Ind. J. Pharm. Edu. Res., 2023; 57(3s):s499-s506.
https://www.ijper.org

Review Article

Analyzing Biosimilars in Brazil: Comprehensive Specifications of the Regulatory System

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ABSTRACT

The largest nation in South America, Brazil, is now the world's second-largest market for pharmaceuticals thanks to the country's economic growth. The Brazilian Health Surveillance Agency, also known as the National Agency for Health Surveillance (Agencia Nacional de Vigilancia Sanitaria - ANVISA), was founded in 1999 with the primary objective of protecting and strengthening public health surveillance over Brazilian products and services. Biological products, also known as biopharmaceuticals, are medications that are derived from biological systems and then created utilizing contemporary biotechnological techniques. These biological products are very different from traditional synthetic drugs in a number of important respects. Biosimilars are required to satisfy a variety of regulatory requirements before being given permission to enter the market in various regions. Other issues that are related to this need to be established by national authorities. These issues include interchangeability, labelling, and prescription information. The Brazilian health monitoring agency follows the fundamental criteria established by the World Health Organization for evaluating bio-similarity; nevertheless, it does not make use of the name "biosimilar." The objective of this article is to present the Brazilian biosimilar law.

Keywords: ANVISA, Regulations, Guidelines, Biosimilars, Regulations, Pathway.

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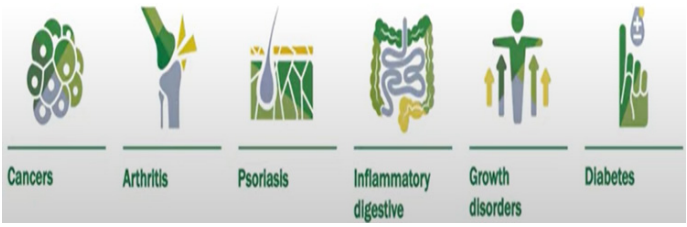
Received: x-x-x;
Revised: x-x-x;
Accepted: x-x-x.

INTRODUCTION

Biological products, often known as biopharmaceuticals, are medications made using contemporary biotechnological processes derived from biological systems. In most cases, they are complex sugars, nucleic acids, or tissue extracts, all of which are distinct from traditional synthetic and small-molecule drugs in a variety of respects. DNA recombinant proteins are the most common type of these drugs.[1] DNA recombinant proteins are produced using a technology called Deoxyribonucleic Acid (DNA) recombinant technology.

A. Due to the fact that monoclonal antibodies are particularly focused treatments, this category of biologics is seeing the most rapid growth. They are significantly bigger and more complex molecules, often unstable, not totally described owing to their structure's complexity. Most crucially, due to the inherent variety and microheterogeneity, their identity is primarily defined by the source and the production method.

B. The use of biologics in the treatment of illnesses and other medical issues, including.[2]

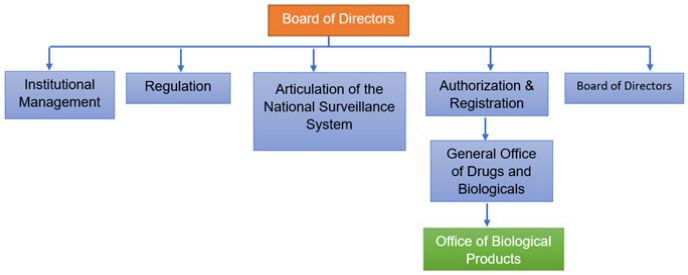


Even when using the same kind of host expression system and technologies that are functionally comparable, it is difficult for many manufacturers to make biological products that are identical to one another. Therefore, lawful follow-on biologics that are created and sold after a patent has expired are referred to as biosimilars to signify that the goods they produce are not identical, but rather ones that are comparable.

