of the BCS-based biowaiver guideline for Latin American countries was also considered, based on the respective regulatory information on bioequivalence studies, which is publicly available.

Results About 50% of the Latin American countries analyzed have no information on the implementation of any bioequivalence standards, while in the countries where bioequivalence studies are considered, the acceptance and application of BCS-based biowaiver requirements is quite heterogeneous. This situation contrasts with the international trend of global harmonization for BCS-based biowaiver guidance, suggesting the need in Latin America to identify opportunities and overcome challenges to improve the development of BCS-based biowaivers to avoid costly and time-consuming in vivo bioequivalence studies.

Conclusions The study shows that the region is in a position to improve access to safe and effective medicines at a reasonable cost by applying BCS-based biowaiver guidance.

Keywords Bioequivalence · Latin America · Dissolution · Biowaiver · BCS · Generic drugs · Drug regulations

Introduction

In recent years, generic or multisource drug products (small molecules) have been gaining ground in terms of production volume and market share. Multisource drug products contain the same active pharmaceutical ingredient (API) or drug substance in the same dosage form, the same strength, and are administered by the same route [1]. These products are marketed by more than one manufacturer and have a lower price compared to their brand-name alternatives, which has led many countries around the world to promote multisource medicine prescription. In developed countries such as the United States, they account for more than 90% of total prescriptions [2], while in the United Kingdom, Canada and Germany they account for more than 60% [3]. These figures are relevant and several factors such as the loss of patent

✉ Miguel Ángel Cabrera-Pérez
macabreraster@gmail.com; macabrera@uclv.edu.cu

1 Unit of Modeling and Experimental Biopharmaceutics, Centre of Chemical Bioactive, Central University of Las Villas, Villa Clara, 54830 Santa Clara, Cuba

2 ANAMED Department, Institute of Public Health, Chile and Faculty of Pharmacy, University of Valparaiso, Valparaiso, Chile

3 General Office of Medicines and Biological Products, Brazilian Health Regulatory Agency (ANVISA), Brasília, DF, Brazil

4 Department of Pharmacy, Institute of Pharmacy and Foods, 17100 Havana, Cuba

5 Department of Pharmacy, Chemistry Faculty, UNAM, Mexico, DF, Mexico

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protection for popular brand-name drugs, the lack of government support and the development of new and complex multisource products are driving this growth [4].

Today, the application of bioequivalence assays as a surrogate indicator of safety and efficacy of multisource drug products is a requirement of major drug regulatory agencies [5]. The Food and Drug Administration (FDA), the World Health Organization (WHO) and the European Medicines Agency (EMA) provide for mandatory bioequivalence studies for the registration and marketing of multisource drugs, through comparative human pharmacokinetic or pharmacodynamic studies, comparative clinical trials or comparative in vitro tests based on the Biopharmaceutical Classification System (BCS) [1, 6, 7].

BCS is a scientific framework that was created to classify the API of immediate release solid oral dosage forms based on their aqueous solubility and intestinal permeability properties [8]. According to both properties, BCS classifies all drugs as belonging to one of four classes: Class 1 (high solubility/high permeability), Class 2 (low solubility/high permeability), Class 3 (high solubility/low permeability) and Class 4 (low solubility/low permeability) [9]. The combination of these properties with the dissolution rate of the API are considered the three most important factors that modulate the rate and amount of the drug absorbed (bioavailability). Once the drug has been classified, it is possible to establish whether in vitro dissolution tests can replace in vivo bioequivalence studies, known as "biowaiver" [8].

A biowaiver eliminates unnecessary exposure of healthy individuals to drugs, reduces the regulatory burden and provides economic relief, while maintaining a high standard of public health for therapeutic equivalence [10]. Harmonization between FDA, WHO and EMA with respect to BCS biowaiver considerations have been widely documented. Although there are several similarities in the definition of highly soluble and highly permeable compounds, significant differences in this regulatory guidance remain between these organizations [11–13].

These efforts have recently led to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH M9 guideline) to published a consensus guideline for BCS-based biowaiver to create an understanding of its applicability and the conditions of waiving, which will apply worldwide [14]. This guideline would be relevant for reducing in vivo bioequivalence studies and therefore improve patient access to medicines and help many generic pharmaceutical companies and regulatory agencies to produce and approve safe and effective drugs, respectively. At the same time, the International Pharmaceutical Federation (FIP) (www.fip.org) has been working in collaboration with WHO on the topic of biowaiver of drug products. To date, FIP has published more than 40 biowaiver monographs of drugs included in the WHO Essential Medicines List, which has increased the international relevance of BCS-based approval.

In contrast, the application of in vitro bioequivalence requirements by national regulatory agencies in Latin America is highly variable [15]. Since 2007, countries such as Chile, Brazil, Uruguay and Argentina were among the first in the region to introduce BCS-based biowaiver strategies; other countries, such as Mexico and Guatemala, limited these studies to few drugs, while the immense majority of countries in the region have not yet implemented any bioequivalence standards [15]. This situation, joined to the pressure of cost containment and poor manufacturing practices, contributes to the prevalence of low-quality and counterfeit medicines in some Latin American and Caribbean countries [16].

Bearing in mind the above situation, the main objectives of this paper are to describe the current status of implementation of the BCS-based biowaiver and the impact of this guideline on multisource drug policy in Latin America, as well as to identify the main challenges and opportunities for further harmonization and application of the BCS regulatory requirements to demonstrate therapeutic interchangeability of multisource products and to improve access to safe and effective medicines.

Materials and Methods

Considering that mostly all Latin American countries follow the regulations raised by WHO (https://www.who.int/) and FDA (https://www.fda.gov/) regulatory agencies, these current BCS-based biowaiver guidances were summarized and compared. At the same time, the ICH consensus guideline on BCS-based biowaivers (https://www.ich.org/) was also discussed [17].

