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Knowledge-Based: Facilitating Access to Medicines in Latin America

Talita da Silva Ferreira[1*], Giovanni M. Pauletti[2], Eduardo Agostinho Freitas Fernandes[3], Alexis Aceituno[4], Miguel Ángel Cabrera-Pérez[5], Diego Gutierrez Triana[6] and Luis Vázquez-Suárez[7]

[1,7]Department of Business Administration and Instituto Multidisciplinar de Empresa (IME), Campus Unamuno, Edificio FES, Salamanca, Spain

[2]Department of Pharmaceutical and Administrative Sciences, University of Health Sciences and Pharmacy in St. Louis, 1 Pharmacy Place, St. Louis, MO, 63110 USA International Pharmaceutical Federation, Andries Bickerweg 5, 2517 JP the Hague Netherlands

[3]Coordination of Therapeutic Equivalence, National Health Surveillance Agency (Anvisa) SIA, Trecho 5, Área Especial 57, 71205-050, Brasilia, Andrés Figueroa Campos - National Drug Agency Department, Institute of Public Health, 7780050 Santiago, Chile

[4]National Drug Agency Department, Institute of Public Health, 7780050 Santiago, Chile

[5]Departamento de Ciencias Farmacéuticas, Facultad de Ciencias, Universidad Católica del Norte, Angamos 0610, Antofagasta, Chile

[6]Udelá soluciones regulatorias, El nogal, Cl 79b-5, Bogotá, Colombia

ABSTRACT

Purpose: The World Health Organization (WHO), with the scientific support of the International Pharmaceutical Federation (FIP), guides the development of multisource pharmaceutical products for market authorization using in vivo bioequivalence studies or, where applicable, in vitro biowaiver strategies based on the Biopharmaceutical Classification System (BCS). A review of the regulatory framework guiding generic medicines approval in Latin American countries revealed that less than 50% of regional health authorities offer a generic medicines development pathway utilizing a BCS-based biowaiver strategy.

Design/Methodology/Approach: Aligned with the ONE FIP Strategy to facilitate access to medicines, a regional case study was carried out to implement and harmonize BCS-based biowaiver knowledge in Latin American countries. A steering committee involving regional representatives from health authorities, the pharmaceutical industry, and universities were established to coordinate to develop activities. A series of digital engagement events were held in Spanish and English with representatives from Latin America to share knowledge on BCS-based regulatory strategy, promote collaborations, and explore the alignment of biowaiver approval and regulatory pathways among Latin American countries.

Findings: Feedback from diverse Latin American stakeholders demonstrated inconsistent implementation of bioequivalence testing within the region. However, there is support for a synergistic approach among countries to reduce duplication and increase efficiency in market authorization for generic medicines. This includes alignment with the WHO Prequalification of Medicines program as well as the development of a computational database for the classification of active pharmaceutical ingredients to demonstrate therapeutic interchangeability of immediate-release oral dosage forms according to the BCS.

Originality/Value: FIP-facilitated digital learning opportunities raised awareness of the BCS-based biowaiver regulatory strategy among Latin American stakeholders. It resulted in a plan to continually strengthen collaborative efforts in the region to harmonize regulations relevant to drug development generics medicines to introduce cost-effective medicines products that benefit public health.

***Corresponding author**

Talita da Silva Ferreira, Department of Business Administration and Instituto Multidisciplinar de Empresa (IME), Campus Unamuno, Edificio FES, Salamanca, Spain.

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Introduction

Latin America is essential for economic development and access to low-cost medicines. The region is home to a diverse range of countries with varying levels of economic growth with substantial natural resources and strategic geographic locations for medicine manufacturing.

In terms of access to generic medicines, Latin America faces several challenges, including high prices, limited availability of equipment, and infrastructure of laboratories capable of analyzing products. These challenges are compounded by social

and economic inequality, which means many people in the region struggle to access even essential health services.

To address these challenges, governments and international organizations have been working to promote greater access to quality medicines in the region. This includes efforts to increase the production and distribution of generic medicines, which can be more affordable than brand-name drugs [1].

The commercialization of safe and quality medicines requires three stakeholders: the industry, the regulatory authorities, and the academic institutions. Medicines-related legislation must be developed on a scientific basis, and it is also essential that it be harmonized, ideally at the global level.

The strategy to harmonize regulations in medicines is to form a group of professionals to develop their activity in the region to guarantee that the industry sets the required standards and can be evaluated with knowledge by the authorities.

Based on this, the harmonization of biowaiver is a strategy to engage with health authorities, pharmaceutical industries, and universities to align requirements to introduce generic medicines in different countries.

Biowaiver is a concept used in developing pharmaceutical products to allow the waiver of in vivo studies necessary to approve generic medicines. Bioequivalence is the extent to which two medicines contain the same active ingredient in the same pharmaceutical form and have the same pharmacological properties when administered to a patient in the same way [2].

A biowaiver may be granted if sufficient scientific evidence demonstrates that the generic medicine is equivalent to the reference medicine without the need to conduct costly and time-consuming studies in humans. The decision to grant a biowaiver is based on various factors, including the drug's physicochemical properties, pharmacokinetics, and the formulation and manufacturing processes used to produce it [2].

Biowaivers are granted for certain medicines that meet specific criteria set by regulatory agencies such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Chilean Institute of Public Health (ISP), National Health Surveillance Agency (ANVISA), and others. Using biowaivers can help reduce the cost and time required for generic medicines development and approval, increasing patient access to affordable products. However, biowaivers are crucial to ensure that generic medicines' quality, safety, and efficacy are not compromised.

