

Knowledge-based: facilitating access to medicines in Latin America

Baseado no conhecimento: facilitando o acesso a medicamentos na América Latina

Basado en el conocimiento: Facilitar el acceso a los medicamentos en América Latina

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ABSTRACT

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. 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. 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. 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.

Keywords: knowledge, strategy, regulatory, Latin America, generic, medicines.

RESUMO

A Organização Mundial da Saúde (OMS), com o apoio científico da Federação Farmacêutica Internacional (FIP), orienta o desenvolvimento de produtos farmacêuticos de múltiplas fontes para autorização de comercialização utilizando estudos de bioequivalência in vivo ou, quando aplicável, estratégias de bioisenção in vitro baseadas na Classificação Biofarmacêutica Sistema (BCS). Uma revisão do quadro regulamentar que orienta a aprovação de medicamentos genéricos nos países da América Latina revelou que menos de 50% das autoridades regionais de saúde oferecem um caminho de desenvolvimento de medicamentos genéricos utilizando uma estratégia de bioisenção baseada no BCS. Alinhado com a Estratégia ONE FIP para facilitar o

acesso a medicamentos, foi realizado um estudo de caso regional para implementar e harmonizar o conhecimento sobre bioisenção baseado em BCS em países latino-americanos. Foi criado um comitê diretor envolvendo representantes regionais das autoridades de saúde, da indústria farmacêutica e das universidades para coordenar o desenvolvimento de atividades. Uma série de eventos de engajamento digital foram realizados em espanhol e inglês com representantes da América Latina para compartilhar conhecimento sobre a estratégia regulatória baseada no BCS, promover colaborações e explorar o alinhamento da aprovação da bioisenção e dos caminhos regulatórios entre os países latino-americanos. O feedback de diversas partes interessadas da América Latina demonstrou uma implementação inconsistente de testes de bioequivalência na região. Contudo, existe apoio para uma abordagem sinérgica entre os países para reduzir a duplicação e aumentar a eficiência na autorização de introdução no mercado de medicamentos genéricos. Isto inclui o alinhamento com o programa de Pré-qualificação de Medicamentos da OMS, bem como o desenvolvimento de uma base de dados computacional para a classificação de ingredientes farmacêuticos ativos para demonstrar a intercambiabilidade terapêutica de formas farmacêuticas orais de liberação imediata de acordo com o BCS. As oportunidades de aprendizagem digital facilitadas pelo FIP aumentaram a conscientização sobre a estratégia regulatória de bioisenção baseada no BCS entre as partes interessadas latino-americanas. Resultou num plano para reforçar continuamente os esforços de colaboração na região para harmonizar os regulamentos relevantes para o desenvolvimento de medicamentos e medicamentos genéricos para introduzir medicamentos com boa relação custo-benefício que beneficiem a saúde pública.

Palavras-chave: conhecimento, estratégia, regulatório, América Latina, genérico, medicamentos.

RESUMEN

La Organización Mundial de la Salud (OMS), con el apoyo científico de la Federación Farmacéutica Internacional (FIP), orienta el desarrollo de productos farmacéuticos de múltiples fuentes para su autorización en el mercado mediante estudios de bioequivalencia in vivo o, cuando proceda, estrategias de exención de la producción de bioproductos in vitro basadas en el Sistema de Clasificación Biofarmacéutica (BCS). Un examen del marco reglamentario que orienta la aprobación de medicamentos genéricos en los países de América Latina reveló que menos del 50% de las autoridades sanitarias regionales ofrecen una vía de desarrollo de medicamentos genéricos que utiliza una estrategia de exención biológica basada en el BCS. En consonancia con la Estrategia «UN FIP» para facilitar el acceso a los medicamentos, se llevó a cabo un estudio de caso regional para aplicar y armonizar los conocimientos sobre la bioexención basados en la ECB en los países de América Latina. Se estableció un comité directivo integrado por representantes regionales de las autoridades sanitarias, la industria farmacéutica y las universidades para coordinar las actividades de desarrollo. Se llevaron a cabo una serie de eventos de participación digital en español e inglés con representantes de América Latina para compartir conocimientos sobre la estrategia regulatoria basada en BCS, promover colaboraciones y explorar la alineación de la aprobación de la exención biológica y las vías regulatorias entre los países latinoamericanos. Los comentarios de diversas partes interesadas latinoamericanas demostraron una implementación inconsistente de las pruebas de bioequivalencia dentro de la región. Sin embargo, se apoya un enfoque sinérgico entre los países para reducir la duplicación y aumentar la eficiencia en la autorización del mercado de medicamentos genéricos. Esto incluye la alineación con el programa de Precalificación de Medicamentos de la OMS, así como el desarrollo de una base de datos computacional para la clasificación de ingredientes farmacéuticos activos para demostrar la intercambiabilidad terapéutica de las formas de dosificación oral de liberación inmediata de acuerdo con el BCS.