Official and publicly available information on bioequivalence and therapeutic interchangeability of multisource products from regulatory authorities in Latin America was analyzed and used to select the countries of the study. The websites of the regulatory agencies, Ministries of Health and other government entities were consulted for each of the selected countries to review the most recent and relevant information about the implementation of the BCS-based biowaiver, as well as the existence of data on drug approvals by the BCS biowaiver, the list of biowaiver candidate drugs, the centers accredited for in vitro bioequivalence assays, and other related information. An analysis of the differences in the implementation of the BCS-based biowaiver in the Latin American region was exemplified by the cases of Chile, Brazil and Mexico. In the case of Chile was also analyzed the number of abbreviated new drug applications (ANDAs)

approved in the last decade and their distribution by therapeutic area.

All APIs listed by Latin American regulatory authorities for which a biowaiver decision based on BCS (BCS Class 1 and 3) has been obtained or granted were analyzed. A combined classification scheme, integrating a wide range of in silico, ex vivo, in situ and in vitro permeability models, was used to improve the accuracy of the provisional BCS classification (majority voting system) [18]. Drug compounds with a narrow therapeutic index; with poor solubility according to the BCS classification (BCS Class 2 and 4) or with a high health risk were not considered [1]. The information collected was summarized in tables to make comparisons between countries.

Results

International BCS-Based Biowaiver Guidelines Comparison

Since the first FDA publication in 2000 on the use of the BCS-based biowaiver to demonstrate the interchangeability of multisource drugs, other regulatory authorities and international agencies have published their own guidelines. These documents differ significantly from the first proposal published. One of the main differences is related with the classification of API with high solubility. For WHO and ICH, an API is considered highly soluble when the highest single therapeutic dose is soluble in 250 mL or less of aqueous media in the pH range of 1.2–6.8 at $37 \pm 1°$. Meanwhile, for the FDA guideline the dose considered is the highest strength dose. Other differences are the cutoff value for high permeability drugs (absolute bioavailability, $F \geq 85$), the pH range considered for high solubility studies (between 1.2 and 6.8), and the BCS classes for biowaiver (Class 1 and 3) [1, 6, 7]. Table 1 shows in detail a comparison of the updated BCS-based biowaivers from these regulatory authorities (FDA and WHO) as well as the new ICH guideline [14].

Analysis of BCS-Based Biowaiver Guidelines in Latin America

The implementation of BCS-based biowaiver requirements in Latin American countries is quite different among regulatory authorities [15, 19]. As can be seen in Table 2, there is no clear harmonization among regulatory agencies. Some particular views on the application and interpretation of the BCS-based biowaiver are described below.

Brazil

Brazil was one of the first countries in Latin America to include bioequivalence as a requirement for generic drug registration [15] and in 2011, the principles of the BCS-based biowaiver were added to the legal framework of the Brazilian Health Regulatory Agency (Anvisa) [20]. Although the applicability of the biowaiver to identify the low risk of obtaining nonbioequivalent results for BCS Classes 1 and 3 has been corroborated in 500 bioequivalence studies randomly taken from the razilian System of Bioequivalence and Pharmaceutical Equivalence database [21], only a positive list of 21 Class 1 APIs are candidates for the biowaiver and the drug products containing one of these APIs will have the possibility of obtaining a national registration [22].

All applicants for BCS biowaiver candidates must submit to Anvisa the test of API solubility and the comparability of the test product's dissolution profile with the local reference product, following the protocol established in the bioequivalence guideline [20]. If high solubility of the API and comparability of the dissolution profiles (similarity factor, f2) are not achieved, the BCS biowaiver will not be granted and in vivo bioequivalence must be demonstrated for the registration of the drug product.

Chile

In 2004, Chile started the implementation of a "policy of generic bioequivalents" that required in vivo bioequivalence studies or in vitro biowaivers of several APIs [23]. In 2018, Chile updated the guidance for biowaiver studies for APIs classified as BCS Class 1 and 3 [24], as well as the list of medicines that can demonstrate therapeutic equivalence [25].

In the last 10 years, the Institute of Public Health (ISP in Spanish) has accepted a large number of biowaiver studies. More than 270 applications of multisource products have demonstrated the therapeutic interchangeability through comparative dissolution studies (www.ispch.cl). Figure 1 shows the rate at which BCS based applications have been approved by ISP over the years. Since 2009, the rate of applications for ANDA has grown to a maximum of 75 approvals by 2015. From 2016 to 2019 there was a decrease in the number of drug products that were waived from in vivo bioequivalence studies by the BCS dissolution studies.

A further analysis to assess the trend among the different therapeutic areas was carried out. In order to create a meaningful comparison, different drug indications in similar therapeutic areas were combined. Figure 2 shows the distribution of drug products by therapeutic classes. Fifty-six percent of these approvals were in the central nervous system and pain control areas.

Table 1 A summary of an update of BCS-based biowaiver requirements for the FDA, WHO and ICH