Considering that most Latin American countries follow the regulations implemented by the World Health Organization (WHO), FDA, and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH M9 guideline), in collaboration with International Pharmaceutical Federation (FIP), a case study was conducted to implement and harmonize the BCS-based biowaiver knowledge in the Latin American region [1].

This project was aligned with the Sustainable Development Goals of the United Nations 2030 Agenda, mainly with Good Health and well-being [3]. It is also aligned with WHO's Essential Medicines and Health Technologies (EMT) program, which aims to increase people's access to high-quality, safe, effective, and affordable essential medicines and health products [4].

Literature Review

Knowledge-Based

The theory of knowledge-based resources is part of Strategic Management. Grant points out that knowledge is the key to companies' strategy, and the knowledge-based view focuses on acquiring and transferring this resource among companies, universities, and regulatory agents [5]. At the same time, Spender understands that the knowledge base is part of the strategic business, and the creation of value for companies and stakeholders must be in a continuous learning process [6].

According to Nonaka, the learning process is developed by "learning by doing" [7]. The professionals share explicit that is gradually converted to tacit knowledge [8]. Managers use this knowledge to make decisions aligned with their competitive strategies [8].

Regulatory knowledge combines tacit and explicit knowledge, representing a package of data and information that pharmaceutical companies must apply for successful market authorization in each country. These documents constitute the request for Market Authorization (MA), which each health authority will analyze before approving a drug product.

In the study by Devarakonda & Reuer, the transfer of knowledge between companies and universities to develop pharmaceutical products was analyzed. The importance of knowledge in the diversification process of pharmaceutical companies was essential to implement internationalization strategies in other countries [9].

Considering this, Lilleoere & Hansen explored the sharing of tacit and explicit knowledge in a pharmaceutical company in Europe between R&D professionals with different cultures [10]. This study showed that knowledge could reduce time to market and create a competitive advantage in the pharmaceutical field. The single case study with groups of professionals can be generalized and applied in different companies and countries.

Nonaka, Kodama, Hirose & Kohlbacher argue that companies must constantly explore and exploit knowledge for competitiveness and sustainable growth. Internalization is a way of knowledge exploration, and the interaction among professionals and companies is knowledge exploitation [11].

Regulatory agencies from Brazil, Chile, and Colombia have been adopting different approaches to regulating pharmaceutical products that involve the participation of private interests, making regulatory knowledge an essential resource to international strategies [12].

Based on that, a study conducted by a group of researchers analyzed the harmonization of regulatory knowledge among Latin American countries to classify pharmaceutical drugs as exempt from conducting bioequivalence studies in humans during the development of generic drug products [1]. The Biopharmaceutical classification system (BCS) is essential to expand access to new pharmaceutical products, reducing the time of approval and costs to introduce low-cost products into other markets.

Hauray analyzed the different kinds of knowledge and the impact of technical knowledge transformed into a regulatory decision [13]. In his perspective, health authorities have a valuable contribution

to the regulatory decision process due to the harmonization of requirements for medicines.

Wiktorowicz, et al. analyzed the regulatory framework of ICH founders, including the United States. They understand that the transnational and national regulatory processes support the international strategies to expand the developed markets' access to new pharmaceutical products [14]. Unlike EMA and ANVISA, the FDA is a regulatory agency that uses a managerial discretion model of decision-making based on the participation of private interests.

Due to COVID-19, health authorities from Latin American countries have aligned regulatory knowledge to expand access to pharmaceutical products. According to Nonaka & Takeuchi , must exploit knowledge and strategy to adapt to a pandemic [8]. They recognize that strategy is oriented to the future, and knowledge supports stakeholders in practicing their experiences.

In a study conducted on pharmaceutical companies, Bell & Cooper identified regulatory knowledge as the most crucial type required to support international entry modes [15]. This study conducted ten longitudinal case studies with small and medium-sized enterprise (SME) pharmaceutical industries. Bell & Cooper understand that regulatory knowledge is the most important type of knowledge for international-market entry [15].

A recent survey of articles published in one of the top management journals indicates that knowledge has become one of the most popular research areas in Strategic Management [16]. Knowledge of each country directly influences modes of international entry, enhancing healthcare education among pharmaceutical professionals and supporting communication strategies.

Knowledge of Biopharmaceutics Classification System (BCS)
BCS is a framework proposed by Gordon Amidon, et al. to classify drugs according to aqueous solubility and permeability to establish their potential limiting factors for oral absorption [17,18]. These parameters and the release and dissolution rate from the pharmaceutical form determine the absorption process of oral medicines.

BCS classification divides drugs into four categories [19].

- Class I: High permeability and high solubility drugs.
- Class II: High permeability and low solubility drugs.
- Class III: Low permeability and high solubility drugs.
- Class IV: Low permeability and low solubility drugs.

Determining these parameters and the drug classification according to BCS is a valuable tool for developing generic medicine and guiding the formulation process of new drugs. Solubility is related to drug physicochemical properties (particle size, crystal form, ionization capacity, and counterion), and dissolution from the dosage form is related to drug solubility. However, it can be influenced by excipients and manufacturing variables. On the other hand, the formulation can also affect physiological variables (gastric emptying, luminal volume, pHs) and membrane permeability [20].

In the context of international research and industry, the BCS is the framework adopted by the FDA (CDER/FDA) and the EMA for granting biowaivers (i.e., permission to demonstrate bioequivalence with in vitro dissolution studies) of medicines intended for oral administration without the need to use human in vivo bioequivalence studies [21,22].