Not until 2002 did Brazil enact any legislation that were explicitly related to biological goods. Following the publication of the guidelines for biological products in 2002 (RDC 80/2002), "follow-on biological products" and "originator biologicals" were required to comply to the guidelines.[3] In 2010, Brazil passed regulations that would specifically address and provide pathways for issuing licenses for more biological products via a comparability mechanism. These regulations were in response to the country's introduction of additional biological goods. The World Health Organization's Guidelines for Similar Biological Products are only one of the numerous laws and directives on

DOI: 10.5530/ijper.57.3s.57

which the Brazilian regulations (RDC 55/2010) are founded. Although they conform to the same scientific principles as the guidelines of the WHO, there are some differences between the two sets of standards since Brazil has specific requirements.[4]



Responsibilities

ANVISA is in charge of the registration of pharmaceutical drugs as well as the licensing of pharmaceutical labs and other businesses involved in the pharmaceutical manufacturing process. In addition to this, the agency is in charge of formulating laws that are relevant to clinical trials (particularly in terms of the Chemistry, Manufacturing, and Control (CMC) of pharmaceuticals and the safety of subjects). ANVISA collaborates on the medication price regulation process with the Chamber of Drug Market Regulation (CMED), which is comprised of members from a variety of ministries, including the Ministry of Health.[5] Human clinical trials that adhere to ethical standards are overseen by an Ethics Committee (EC) that is affiliated with the Ministry of Health. The ANVISA is in charge of a wide variety of different health-related domains. The agency, in conjunction with the states and other local municipalities, conducts inspections of manufacturers, checks the quality of medications, engages in post-marketing monitoring, performs pharmacovigilance activities, and supervises the promotion and marketing of pharmaceutical products. In addition, ANVISA, in collaboration with the National Industrial Property Institute, reviews patent applications linked to pharmaceutical methods and products (INPI).[6]

Regulatory pathways for approval of biological products

In the terminology used by ANVISA, there are two terms that are used: 'new biologic product,' which refers to a new biologic entity that has not yet been registered; and 'biologic product,' which refers to copies or follow-on products that contain an active substance that has already been registered by the agency. Both of these terms refer to new biologic entities. The purpose of this nomenclature is to make it abundantly evident that bio similarity is not always a prerequisite for the approval of copy biological goods. This is the obvious goal of this nomenclature. Although using the term "biologic goods" for copies, regardless of whether they are comparable to the originals or not, is misleading and, as a result, is seen as improper.[7]

According to Brazilian regulation, the applicant may submit a 'biologic product' via three possible pathways (Figure 1).

A full data package pathway (Complete Dossier)

This is the mandatory pathway to obtain marketing authorization for a new biological product, with a new biological substance, not yet registered in Brazil.

The application dossier must include complete data about the development and characterization of the biological substance and the product itself, a detailed description of the production process, and quality control, demonstrating consistency in the manufacture of the drug. The company must also present substantial evidence of clinical safety and efficacy, through non-clinical and clinical studies in Phases I, II, and III.

The biological product approved through this pathway is eligible to become a comparator or reference product for the registration of subsequent products with the same biological substance.[8]

A comparative development pathway

This route permits the registration of a "clone" of an authorized comparator product by requiring the submission of a comprehensive dossier after the expiry of patent protection for the original product.

In scientific papers and by international authorities, biological products that are registered via this process are often referred to as biosimilars. It is noteworthy to note, however, that at the time RDC 55/2010 was published, ANVISA decided not to use this phrase and instead refers to the different forms of biological products as simply "biological products."

Any firm that decides to adopt the comparative route is required to conduct comparative studies in order to prove that the biological product that is going to be registered is qualitatively and quantitatively equivalent to the comparator product in terms of both safety and effectiveness.[9]

There is no comprehensive list of biological comparator items that can be found on the ANVISA website. Because of this, before beginning the development of a biosimilar, firms are strongly encouraged to consult with ANVISA to establish whether or not the product that will serve as a comparison may be regarded as legitimate.