Criteria	Regulatory agency		
	FDA	WHO	ICH
BCS guideline(s) referenced	Waiver of in vivo Bioavailability and Bioequivalence Studies for Immediate- Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System: guidance for industry (FDA, 2017) [6] Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances. 2018 [40]	Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. (2017) [1] General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications (2019) [41]	ICH guideline M9 on biopharmaceutics classification system based biowaivers [14]
BCS class considered for biowaiver	BCS Class I and III	BCS Class I and III	BCS Class I and III
Formulation			
Type	Immediately release (IR) solid dosage oral form	IR solid dosage oral form	IR solid dosage oral form
Excipients	Class I: The quantity of excipients in the IR drug products should be consistent with the intended function; does not contain any excipients will affect the bioavailability of the drug (e.g., excess of surfactants and sweeteners) Class III: Qualitatively the same and quantitatively very similar	Class I: well-known excipients in usual amounts; critical excipients should not differ qualitatively or quantitatively Class III: Qualitatively the same and quantitatively very similar	Class I: qualitative and quantitative differences in excipients are permitted, except for excipients that may affect absorption, which should be qualitatively the same and quantitatively similar, i.e., within ± 10.0% of the amount of excipient in the reference product Class III: all of the excipients should be qualitatively the same and quantitatively similar (except for film coating or capsule shell excipients)
API	Excluded Narrow Therapeutic Index (NTI) drugs. The site of conversion of prodrug will determine whether permeability of prodrug or active drug should be determined. Not for drugs to be absorbed in the oral cavity	Excluded NTI drugs. Not for drugs with sublingual and buccal absorption	Excluded NTI drugs
Solubility assay (high)			
Method	Shake-flask or other justified methods	Shake-flask or other justified methods	Shake-flask or other justified methods
Dose (unit studied)	Highest strength dose	Highest single therapeutic dose	Highest single therapeutic dose
Volume	Soluble in 250 mL or less of aqueous media	Soluble in 250 mL or less of aqueous media	Soluble in 250 mL or less of aqueous media
pH	pH range 1–6.8 (both pH values and pH = pK_a, pH = pK_a + 1 and pH = pK_a − 1)	pH range 1.2–6.8	pH range 1.2–6.8. Solubility at the pK_a of the drug substance should be evaluated if it is within the specified pH range
Temperature	37 °C ± 1	37 °C ± 1	37 °C ± 1
No. assays	Tree replicates at each pH value	Tree replicates at each pH value	Tree replicates at each pH value
Permeability assay (high)			

Table 1 (continued)

Criteria	Regulatory agency		
	FDA	WHO	ICH
Preferred method	The systemic bioavailability (BA) ≥ 85 based on mass balance and absolute BA studies If ≥ 85% of the administered dose is recovered in urine as parent or metabolite In vivo intestinal perfusion in humans (an alternative)	The systemic bioavailability (BA) ≥ 85 based on experimental mass balance and absolute BA studies (experimental or published human data)	The systemic bioavailability (BA) ≥ 85 based on mass balance and absolute BA studies If ≥ 85% of the administered dose is recovered in urine as parent or metabolite
Accepted method	In vivo intestinal permeation in animals, in vitro permeation in human and animals, in vitro permeability with epithelial cell monolayers (e.g. Caco-2)	In vivo intestinal perfusion in humans (an alternative)	Human in vivo data derived from published literature
Supportive method	Literature data of in vitro or in vivo permeability studies	In vivo or in situ perfusion intestinal studies in animal models, as well as in vitro cell methods	In vitro cell permeability assays (Caco-2)
Dissolution assay			
Profile	Class I: ≥ 85% (30 min) Class III: ≥ 85% (15 min)	Class I: ≥ 85% (30 min) Class III: ≥ 85% (15 min)	Class I: ≥ 85% (30 min) Class III: ≥ 85% (15 min)
Apparatus and rotation	Apparatus I at 100 rpm or Apparatus II at 50 rpm or 75 rpm (justified)	Apparatus I at 100 rpm or Apparatus II at 75 rpm	Apparatus I at 100 rpm or Apparatus II at 50 rpm
Medium volume	500 mL	900 mL or less	900 mL or less
Type of medium	0.1 N HCL or Simulated Gastric Fluid USP without enzymes pH 4.8 buffer pH 6.8 or Simulated Intestinal Fluid USP without enzymes	pH 1.2 (HCl) pH 4.5 (buffer acetate) pH 6.8 (buffer phosphate)	pH 1.2 (HCl) pH 4.5 (buffer acetate) pH 6.8 (buffer phosphate)
Use of enzyme	Only for gelatin formulations	Only for gelatin formulations	Only for gelatin formulations
Use of surfactant	No	No	No
Comparative test	Similarity factor f2 ≥ 50 or other appropriate statistical method	Similarity factor f2 ≥ 50 or other appropriate statistical method	Similarity factor f2 ≥ 50 or other appropriate statistical method
Sampling time	5, 10, 15, 20 and 30 min	10, 15, 20, 30 and 45 min	Not declared
Number of batches	Not specified	Not specified	One
Unit tested	12	12	12
Fixed dose combination	All APIs must comply	Waiver for only 1 component	All APIs must comply
Biowaiver for other strengths	No	Yes (under certain conditions)	Yes (under certain conditions)

A detailed explanation is described in each regulatory guideline or in published papers [11, 12, 19]

FDA Food and Drug Administration, *WHO* World Health Organization, *ICH* International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

Table 2 Main regulations associated with the BCS-based biowaiver in some Latin American regulatory agencies

Country	Agency	BCS-based biowaiver (Y/N)	BCS class for biowaiver	API list for biowaiver (Y/N)	Laboratories for biowaiver studies (Y/N)	BCS-Biowaiver guideline referenced (Ref.)	Comments
Brazil	Anvisa	Y	I	Y [22]	Y	Resolution of the collegiate board of directors—RDC no. 37. Ministry of health (2011) [20] Instrução Normativa n. 10, de 29 de setembro de 2016. Determina a publicação da "Lista de fármacos candidatos à bioisenção baseada no Sistema de Classificação Biofarmacêutica (SCB)" e dá outras providências [22]	The application of BCS is limited to a short list of API with high absorption in human (Fa ≥ 85)
Chile	ISP	Y	I and III	Y [42, 43]	Y	Guide to qualify for biowaiver from comparative bioavailability studies (2018) [24] Exempt Decree No. 115. Regulation that determines the active principles contained in pharmaceutical products that must demonstrate their therapeutic equivalence and the list of pharmaceutical products that serve as reference for them [25]	
Cuba	CECMED	Y	I, II and III	N	N	Regulation 18–07: Requirements for bioavailability and bioequivalence studies (2007) [44] Regulation No. 48/2007 Requirements for applying and/or designing a dissolution test in capsules and tablets of immediate release (2007) [45]	Guideline only mentioned in vitro biowaiver assay. There is not a harmonization with current guidelines of FDA and WHO
Colombia	INVIMA	Y	I and III	Y[46]	Y	Resolution 1124/2016 Guide containing criteria and requirements for the study of bioavailability and bioequivalence of drugs (2016) [47]	The technical annex 2 of the resolution show a list of API need in vitro bioequivalence studies