Gastric emptying is the limiting step in absorption for class I drugs, with solubility and permeability high. Class II drugs, solubility, and dissolution rate could be the limiting processes for absorption. For class III drugs, membrane permeation is the limiting step. Finally, the limiting process could be one or the other in class IV drugs, which have low solubility and permeability. This information can be used as a guide to optimizing formulation development.

Therefore, the knowledge-based drug classification according to the BCS allows us to predict the limiting steps and simplify the introduction of generic products in the market.

Parameter Definition and Harmonization of Class Boundaries
The parameter definition, class boundaries, and protocols to determine solubility and permeability must be agreed upon. Exhaustive studies of these parameters as a tool for generics formulation have made it possible to improve the classification system. In this sense, Tsume, et al. performed a study to determine the influence of the acidic or essential nature of the active ingredient of class II and IV drugs in the compound's solubility, the formulation factors, and also the luminal environment in vivo [23]. Because of this study, they proposed an extension of the BCS classification of classes II and IV in which the acidic (a), base (b), or neutral (c) nature of the compounds is considered [23].

There are many methods to determine solubilities, such as flask stirring method or potentiometric titration by selecting using both the buffer solutions described by United States Pharmacopeia (USP) and the new biorelevant media to determine it. Although measuring solubility for developing new drugs seems simple and easily applicable, discrepancies between the values published by different research groups due to the conditions in which solubility is measured can be observed. Avdeef conducted an extensive bibliographic review in which he examined more than 800 publications that described the measurement of solubility in an equilibrium of slightly soluble ionizable drugs using the flask agitation method or other related ones [24]. Most of the studies reviewed did not report pH data, and in other cases, many factors were identified that affected the quality of the measurement.

On the other hand, the determination of permeability and solubility of generic medicines is more complex. The permeability class of drugs in humans can be determined by mass balance studies, systemic bioavailability, or intestinal perfusion approximations [25]. Generally, it is accepted that a demonstration in humans of an oral fraction absorbed higher than 85% corresponds to a high permeability class. The use of alternative methods to predict oral fraction absorption (perfusion studies in humans or animals, excised intestinal tissue methods, or cell culture methods) is not harmonized [25]. The FDA approved rat infusion methods for BCS permeability classification as the most reliable and monetary effective, but it requires method suitability demonstration and validation. In addition, another advantage of intestinal perfusion in rats is that it allows us to know the drug permeability value in each fragment of the rodent's intestine. There is more than one method to perform. It has been shown that the intestinal single-pass perfusion (SPIP) Model and the Doluisio (closed-loop) models are equally valuable methods for obtaining intestinal permeability values. It can predict Fabs and the BCS classification [25].

The accepted methods for permeability classification are not harmonized, and in those countries where the same methods are accepted, the assay protocols and the classification methods (i.e., high permeability associated value, direct comparison versus HP

drug model, or confidence interval approach) could be different [1].

Harmonization of Knowledge for Biowaiver Granting in Latin America

The harmonization of knowledge for granting a biowaiver in Latin America involves standardizing regulatory requirements and guidelines for approving generic drugs. This process aims to facilitate the approval of generic drugs, ensuring their safety, efficacy, and quality [1].

Latin American countries have made significant progress in harmonizing their regulatory requirements for granting a biowaiver in recent years de [1]. The Pan American Health Organization (PAHO) played a crucial role in this process, providing technical support and guidance to regulatory authorities in the region.

One of the main challenges for harmonizing the granting of biowaiver in Latin America is the need for more scientific data on the bioequivalence of medicines. This issue is particularly relevant for locally produced drugs that may need to be extensively studied in other regions. Some Latin American countries have established networks to share scientific data and research collaboration [1].

Another challenge for harmonizing the granting of biowaiver in Latin America is adapting regulatory requirements to each country's specific conditions. This involves considering local drug manufacturing capacity, healthcare infrastructure, and patient needs.

The countries of Latin America are willing to take a step forward to reach general agreements that allow generics to be marketed with the maximum quality standards.

The first step is to agree in the BCS classes that can request a biowaiver.

The second step is to harmonize the class boundary limits.
The third is to agree on the experimental methods for parameter determination, as the experimental conditions can affect the quality of the results and their reproducibility.

Brazil

In Brazil, the granting of biowaivers for the approval of generic drugs is regulated by the National Health Surveillance Agency (ANVISA). ANVISA has established specific guidelines and requirements for the approval of generic drugs, including using biowaivers in some instances [26].

ANVISA follows the BCS system to determine the eligibility of drugs for biowaiver. Brazilian guidelines for biowaivers are like those established by other regulatory agencies, such as the FDA and EMA. The guidelines consider the drug's physicochemical properties, pharmacokinetics, and the formulation and manufacturing processes used to produce it.

ANVISA also requires the presentation of detailed information about the quality and safety of the medicine, including data on its stability, impurities, and toxicity. This information is used to assess the risk of bioequivalence issues and determine the product's suitability for biowaiver [27].

Using biowaivers in Brazil can reduce the cost and time required for developing and approving generic drugs. However, using biowaivers is essential to ensure that generic medicine's quality, safety, and efficacy are not compromised. ANVISA has established strict standards for approving generic drugs, including those with biowaivers, to ensure the safety and efficacy of drugs available on the Brazilian market.

The RDC 749/2022 is a recent regulatory resolution issued by ANVISA that provides guidelines for submitting biowaiver applications for immediate-release solid oral dosage forms [27].

According to ANVISA, the resolution outlines the criteria for determining the eligibility of drugs for biowaiver based on their solubility, permeability, and therapeutic dose [27]. The resolution also establishes the documentation requirements for biowaiver applications, including information on drug quality, bioavailability, and bioequivalence studies.