Las oportunidades de aprendizaje digital facilitadas por la FIP sensibilizaron a las partes interesadas latinoamericanas sobre la estrategia reguladora de la bioexención basada en el BCS. El resultado fue un plan para fortalecer continuamente los esfuerzos de colaboración en la región a fin de armonizar las reglamentaciones pertinentes para el desarrollo de medicamentos genéricos con el fin de introducir medicamentos costoeficaces que beneficien a la salud pública.

Palabras clave: conocimiento, estrategia, regulación, América Latina, genéricos, medicamentos.

1 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 (Miranda Claudia et al., 2021).

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 (WHO, 2015).

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 (WHO, 2015).

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) (Miranda, Claudia et al., 2021), 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.

This project was aligned with the Sustainable Development Goals of the United Nations 2030 Agenda, mainly with Good Health and well-being (Etukakpan, A. et al., 2023). 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 (Macé et al., 2022).

2 LITERATURE REVIEW

2.1 KNOWLEDGE-BASED

The theory of knowledge-based resources is part of Strategic Management. Grant (1996) 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. At the same time, Spender (1996) 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.

According to Nonaka (1994), the learning process is developed by “learning by doing.” The professionals share explicit that is gradually converted to tacit knowledge (Nonaka & Takeuchi, 1995). Managers use this knowledge to make decisions aligned with their competitive strategies (Nonaka & Takeuchi, 1995).

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 (2018), 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.

Considering this, Lilleoere & Hansen (2011) explored the sharing of tacit and explicit knowledge in a pharmaceutical company in Europe between R&D professionals with different cultures. 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 (2014) 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.

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 (Tucker et al., 2016).

Based on that, a study conducted by a group of researchers (Miranda et al., 2021) 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. 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 (2017) analyzed the different kinds of knowledge and the impact of technical knowledge transformed into a regulatory decision. 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. (2018) 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. 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 (2021), must exploit knowledge and strategy to adapt to a pandemic. 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 (2018) identified regulatory knowledge as the most crucial type required to support international entry modes. This study conducted ten longitudinal case studies with small and medium-sized enterprise (SME) pharmaceutical industries. Bell & Cooper (2018) understand that regulatory knowledge is the most important type of knowledge for international-market entry.

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 (Serenko, 2021). Knowledge of each country directly influences modes of international entry, enhancing healthcare education among pharmaceutical professionals and supporting communication strategies.

2.2 KNOWLEDGE OF BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

BCS is a framework proposed by Gordon Amidon et al. (1995) to classify drugs according to aqueous solubility and permeability to establish their potential limiting factors for oral absorption (Bermejo & Amidon, 2003). 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 (Baena, 2008):

- 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 (Butler; Dressman, 2010).

In the context of international research and industry, the BCS is the framework adopted by the FDA (CDER/FDA, 2000) and the EMA (Morais et al., 2010) 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.

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.

2.2.1 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, Tsum et al.(2004) 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*. 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 (Tsum et al., 2014).

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 (2015) 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. 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 (Lozoya-Agullo et al., 2015). 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 (Lozoya-Agullo et al., 2015). 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 F_{abs} and the BCS classification (Lozoya-Agullo et al., 2015).

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 (Miranda Claudia et al., 2021).

3 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 (Miranda Claudia et al., 2021).

Latin American countries have made significant progress in harmonizing their regulatory requirements for granting a biowaiver in recent years de (Miranda Claudia et al., 2021). 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 (Miranda Claudia et al., 2021).

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.

3.1 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 (Storpirtis et al., 2014).

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 (Morais, D. C. et al, 2020).

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 (ANVISA, 2022).

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 (Soares, F. S., 2021).

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 (ANVISA, 2022).

According to ANVISA (2022), the resolution outlines the criteria for determining the eligibility of drugs for biowaiver based on their solubility, permeability, and therapeutic dose. 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.

3.2 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 (Saavedra et al., 2011).

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 (Saavedra et al., 2011).

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. 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" (Miranda Claudia et al., 2021).

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 (Saavedra et al., 2011).

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 (Stojanova, J., 2020), 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. "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 (ISP, 2018).

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.

3.3 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 (Colombian Ministry of Health BCS, 2016).

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 (WHO, 2015).

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.

4 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 (Yin, 2014).