Table 2 (continued)

Country	Agency	BCS-based biowaiver (Y/N)	BCS class for biowaiver	API list for biowaiver (Y/N)	Laboratories for biowaiver studies (Y/N)	BCS-Biowaiver guideline referenced (Ref.)	Comments
El Salvador	DNM	Y	I and III	N	N	Salvadoran technical regulations (RTS 11.02.01:16). Pharmaceutical products. Medicines for human use. Bioequivalence and interchangeability (2016) [48]	The annex of the resolution shows a list of API need in vivo bioequivalence studies
Ecuador	ARCSA	Y	I and III	N	Y	Health registration replacement regulation for medicines in general (Agreement No. 00000586)/Reform 2016 [49]	A draft of a new version (2017) was revised (https://www.controlsanitario.gob.ec/wp-content/uploads/downloads/2017/11/Borrador_NTS_bioequivalencia.pdf)
Panama	DNFD	Y	I, II and III	Y	Y	Amendment of executive decree No. 6 of 2005 on therapeutic equivalence and interchangeability (2005) [50] Law 1/2001. About medicines and other products for human health (2001) [51]	Applied for drugs included in Category B
Peru	DIGEMID	Y	I and III	Y [52]	Y	Supreme decree No 024-2018-SA Regulations governing the Interchangeability of medicines (2018) [53] Ministerial resolution 366 of 2019 concerning reference products in therapeutic equivalence trials (2019) [54]	
Mexico*	COFEPRIS	N	Not defined	Y [55]	Y	Official Mexican Norm NOM-177-SSA1-2013, which establishes the tests and procedures to demonstrate that a drug is interchangeable (2013) [56]	Guideline mention dissolution tests as an interchangeability assay for immediately release solid dosage forms “B test”
Venezuela	INHRR	Y	I and III	N	N	Resolution No 212, by which the Venezuelan norms of bioavailability and bioequivalence of pharmaceutical products are dictated (2006) [57]	There is an update reference list for API need in vivo bioequivalence studies

Table 2 (continued)

Country	Agency	BCS-based biowaiver (Y/N)	BCS class for biowaiver	API list for biowaiver (Y/N)	Laboratories for biowaiver studies (Y/N)	BCS-Biowaiver guideline referenced (Ref.)	Comments
Argentina	ANMAT	Y	I and III	N	Y	Disposition 758/2009: Biowaiver criteria for bioequivalence studies for immediate release oral solid drugs (2009) [58] Guidance for applying for biowaivers of active pharmaceutical ingredients with bioequivalence requirement (2016) [59]	Lists of medicinal products marketed with proven in vivo bioequivalence (https://www.anmat.gov.ar)
Costa Rica	MINSA	Y	I, II and III	Y	Y	Technical guide for the presentation and evaluation of comparative dissolution profile studies (2009) [60]	For some API are needed in vivo and in vitro bioequivalence studies
Uruguay	MSP	Y	I and III (justified)	Y [61]	Y	Decree No. 87/016: Amendment of decree No. 12/007 on the interchangeability of medicines (2016) [62] Decree 12/007: Interchangeability of medicines (2007) [63]	A list for API need in vivo and in vitro bioequivalence studies

Other countries without information about BE studies Bolivia, Paraguay, Nicaragua, Belize, Surinam, Guyana, Guatemala, Jamaica, Honduras, Dominican Republic, Haiti, Trinidad and Tobago

ANVISA Agencia Nacional de Vigilancia Sanitaria (Brazil, https://www.portal.anvisa.gov.br), *ISP* Instituto de Salud Pública (Chile; https://www.ispch.cl), *CECMED* Centro para el control estatal de medicamentos y dispositivos médicos (Cuba; https://www.cecmed.cu), *INVIMA* Instituto Nacional de Vigilancia de Medicamentos y Alimentos (Colombia; https://www.invima.gov.co), *ARCSA* Agencia Nacional de Regulación, Control y Vigilancia Sanitaria (Ecuador; https://www.controlsanitario.gob.ec), *DIGEMID* Dirección General de Medicamentos Insumos y Drogas (Perú; https://www.digemid.minsa.gob.pe), *COFEPRIS* Comisión Federal para la Protección contra riesgos sanitarios (Mexico; https://www.gob.mx), *ANMAT* Administración Nacional de Medicamentos, Alimentos y Tecnología (Argentina; https://www.argentina.gob.ar), *DNM* Dirección Nacional de Medicamentos (El Salvador; https://www.medicamentos.gob.sv), *INHRR* Instituto Nacional de Higiene Rafael Rangel (Venezuela; https://www.inhrr.gob.ve), *MINSA* Ministerio de Salud (Costa Rica; https://www.ministerio de salud.go.cr), *MSP* Ministerio de Salud Pública (Uruguay; https://www.gub.uy), *DNFD* Dirección Nacional de Farmacias y Drogas (Panamá; https://www.minsa.gob.pa), *DNVS* Dirección Nacional de Vigilancia Sanitaria (Paraguay), *MINSA* Ministerio de Salud (Nicaragua), *AGEMED* Agencia Estatal de Medicamentos y Tecnologías en Salud (Bolivia), *BE* bioequivalence