The resolution also establishes the documentation requirements for biowaiver applications, including information on drug quality, bioavailability, and bioequivalence studies. Applicants must provide a detailed description of the manufacturing process, including information on the drug product's formulation, stability, and impurities.

In addition to the documentation requirements, the resolution outlines the process for ANVISA's evaluation of biowaiver applications. ANVISA will review the submitted documentation to assess the quality, safety, and efficacy of the drug product and will conduct additional tests and studies as needed to ensure the validity of the biowaiver.

The issuance of RDC 749/2022 is expected to streamline the regulatory process for generic drug approval in Brazil by providing clear guidelines for submitting and evaluating biowaiver applications. It will help to reduce the time and cost required for the approval of generic drugs while ensuring the safety and efficacy of drugs available in the Brazilian market.

Chile

The Chilean Institute of Public Health (ISP) is an autonomous body and a technical benchmark for the state in medicines. One of its departments is the National Medicines Agency (ANAMED), which is in charge of health authorizations, registration of pharmaceutical and cosmetic products, and control and active surveillance of the same [27].

In 2005, the ISP issued Exempt Resolution No. 727, a "Defines the criteria for establishing therapeutic equivalence to pharmaceutical products in Chile." This standard laid the foundations for developing bioequivalence in Chile regarding infrastructure, parameters, and criteria [28].

The year 2008 began the certification of the first centers for in vivo bioequivalence studies and biowaiver centers for in vitro studies, both nationally and internationally. In addition, in vivo bioequivalence centers certified by ANVISA were recognized [27]. With this, it was possible to have the infrastructure, equipment, and authorized procedures to begin the execution of the studies required by the regulations. In the same year, the ISP began to teach courses on bioequivalence, biopharmaceutical classification system, solubility, drug permeability, and comparative dissolution profile studies aimed at the pharmaceutical sector, in charge of academics and regulators, both national and international. With this, a critical mass of professionals specializing in bioequivalence began to form.

The ISP issued two technical guidelines for the pharmaceutical industry with specific recommendations for carrying out therapeutic equivalence studies. The technical G-BIOF 01 "Guide for conducting comparative bioavailability studies in solid pharmaceutical forms for oral administration and systemic action" and the G-BIOF 02 - "Guide for applying for biowaiver from comparative bioavailability studies" [1].

The demonstration of therapeutic equivalence has been required through lists of active ingredients issued by the ISP, indicating deadlines for compliance of 12 months for in vitro studies and 18 months for in vivo studies from the publication date. The first list of requirements was included in Exempt Resolution No. 3225 of 2008 with two active ingredients, chlorphenamine, and carbamazepine, in immediate-release pharmaceutical products.

In 2012, the Chilean Ministry of Health issued Decree No. 500, which includes all the drug substances, taking the definitive step for ANAMED to have the necessary regulatory tools to demand compliance with bioequivalence regulations [28].

The following decrees demanding the demonstration of therapeutic equivalence modified Decree No. 500. Thus, at the beginning of 2012, Decree No. 864 was issued, including twelve active ingredients, and later the same year, Decree No. 981 with one hundred additional active ingredients, all aimed at immediate release pharmaceutical products.

As of 2014, Decree No. 123 includes modified-release oral pharmaceutical forms with 34 additional active ingredients. Later, in 2018, Decree No. 115 was issued, which includes 194 active ingredients in immediate, modified-release products and extends the regulations to chewable, dispersible pharmaceutical forms and fixed associations to give a total of 207 active ingredients in demand.

The last bioequivalence requirement to date was issued in 2019 with Decree No. 65, which requires demonstrating the therapeutic equivalence of 23 active ingredients to mono-drug products, fixed-dose combinations, and different release types. In addition, in the second item of the decree, "mature" products or non-new active ingredients are defined, such as those with more than ten years of presence in the market, which have maintained their formula and manufacturer or demonstrate the technological transfer of the method, they have not shown quality failures and have not generated pharmacovigilance alerts. These products can demonstrate therapeutic equivalence by documenting the validation of the production process. In addition, the technical guides G-BIOF 01 and G-BIOF 02 were updated, and the G-VMBA 01 guides "Guide for performing the validation of bioanalytical methodology for in vivo bioequivalence studies" and G-MOVAL 01 were published [29]. "Technical Guide for the presentation of modifications to validated production processes of solid pharmaceutical forms post demonstration of Therapeutic Equivalence." The latter classifies post-demonstration bioequivalence changes concerning their risk of causing bioequivalence and establishes specific requirements for each type of change and formulation so that licensees can demonstrate that the bioequivalence of their products is maintained [30].

Pharmaceutical products that seek to demonstrate bioequivalence must comply, among other regulatory points, with the validation of the production process and present an in vivo study or a biowaiver from in vivo bioequivalence studies based on the BCS or based on the power proportionality.

As of this manuscript's preparation date, more than 3,000 products have demonstrated bioequivalence in Chile, which means 58% compliance with the bioequivalence requirement. Of the 3,000 bioequivalent pharmaceuticals listed above, 19% correspond to biowaiver studies based on BCS, and 21% reach biowaiver based on the proportionality of potency. The demonstration of in vitro bioequivalence represents 40% of all equivalent therapeutic products.

Products therapeutically equivalent to the reference product are identified with a logo that says "Bioequivalent" on their sales packaging, which facilitates their identification by the population.

Colombia

In Colombia, the first specific bioequivalence (BE) guideline was issued in 2001 through resolution 1400. In 2016, resolution 1124 was published, updating the bioequivalence guidelines, which govern until this article's publication date [31].