As Yin (2014) explained, the exploratory case study typically involves collecting data through various sources such as interviews, observations, surveys, and documents. 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.

Figure 1. Series of digital engagement events



Source: Researcher (2022).

5 FINDINGS ANALYSIS

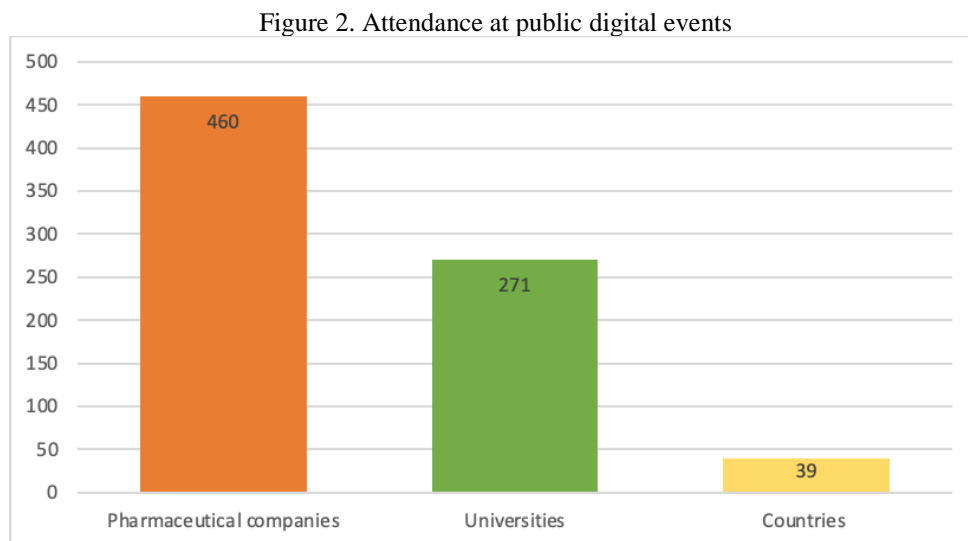
The investigation revealed inconsistencies in the implementation of bioequivalence tests in the Latin American region, which can lead to differences in the safety and efficacy of generic medicines. However, stakeholders expressed support for a synergistic approach across countries to reduce duplication 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.

6 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.



Source: Researcher (2022).

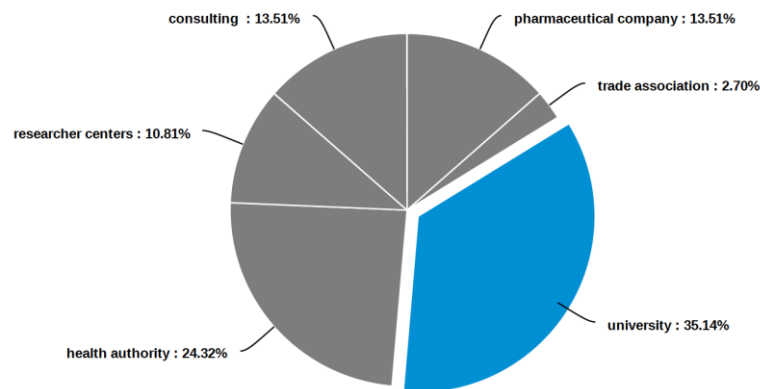
The statement declared that health authorities had discussed the public health implications of knowledge of the BCS-based biowaiver, which may include the potential for greater availability and affordability of generic medicines and the need to ensure the safety and efficacy of these medications is not 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

Specify your work environment



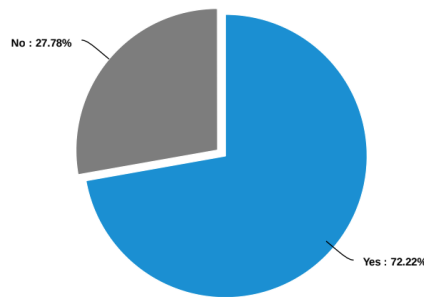
Source: Researcher (2022).



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 (1994) points out that tacit knowledge comes from within and is unique to each professional. 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

Does your country have a defined legislation for a Biowaiver regulatory approval pathway?



Answer	Count	Percent	20%	40%	60%	80%	100%
Yes	26	72.22%					
No	10	27.78%					
Total	36	100 %					

Source: Researcher (2022).

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 (1996) understands that a company's most important strategic resource is its knowledge. The companies must know to manage this resource to compete in specialized markets. According to Grant (1996), companies' role is to apply tacit and explicit knowledge acquired by its professionals to implement competitive strategies.

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 in the Latin American region.

7 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.

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.

8 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.

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