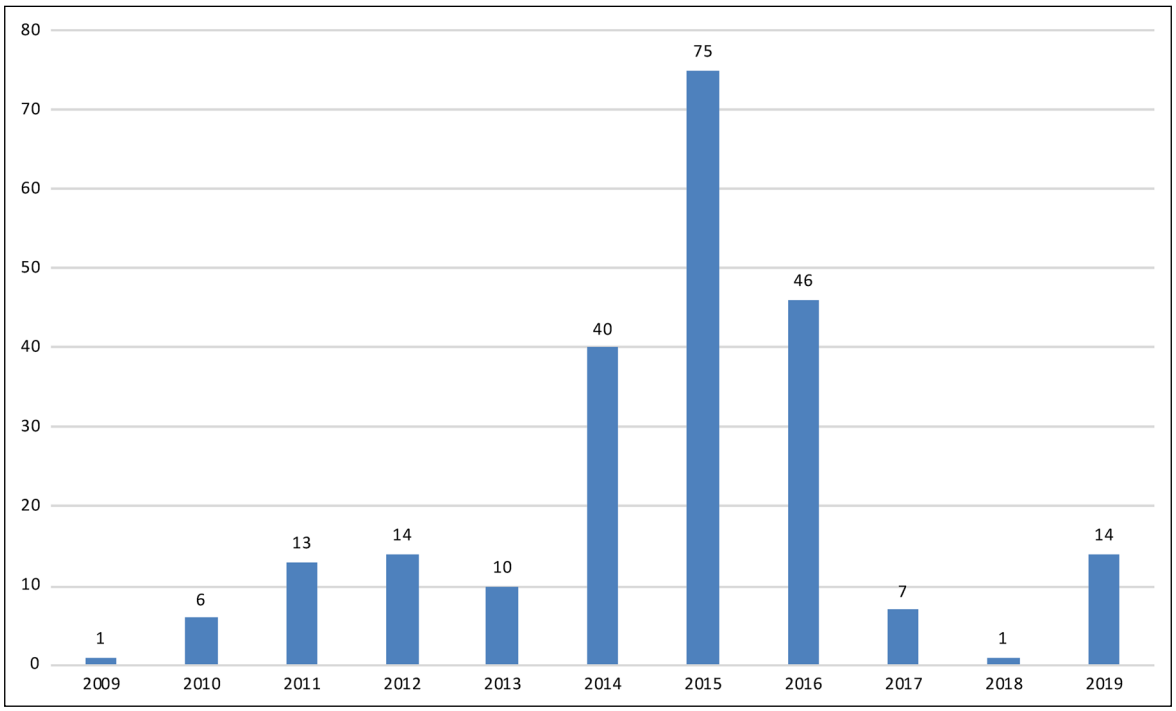

Fig. 1 Number of ANDAs approved, based on BCS, from 2009 to 2019 in Chile

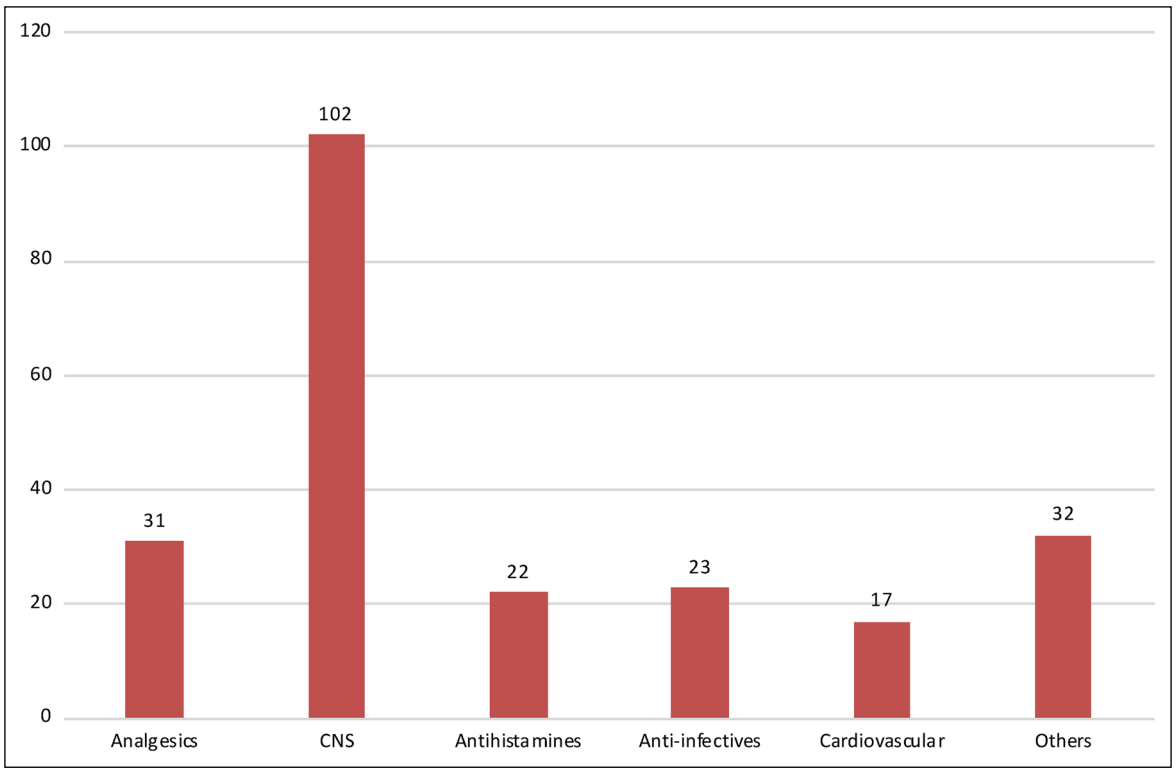

Fig. 2 ANDAs approved, based on BCS, from 2009 to 2019 in Chile by therapeutic area

Among the main factors that have contributed to the large number of biowaivers that have been approved by the ISP in recent years are the fact that drug permeability can be documented by bibliographic information and also the high number of national and international centers accredited by ISP to perform biowaiver studies [23]. In addition, when there is reasonable doubt about the permeability classification of a drug candidate, ISP considers the drug as Class 3, with the corresponding biowaiver requirements [24].