This 1124 resolution contains three technical annexes and legal aspects. Annex 1 contains the technical guidelines for conducting bioequivalence studies in vivo and in vitro. The second Annex is the list of active pharmaceutical ingredients and pharmaceutical forms for which bioequivalence is required. The third annex is the guideline for granting good bioequivalence practices.

Moreover, annex 1 is based on the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability," Annex 7 of World Health Organization report 49 [2].

It was contemplated that the implementation of bioequivalence would be gradual, so a list of 91 active pharmaceutical ingredients (APIs) and some pharmaceutical forms was established for which the demonstration of bioequivalence is required. The objective was to increase the number of APIs in the list gradually.

In biowaivers, those based on pharmaceutical forms are considered first.

In the following cases, it is not required to present bioequivalence studies:

- Products designed to be administered by parenteral route (intravenous, subcutaneous, or intramuscular) as an aqueous solution.
- Solutions for oral use with similar excipients
- Powders for reconstitution to an aqueous solution
- Gases
- Otic or ophthalmic products are prepared as aqueous solutions.
- Topical products are prepared as aqueous solutions.

On the other hand, biowaivers based on the BCS are possible, where the following aspects are reviewed:

a) Solubility and permeability (Considering both aspects, biowaivers are only feasible in class one or three).

b) Similarity in dissolution profiles in pH 1.2 media; 4.5 and 6.8

c) An analysis of the excipients used in the formulation

d) That they are not an API with a narrow therapeutic index.

On this topic, it is essential to point out that in Colombia, the solubility test is not accepted in the literature. The interested party must carry out the test with their raw material.

If the comparator and the multisource product rapidly dissolve, the two products are deemed equivalent, and a profile comparison

is unnecessary.

Finally, the other biowaivers contemplated are those of dose proportionality; this framework applies when the in vivo study for the highest strength is already available and aims to approve different strengths of a multisource product based on dissolution profiles (if the formulations have proportionally similar compositions). In this case, the biowaiver applies to Immediate-release tablets, delayed-release tablets and capsules, and extended-release tablets and capsules.

Harmonizing knowledge for granting a biowaiver in Latin America is an ongoing process that requires strong collaboration and communication between regulatory authorities, industry stakeholders, and public health organizations. This process is essential to ensure patients can access the region's safe, effective, and affordable generic medicines.

Research Design

Consistent with the ONE FIP Strategy to facilitate access to medicines, a case study called FIPLABP, was conducted to advocate for broader implementation and harmonization of BCS-based biowaiver knowledge in Latin American countries.

A case study methodology is a research approach that involves an in-depth exploration of a particular phenomenon or case, often within its real-life context. This approach is commonly used in social science, business, and psychology research to gain insights into complex or unique issues that cannot be studied through quantitative research methods [32].

As Yin explained, the exploratory case study typically involves collecting data through various sources such as interviews, observations, surveys, and documents [32]. The data collected is usually qualitative and is analyzed using various methods such as content analysis, thematic analysis, or grounded theory.

Based on that, the FIPLABP used surveys with the strategy to engage with regional health authorities, universities, pharmaceutical companies, and trade associations to facilitate discussions about harmonization of the biowaiver approval pathway and raise awareness regarding BCS misconceptions relevant to the medicine approval pathway.

A plan of action was conducted to implement the activities and harmonize knowledge in the Latin American region.

The case study was initiated officially in July 2021 and was divided into two phases.

- Phase I with countries with biowaiver implemented but differ from ICH M9, and countries with biowaiver implemented according to ICH M9.
- Phase II with countries that do not have biowaiver implemented.

During the years 2021 and 2022, a series of digital engagement events were held in Spanish and English with representatives from Latin American health authorities, as well as the broader scientific community in the pharmaceutical industry and academic institutions of the region to disseminate knowledge about a BCS-based regulatory strategy, promote collaborations, and to explore the alignment of biowaiver approval and regulatory pathway among Latin American countries.