A prime illustration of this is the growth hormone. In Brazil, consumers may choose from a variety of items that have been on the market and registered for a significant amount of time. In order to gain registration, each one of them was required to submit evidence about the product's quality, safety, and effectiveness. On the other hand, only four goods submitted a full dossier to ANVISA, and these are the only ones that may be

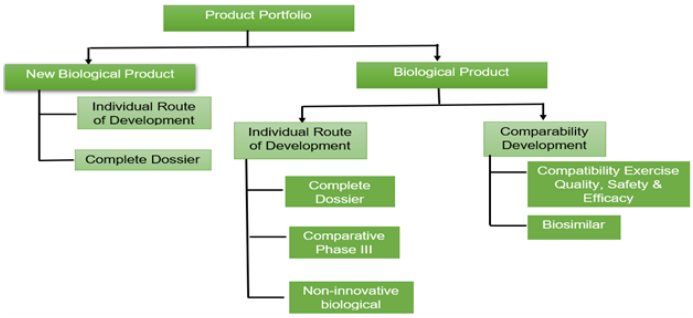


Figure 1: Registration Pathway for Biologics.

used as comparisons. After the competitor has been picked, the corporation is obligated to carry out all of the comparison tests against the chosen competitor.[10,11]

The purpose of the exercise in comparative analysis is to illustrate how similar the two products are to one another. ANVISA has made recommendations accessible for the comparison exercise for the quality qualities, and they may be accessed here (see resolutions and guidance notes). In addition to doing comparative non-clinical and clinical research, businesses are required to employ data extrapolation to support their submissions.

Because there is no need to carry out fresh clinical trials for each indication that was previously authorized for the reference biological product, data extrapolation offers a way for the development of biosimilars that has the potential to save both time and money. Instead, the firm chooses the therapeutic indication that is the most relevant and conducts just one comparative Phase III study. This allows the company to acquire permission for the other indications via extrapolation of data about safety and effectiveness.[12]

The individual development pathway

This procedure requires the presentation of complete data on the development, production, quality control, and non-clinical data. ANVISA accepts non-comparative clinical studies for Phases I and II, but clinical studies for Phase III must be comparative (demonstrating non-inferiority, equivalence, or superiority), except for blood products, vaccines, and biological products for oncology, where the studies can be non-comparative.[13]

This pathway would address those products situated in between the two previous categories. The product is not new, because it contains a biological substance already marketed in the country, and it is not biosimilar, as it was developed independently with no comparability exercise.

For drugs that are registered via separate paths, extrapolation of data is not allowed, and every therapeutic indication that is claimed in the marketing authorization dossier has to be validated by distinct clinical trials.

The prospect of qualifying the proposal for a fast-track examination, also known as an optimized review, is one potential benefit of the individual approach over the comparative road. Alternatively stated: According to Service Orientation 45/2018, the application may be considered for a fast-track assessment if the biological product has previously been authorized by both the Food and Drug Administration in the United States and the European Medicines Agency (via the centralized method). Either the comprehensive assessment reports from these agencies need to be included in the dossier, or the mentioned agencies need to make them immediately accessible to the public. After that, ANVISA will conduct an analysis of a select few parts of the dossier, and it will depend on the assessment reports provided by reference agencies in order to come to a conclusion on the approval of biological goods.[14]

Regulatory Submission Process

The CTD format that is applicable in the countries that are members of the ICH has several regional specificities as well as some commonalities. According to the Brazilian rule, the dossier for product registration is divided into two primary elements:[15,16]

1. Administrative: Compilation of all administrative data, including specific requirements for imported products.

2. Technical: Technical reports, including quality, nonclinical, and clinical information, presenting similarities to the CTD Modules 2, 3, 4, and 5 (Figures 2 and 3).

Institutions involved in the approval process

Reviewing and certifying the regulatory documentation necessary to begin clinical research in this area is within the purview of not one, not two, but three distinct agencies in the country of Brazil: CONEP (Central), CEP (local committee), and ANVISA. The CONEP and ANVISA procedures run concurrently with one another (Figure 4).