Mexico

Mexico's Federal Commission for Protection against Sanitary Risks (COFEPRIS in Spanish) incorporated the bioequivalence requirement into its regulations in 1998 and the guidelines were updated in 2013 allowing the performance of in vitro dissolution studies to document interchangeability of very few multisource products. The possibility to expand the application of biowaiver studies is limited to some legal problems such as the access to the list of excipients of reference products [15]. According to the COFEPRIS website, there are currently 17 Authorized Third Parties to conduct in vitro studies for biowaivers.

In order to improve transparency in regulatory decision-making, several regulatory authorities have listed all drugs for which BCS-based biowaiver have been or could be granted. Table 3 described the APIs that have been subjected to in vitro bioequivalence studies in different Latin American countries and classified as BCS Class 1 and 3.

Discussion

International BCS-Based Biowaiver Guidelines Comparison

Today, several drug regulatory agencies in Latin America are implementing BCS biowaiver mainly based on FDA or WHO guidelines [11]. According to Table 1, there is agreement regarding the classes of BCS, the type of formulation and the definition of highly soluble and highly permeable compounds. However, there are still some significant differences between regulatory authorities and international agencies. Regarding drug solubility, WHO and ICH require that the highest single therapeutic dose be used to demonstrate high aqueous solubility, while the FDA measures the solubility of the highest dosage strength. In some cases, this divergency may result in a drug qualifying for a BCS biowaiver in one regulatory agency but not in others, as well as a mismatch between in vitro bioequivalence studies and in vivo human assays [26, 27]. This discrepancy has been assessed for metoclopramide, verapamil, prednisolone and prednisone [28].

As regards the permeability of drugs, there is consensus on the cutoff value of high permeability as well as on the experimental assay to determine it. However, the role of metabolism and its correlation with permeability is recognized in the harmonised guidances of the WHO and the ICH for use in the classification of this drug property [9]. The FDA considers in vivo or in situ intestinal perfusion studies in animal models, as well as in vitro cells methods, as accepted tools for establishing in vivo permeability only for passively transported drugs, while the WHO considers these approaches as supportive methods. The ICH guideline accepts the use of in vitro Caco-2 cell methods. Although there are clear differences in the determination of permeability, the combined use of different experimental methodologies has demonstrated to be useful in the classification of this property according to the BCS [18].

With regard to establishing rapid or very rapid dissolution testing, the FDA requests a volume of 500 mL to carry out the assay, while the WHO and ICH suggests a volume of 900 mL or less. The use of a lower volume for dissolution testing could prevent the achievement of sink conditions for compounds with high dose values. Something similar occurs with agitation rate, where the FDA and ICH recommend 50 rpm for use in the paddle apparatus, while the WHO recommends 75 rpm. This point has been widely discussed and related to the time limit for complete dissolution (30 min) in standard in vitro dissolution tests. However, some authors have suggested that BCS biowaivers should not be performed at 75 rpm, even in the case of the coning effect, as mentioned by WHO [29]. Other aspects where differences persist are the sampling time and the number of batches of drug products. In our opinion, all these points mentioned above are the most important differences that make it difficult to harmonize the requirements for BCS-based biowaiver.

Analysis of BCS-Based Biowaiver Guidelines in Latin America

In Latin American countries such as Brazil, Chile, Colombia, Salvador, Ecuador, Peru, Venezuela, Argentina and Uruguay there is consensus on the application of the BCS-based biowaiver for API belonging to BCS Class 1 and 3. Other countries such as Panama, Costa Rica and Cuba need to update the in vitro bioequivalence guidance. However, in the case of Cuba all APIs of immediate release solid oral dosage forms of the National List of Essential Medicines have been classified according to the update WHO guideline for BCS based biowaiver [30]. For countries such as Bolivia, Paraguay, Nicaragua, Belize, Suriname, Guyana, Guatemala, Jamaica, Honduras, Dominican Republic, Haiti and Trinidad and Tobago there is no information on the implementation of

Table 3 Active pharmaceutical ingredients, classified as BCS class I and/or III, subject to in vitro bioequivalence studies in different Latin American countries

No	Drug	BCS Class [18]	Brazil [64]	Chile [42]	Colombia [46]	Peru [52]	Uruguay [61]	Mexico [55]	Costa Rica [65]	Biowaiver FIP	WHO list 2017 [33]
1.	Abacavir	III		X			X				X
2.	Acyclovir	III		X						X	
3.	Acetylsalicylic Acid	I	X	X				X		X	X
4.	Alendronate	III		X				X			
5.	Allopurinol	III		X							X
6.	Alprazolam	I		X	X						
7.	Ambroxol	I						X			
8.	Amoxicillin	I								X	X
9.	Anastrazole	I			X						
10.	Apixaban	III			X						
11.	Atenolol	III		X	X				X	X	X
12.	Atomoxetine	I		X							
13.	Biotin	III						X			
14.	Biperiden	III			X						X
15.	Bisoprolol	I	X							X	X
16.	Brompheniramine	I						X			
17.	Bromhexine	I						X			
18.	Caffeine	I	X								X
19.	Capecitabine	I/III	X		X						X
20.	Carbinoxamine	I/III						X			
21.	Cetirizine	III		X							
22.	Cyclobenzaprine	I		X							
23.	Cyclophosphamide	I			X						X
24.	Cinacalcet	III		X							
25.	Citalopram	I		X							
26.	Clodronate	III						X			
27.	Clonazepam	I		X	X						
28.	Chlorphenamine	I		X				X			
29.	Chlorambucil	I			X						X
30.	Desloratadine	I		X							
31.	Donepezil	I		X							
32.	Dimenhydrinate	I						X			
33.	Diphenhydramine	I						X			
34.	Diazepam	I				X					X
35.	Didanosine	III					X		X		