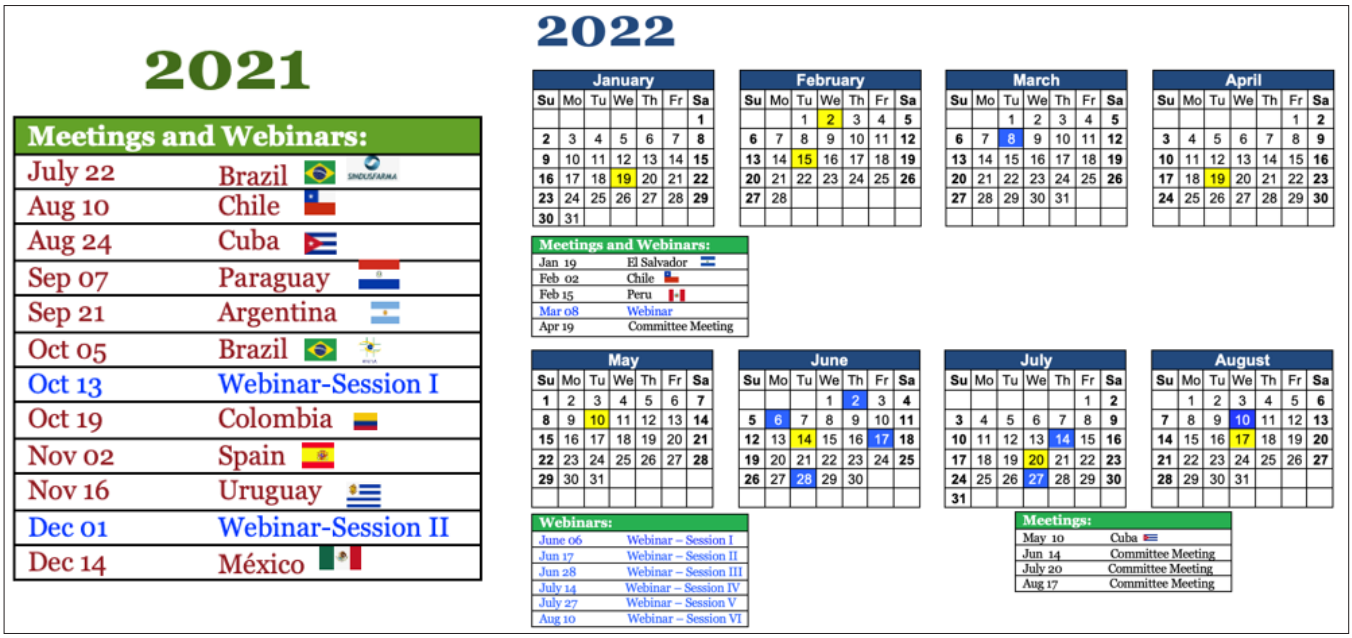

Figure1: Series of Digital Engagement Events

Findings Analysis

The investigation revealed inconsistencies in the implementation of bioequivalence tests in the Latin American region, which can lead to differences in the safety and efficacy of generic medicines. However, stakeholders expressed support for a synergistic approach across countries to reduce duplication and increase efficiency in the marketing authorization of generic medicines. This approach could involve aligning with the WHO Prequalification of Medicines program, which sets quality, safety, and efficacy standards, and developing a computational database for classifying active pharmaceutical ingredients according to the BCS. This can help demonstrate the therapeutic interchangeability of immediate-release oral dosage forms, increasing confidence in the safety and efficacy of generic drugs and facilitating marketing authorization.

Overall, the research results suggest a need for greater collaboration and standardization in generic drug regulation in Latin America. The proposed solutions, such as alignment with the WHO Drug Prequalification program and developing a computational database for classifying active pharmaceutical ingredients, can help resolve inconsistencies in implementing bioequivalence tests and increase efficiency in authorization to market generic drugs.

Interpretation and Discussion

Figure 2 summarize attendance at public digital events organized by FIP with participation from pharmaceutical companies, academic institutions, and health authorities representing Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Mexico, Panama, Peru, and Paraguay to explain public health implications of the BCS-based biowaiver regulatory pathway.

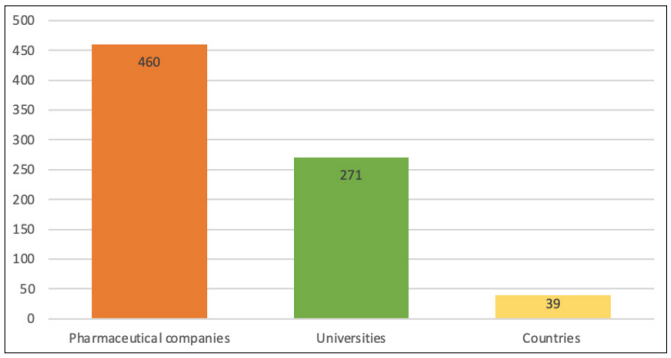

Figure 2: Attendance at Public Digital Events

The statement declared that health authorities had discussed the public health implications of knowledge of the BCS-based biowaiver, which may include the potential for greater availability and affordability of generic medicines and the need to ensure the safety and efficacy of these medications is not compromised. The health authorities also need to harmonize and standardize regulatory policies and procedures related to BCS-based biowaivers in different countries to ensure consistency in the approval of generic medicines and reduce the risk of substandard drugs entering the market.

According to figure 3, most participants (35.14%) were from universities, followed by health authorities (24.32%). Participants working in consulting accounted for 13.51% of the total, as did those from pharmaceutical companies. Research centers represented 10.81% of the participants, while trade associations had the lowest representation, with only 2.70% of participants.

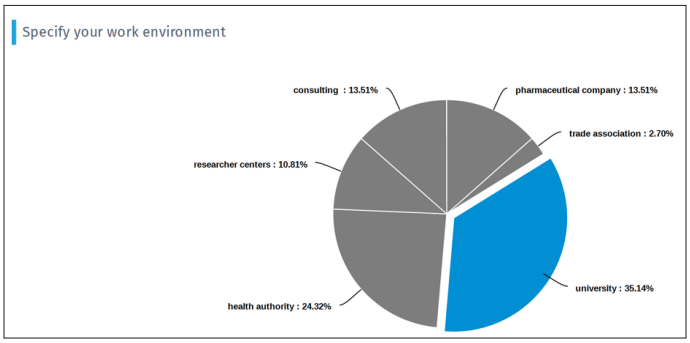

Figure 3: Participant Information

The fact that health authorities were well represented in the event or study, as well as universities and other stakeholders, suggests that there is broad recognition of the importance of this topic and a willingness to collaborate and share knowledge to improve regulatory policies and procedures.

Nonaka points out that tacit knowledge comes from within and is unique to each professional [33]. This knowledge is difficult to capture or store because it depends on each individual to transfer to others and register to be shared with others. Whereas explicit knowledge from books, articles, or documents can be gathered from inside and outside companies and quickly transferred to others. For this author, tacit and explicit knowledge must be interconnected to generate continuous learning for professionals and companies.