Table 3 (continued)

No	Drug	BCS Class [18]	Brazil [64]	Chile [42]	Colombia [46]	Peru [52]	Uruguay [61]	Mexico [55]	Costa Rica [65]	Biowaiver FIP	WHO list 2017 [33]
36.	Dipyrone	I/III	X								
37.	Doxycycline	I	X							X	X
38.	Enalapril	III		X						X	X
39.	Escitalopram	I		X							
40..	Finasteride	I		X							
41.	Folinate	III						X			X
42.	Fluconazole	I	X	X						X	X
43.	Fluoxetine	I		X					X		X
44.	Gabapentin	III			X						
45.	Hydroxyzine	I						X			
46.	Hydroxyurea	III		X							
47.	Ibandronic Acid	III						X			
48.	Isoniazid	I/III	X							X	X
49.	Isotretinoin	I						X			
50.	Lamivudine	III		X	X	X	X		X	X	X
51.	Letrozole	I			X				X		
52.	Levetiracetam	I		X	X					X	
53.	Levocetirizine	I		X							
54.	Levofloxacin	I	X	X						X	X
55.	Linagliptin	III			X						
56.	Melatonin	I						X			
57.	Memantine	I	X								
58.	Methadone	I						X			X
59.	Methylphenidate	I/III		X							
60.	Metformin	III			X						X
61.	Metoclopramide	III		X						X	X
62.	Metoprolol	I	X		X			X			X
63.	Metronidazole	I	X							X	X
64.	Miglitol	III						X			
65.	Miltefosine	III						X			X
66.	Mirtazapine	I		X							
67.	Moxifloxacin	I		X							X
68.	Naratriptan	III		X							
69.	Neostigmine	III						X			X
70.	Nicotine	I						X			X
71.	Nilhidrine	I						X			

Table 3 (continued)

No	Drug	BCS Class [18]	Brazil [64]	Chile [42]	Colombia [46]	Peru [52]	Uruguay [61]	Mexico [55]	Costa Rica [65]	Biowaiver FIP	WHO list 2017 [33]
72.	Paracetamol (Acetaminophen)	III	X	X				X		X	X
73.	Phenylephrine	III						X			
74.	Pramipexol	I	X		X						
75.	Prasterone	I						X			
76.	Prednisone	I		X						X	
77.	Pregabaline	I	X	X	X						
78.	Propranolol	I	X	X	X			X		X	X
79.	Quetiapine	I		X							
80.	Quinagolide	III						X			
81.	Rasagiline	III			X						
82.	Risedronic acid	III						X			
83.	Risperidone	I		X							X
84.	Rivastigmine	I	X								
85.	Ruxolitinib	I			X						
86.	Selegiline	I			X						
87.	Sitagliptin	III			X						
88..	Sotalol	III	X								
89.	Stavudine	I	X				X			X	
90.	Tramadol	I		X							
91.	Temozolomide	I	X		X			X			
92.	Tofacitinib	III			X						
93.	Topiramate	III			X				X		
94.	Topotecan	III			X						
95.	Triprolidine	I						X			
96.	Venlafaxine	I	X	X							
97.	Vigabatrin	I						X			
98.	Zidovudine	I		X	X	X	X		X	X	X
99.	Zolpidem	I		X							
100.	Total		21	41	28	3	5	32	7	19	33

FIP International Pharmaceutical Federation, *WHO* World Health Organization

any bioequivalence standards, which is somewhat alarming (see Table 2).

On the other hand, some regulatory authorities consider a list of APIs for BCS-based biowaiver decisions (Brazil, Chile, Colombia, Peru, Uruguay, Mexico and Costa Rica), while others prefer to specify APIs that must demonstrate bioequivalence through in vivo studies. As can be seen in Table 3, several APIs, classified as BCS Class 1 and/or 3, have been biowaivered from in vivo bioequivalence in one or more Latin American countries. In our opinion, this information provides more transparency for regulatory decision-making and the possibility of knowing which drugs, for which acceptable scientific data, justify waiving bioequivalence studies [31]. In this sense, the impact of the BCS guidance on drug development in USA from 2004 to 2017 has recently been published, evidencing the success of this framework in the development of multisource products and new drugs [32].

Nineteen drugs on the API list (Table 3) have published BCS-monographs by the FIP, which are relevant for subsequent applicants for biowaivers of other immediate release solid oral dosage forms containing the same APIs. At the same time, thirty-three drugs are included in the latest WHO Essential Drug List, demonstrating recognition by different regulatory agencies [33].

Challenges and Opportunities for BCS-Based Biowaiver Implementation in Latin America

The harmonization of pharmaceutical guidelines, in terms of biowaiver requirements, is a pending task in Latin America if unnecessary human bioequivalence studies are to be avoided. Nevertheless, there are several opportunities and challenges to reverse this situation and develop safe, effective and affordable generic drugs (see Table 4).

The Latin American market for multisource products is expected to reach a compounded annual growth rate of 9.3% during the first half of the 2018–2028 period [34], which illustrates the relevance of developing strategies to promote multisource drug products and update medicines policies in Latin America. One of these strategies is the promotion of the use of multisource medicines for off-patent products in order to improve access to medicines for countries with low economic levels [3].

Although the relevance of BCS-bases in vitro bioequivalence studies has been questioned from a risk-based perspective, several authors have assessed the risk analysis for bioinequivalence of a multisource product, demonstrating that current regulatory guidelines for BCS-based biowaiver reduce the incidence for bioinequivalence, improve detection and limit the severity of any unforeseen bioinequivalent product [35, 36].

Recently, the impact of the broad application of the BCS principle by the FDA on its regulated industry has been published [32]. More than 160 applications, based on the BCS approach, have been approved between 2004 and the first quarter of 2017. From all applications submitted and approved over this period, 70% were classified as BCS Class 1, being higher for multisource drugs (92%) compared to the new drugs (58%). These results, along with the demonstrated economic impact of BCS-based biowaivers for Class 1 and 3 compounds [10], suggest that their broad and robust use for new and multisource drugs belongs to these classes, eliminating unnecessary drug exposures in healthy subjects.

Table 4 Opportunities and challenges to improve the develop of BCS-based biowaiver in Latin American countries

Opportunities	Challenges
Increasing growth of global pharmaceutical spending of generic drugs	Lack of confidence in the acceptance of multisource medications by patients and some physician group
Increasing availability of medications that are past patent expiry	Several Latin American countries do not consider the BCS in their regulatory guidelines (improve regulatory and competitiveness standards
BCS-based biowaiver limits the risk for bioinequivalence	Lack of Latin American regulatory harmonization about BCS-based biowaiver
BCS-based biowaiver provides economic relief for governments and patients, while maintaining the high public health standard for therapeutic equivalence	There is not a standard list of API candidates for biowaiver (lack of a database of API classified according BCS)
First steps by the International Council for Harmonization (ICH) to provide regional harmonization of the differences between BCS-based biowaiver guidance (ICH-M9)	There are few accredited laboratories in Latin America to develop in vitro BE assay
The International Pharmaceutical Federation (FIP) has published more than 40 monographs about the BCS-based biowaiver	Limited access to the list of the excipients of the reference products
	It is not globally considered the relevance of excipients in the multisource product formulation
	Limited access to the reference products
	There is not a harmonization about the comparator selection
	The research about regulation of generic drug is scarce in the region
	There some Latin American countries where their generic medicines are available without BE certification

On the other hand, the international relevance of BCS-based biowaiver has been increased by the collaboration of WHO and FIP to publish several biowaiver monographs of compounds belongs to the Essential Medicines List, and for the recently published guideline for BCS-based biowaiver by ICH.

Despite the opportunities shown above, there are some challenges to overcome to improve the development of BCS-based biowaiver in Latin American countries (see Table 4). Today, about 50% of Latin American countries surveyed have no information on the application of bioequivalence studies and even more, in countries where bioequivalence studies are considered, regulatory guidelines do not accept BCS-based biowaiver. This situation makes the marketing of multisource drug products, without bioequivalence testing, a reality in countries such as Bolivia, Paraguay, Nicaragua, Guatemala, Jamaica, Honduras, Dominican Republic, etc. [37].

The lack of confidence for the prescription of multisource drugs, led by some physicians creates weak acceptability for many patients. Sometimes patients, due to the lack of information and/or education about multisource medicines, believe that the low cost of these drug products is a consequence of the poor quality and ultimately the lower efficacy of the medicine [38].

The limited access to the list of excipients in the reference products, as well as their role in the formulation of multisource products are additional factors to slow down the applicability of BCS-based biowaiver [39]. Finally, the lack of a reliable database of APIs classified according to BCS is another challenge to develop a strong biowaiver policy based on the BCS. Although many provisional classification systems exist, only a small list of APIs has been evaluated in human permeability experiments. This situation restricts the application of in vitro bioequivalence to demonstrate the therapeutic interchangeability of multisource products. In general, all these challenges could be successfully fulfilled if the final goal of the Latin American governments and their regulatory agencies is to improve people's access to safe and effective medicines.

Study Limitations and Practical Implications

In this study, an updated analysis was performed with respect to the application of BCS-based biowaiver in the development of multisource products in Latin America. The results of the study have some limitations because it only focuses on the application of BCS to demonstrate the therapeutic interchangeability of multisource products and does not provide an update on the bioequivalence situation in the region. On the other hand, information related to the acceptance and application of the BCS-based biowaiver by Latin American regulatory agencies is scattered, variable and not very well published on their official websites. Despite these limitations, the results achieved in this study have several practical implications. The study identified the main challenges and opportunities in using BCS to demonstrate the therapeutic interchangeability of multisource products based on the best experiences in the region, such as those of Chile, Brazil and Mexico. It also identifies and proposes a list of active pharmaceutical ingredients in which multisource products can demonstrate safety and efficacy, through in vitro bioequivalence studies, promoting the development of safe and effective medicine at a reasonable cost.

Conclusion

The status of in vitro bioequivalence studies, based on the BCS system, in Latin American countries is highly variable. Some countries have successfully implemented the BCS-based biowaiver to demonstrate the interchangeability of multisource drugs, while almost 50% of countries have not yet generated information about the application of bioequivalence studies and not in all countries where the bioequivalence studies are considered, the regulatory guidelines accept BCS-based biowaiver. This situation is in clear contrast with the growing global market of multisource products and the international tendency to bring a global harmonization for BCS-based biowaiver guidance to avoid expensive and time-consuming in vivo bioequivalence studies while also ensuring a low risk for bioinequivalence and high-quality, safe and effective multisource products for the patients. Nevertheless, there are several challenges that Latin American countries need to overcome if they want to increase the registration of multisource products and to improve the access to safe and effective drug products at reasonable costs.

Author Contributions

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work (CM-PA and MÁC-P). Drafting the work or revising it critically for important intellectual content (CM-PA, AAÁ, GMLS, MFC, HJ-C and MÁC-P). Final approval of the version to be published (CM-PA, AAÁ, GMLS, MFC, HJ-C and MÁC-P). Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (CM-PA, AAÁ, GMLS, MFC, HJ-C and MÁC-P).

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Compliance with Ethical Standards

Conflict of interest

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