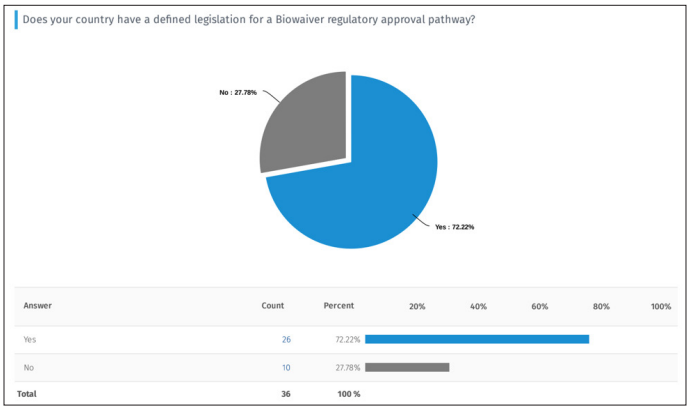

Figure 4: Knowledge-Based for Biowaiver

The statement highlights the public health implications of BCS-based biowaivers, including the potential for greater availability and affordability of generic medicines and the need to ensure the safety and efficacy of these medications are not compromised. This suggests that there is a knowledge of the need to balance the potential benefits of BCS-based biowaivers with ensuring quality and safety standards are met.

Grant understands that a company's most important strategic resource is its knowledge [5]. The companies must know to manage this resource to compete in specialized markets. According to Grant, companies' role is to apply tacit and explicit knowledge acquired by its professionals to implement competitive strategies [5].

Overall, the combination of figures 3 and 4 suggest that there is a significant interest in and engagement with the topic of BCS-based biowaivers among a diverse group of stakeholders and that there is a recognition of the potential benefits and risks associated with this approach to regulatory knowledge to Latin American region.

Conclusion

The information provided suggests that the FIPLABP project is taking a comprehensive approach to addressing the challenges associated with implementing BCS-based biowaivers in Latin America. By tailoring the diagnostics to the region's specific needs regarding human resources and technical support, the project is likely more effective in improving regulatory policies and procedures related to biowaivers [34,35].

The project's focus on assessing the possibility of applying BCS-based biowaivers to speed up the establishment of bioequivalence requirements in countries where regulations are not fully implemented is also notable. The project is considering the region's regulatory landscape and is looking for ways to improve regulatory efficiency while maintaining the safety and efficacy of drugs.

The involvement of a Steering Committee with representatives from each stakeholder group is also a positive development, as it suggests that there is a coordinated effort to disseminate knowledge and promote collaborations among different groups in the region. The focus on generating scientific evidence in support of biowaiver approval and the regulatory pathway is also likely to be beneficial in terms of building consensus and improving regulatory policies and procedures.

Overall, the information provided suggests that the FIPLABP project is taking a comprehensive and collaborative approach to addressing the challenges associated with implementing BCS-based biowaivers in Latin America. By focusing on tailoring the diagnostics to the specific needs of the region, assessing the possibility of applying biowaivers in countries with incomplete regulatory frameworks, and involving a Steering Committee with representatives from each stakeholder group, the project is likely to be more effective in achieving its goals of improving regulatory policies and procedures related to biowaivers.

Scientific and Managerial Implications

The information provided suggests potential risks to the development of the FIPLABP project, such as the rejection of proposed methodologies by the pharmaceutical industry and local health regulatory agencies. This highlights the importance of stakeholder engagement and collaboration in the project support of participating universities, BCS centers, health regulatory agencies, and trade associations with specialized knowledge and experiences that can help mitigate these risks.

Notably, the project has produced key findings summarized in a White Paper and prepared for scientific publications. This suggests that the project is committed to disseminating its results and engaging with the broader scientific community. This could have positive implications for the wider adoption and implementation of BCS-based biowaivers in Latin America.

Overall, the information provided suggests that while there are potential risks to the project's development, the support and collaboration of stakeholders with specialized knowledge and experiences can help mitigate these risks. The focus on disseminating key findings through scientific publications also suggests a commitment to engaging with the wider scientific community and promoting the adoption and implementation of BCS-based biowaivers in Latin America.

References

1. Miranda C, Aceituno A, Fernández M, Mendes G, Rodríguez Y, et al. (2021) ICH Guideline for Biopharmaceutics Classification System-Based Biowaiver (M9): Toward Harmonization in Latin American Countries. Pharmaceutics 13: 363.
2. World Health Organisation (WHO) (2015) Annex 7. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex7-TRS992.pdf.
3. Etukakpan A, Uzman N, Ozer O, Tofade T, Leite S N, et al. (2023) Transforming pharmaceutical education: A needs-based global analysis for policy development. Exploratory Research in Clinical and Social Pharmacy 9: 100234.
4. Macé C, Rägo L, Ravinetto R (2022) How the concept of WHO-listed authorities will change international procurement policies for medicines. BMJ Global Health 6: e008109.
5. Grant R M (1996) Toward a knowledge□based theory of the firm. Strategic management journal 17: 109-122.
6. Spender J C (1996) Making knowledge the basis of a dynamic theory of the firm. Strategic management journal 17: 45-62.
7. Nonaka I (1994) A dynamic theory of organizational knowledge creation. Organization science 5: 14-37.
8. Nonaka I, H Takeuchi (1995) The Knowledge-creating Company: How Japanese Companies Create the Dynamics of Innovation. Oxford University Press https://global.oup.com/academic/product/the-knowledge-creating-company-9780195092691?cc=us&lang=en&.
9. Devarakonda S V, Reuer J J (2018) Knowledge sharing and safeguarding in R&D collaborations: The role of steering committees in biotechnology alliances. Strategic Management Journal 39: 1912-1934.
10. Lilleoere A M, Hansen E H (2011) Knowledge-sharing enablers and barriers in pharmaceutical research and development. Journal of knowledge management https://www.emerald.com/insight/content/doi/10.1108/13673271111108693/full/html.
11. Nonaka I, Kodama M, Hirose A, Kohlbacher F (2014) Dynamic fractal organizations for promoting knowledge-based transformation–A new paradigm for organizational theory. European Management Journal 32: 137-146.
12. Tucker G, DeSilva B, Dressman J, Ito M, Kumamoto T, et al. (2016) Current challenges and potential opportunities for the pharmaceutical sciences to make global impact: an FIP perspective. Journal of pharmaceutical sciences 105: 2489-2497.
13. Hauray B (2017) From regulatory knowledge to regulatory decisions: the European evaluation of medicines. Minerva 55: 187-208.
14. Wiktorowicz M, Moscou K, Lexchin J (2018) Transnational pharmacogovernance: emergent patterns in the jazz of pharmaceutical policy convergence. Globalization and health 14: 86.
15. Bell VA, Cooper SY (2018) Institutional knowledge: Acquisition, assimilation and exploitation in internationalization. International Marketing Review 35: 475-497.
16. Serenko A (2021) A structured literature review of scientometric research of the knowledge management

discipline: a 2021 update. Journal of Knowledge Management https://www.emerald.com/insight/content/doi/10.1108/JKM-09-2020-0730/full/html.

17. Amidon G L, Lennernäs H, Shah V P, Crison, J R (1995) A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical research 12: 413-420.
18. Bermejo M, Amidon G L (2003) Modern biopharmaceutics. 6th version, TSRL inc., Michigan, USA.
19. Baena Y (2008) The biopharmaceutic drug classification, the theoretical basis and its importance in the biowaiver studies. Colombian Journal of Chemical-Pharmaceutical Sciences 37: 18-32.
20. Butler J M, Dressman J B (2010) The developability classification system: application of biopharmaceutics concepts to formulation development. Journal of pharmaceutical sciences 99: 4940-4954.
21. CDER/FDA (2000) Guidance for industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate release dosage forms based on a biopharmaceutical classification system. Center for Drug Evaluation and Research https://www.gmp-compliance.org/guidelines/gmp-guideline/fda-guidance-for-industry-waiver-of-in-vivo-bioavailability-and-bioequivalence-studies-for-immediate-release-solid-oral-dosage-f.
22. Morais J A G, Lobato M D R (2010) The new European Medicines Agency guideline on the investigation of bioequivalence. Basic & clinical pharmacology & toxicology 106: 221-225.
23. Tsume Y, Mudie D M, Langguth P, Amidon G E, Amidon G L (2014) The Biopharmaceutics Classification System: subclasses for in vivo predictive dissolution (IPD) methodology and IVIVC. European Journal of Pharmaceutical Sciences 57: 152-163.
24. Avdeef A (2015) Suggested improvements for measurement of equilibrium solubility-pH of ionizable drugs. ADMET and DMPK 3: 84-109.
25. Lozoya-Agullo I, Zur M, Wolk O, Beig A, González-Álvarez I, et al. (2015) In-situ intestinal rat perfusions for human Fabs prediction and BCS permeability class determination: Investigation of the single-pass vs. the Doluisio experimental approaches. International journal of pharmaceutics 480: 1-7.
26. Storpirtis S, Gai M N, Cristofoletti R (2014) Generic and similar products in Latin American countries: Current aspects and perspectives on bioequivalence and biowaivers. Pharmaceuticals Policy and Law 16: 225-248.
27. Brazilian Health Regulatory Agency (Anvisa) (2022) Resolution of the collegiate board – RDC no. 749, of September 5, 2022. Provides for exemption from bioequivalence/relative bioavailability studies. Ministry of Health - Nac Agency https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/medicamentos/bioequivalencia/pr-749_2022_ver_01_19_04_2023-1.pdf.
28. Saavedra I, Itarriaga V, Ávila L, Quiñones L (2011) Biowaiver studies (in vitro) to establish drug equivalence. Cuad Méd Soc (Chile) 51: 66-76.
29. Stojanova J, Lutz M, Lazcano G, Arancibia M (2020) Chilean legislation on bioequivalence and biosimilarity and current controversies related to drug interchangeability. Medvave 20: e7825.
30. ISP (2018) Guide to qualify for bioexemption from comparative bioavailability studies (G-BIOF 02) https://www.ispch.cl/sites/default/files/G-Biof%2002%20-%20Gu%C3%ADa%20para%20optar%20a%20bioexenci%C3%B3n%20de%20estudios%20de%20biodisponibilidad%20comparativa.pdf.
31. Colombian Ministry of Health. Resolución 1124 de 2016. By which the Guide is established that contains.
32. Trista Hollweck (2014) Robert K. Yin (2014). Case Study Research Design and Methods (5th ed). CJPE 30: 108-110.
33. Nonaka I, Takeuchi H (2021) Humanizing strategy. Long Range Planning, 102070 https://doi.org/10.1016/j.lrp.2021.102070.
34. Colombian Ministry of Health. Resolution 1124 of (2016) By which the Guide is established that contains the criteria and requirements for the study of Bioavailability and Bioequivalence of medicines, the list of those who must present them is defined and the conditions of the Institutions that carry them out are established. Ministry of Health and Social Protection.
35. Miranda-Pérez de Alejo C, Aceituno Álvarez A, Mendes Lima Santos G, Fernández Cervera M, Jung-Cook H, et al. (2021) Policy of Multisource Drug Products in Latin America: Opportunities and Challenges on the Application of Bioequivalence In Vitro Assays. Therapeutic Innovation & Regulatory Science 55: 65-81.