The Comisso Nacional de Ética em Pesquisa (CONEP), which translates from Portuguese as the National Committee of Ethics in Research; this committee is the Central Ethics Committee, which is related to the Ministry of Health, and it is responsible for reviewing and approving the ethical aspects of a clinical trial in Brazil.

The Comisso Nacional de Ética em Pesquisa (CONEP), which translates from Portuguese as the National Committee of Ethics in Research.[17]

It is the responsibility of the Coordinating CEP to submit the clinical trial to the CONEP, and they will engage directly with the CONEP about the study assessment. If the CONEP decides that the research may proceed, a formal letter will be produced.

	New Biological Products	Biological Products (not new)	
		Comparability	Stand Alone
CMC	Needed	Comparative	Needed
Pre-clinical	Needed	Comparative	May be reduced
Clinical 1 and 2	Needed	Comparative	When needed, may not be comparative
Clinical 3	Needed	Comparative	Comparative with exceptions
Immunogenicity	Needed	Comparative	Needed
Same comparator	Not applicable	Yes	Not applicable
Risk management plan	Needed	Needed	Needed
Extrapolation	Not applicable	Possible	Not possible

Figure 2: Regulatory requirements for the license of Biological and Biosimilar products.

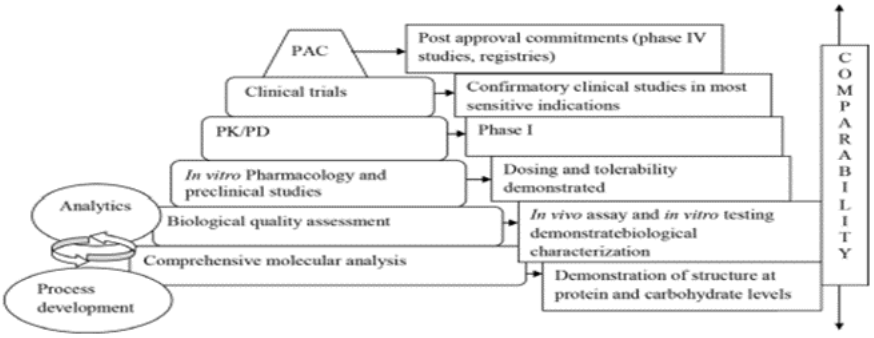


Figure 3: Biosimilar Development process.[22]

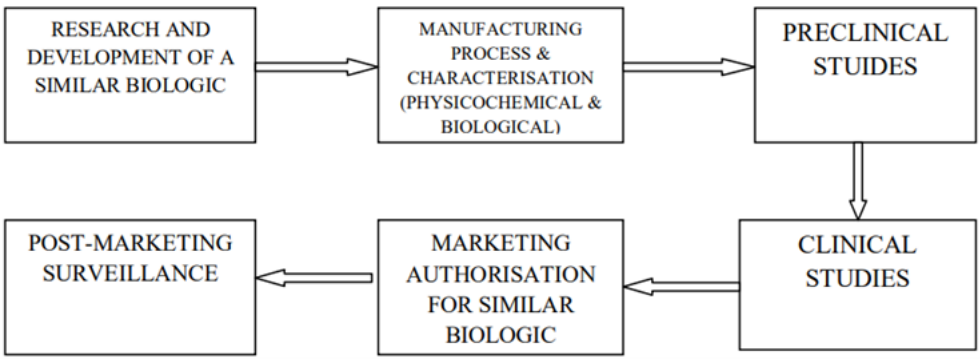


Figure 4: Steps involved in the Development and Marketing of a Biosimilar.

In the event that a query is not answered, CONEP will send it to the Coordinating site via the Coordinating CEP. There are three different ways in which questions may be posed:

Concerns were voiced: In this scenario, the Coordinating CEP gets a list of concerns from the CONEP, which it then relays to the Coordinating Site and the Sponsor. The replies and comments will be prepared by the Sponsor on a question-by-question basis, and then they will be sent to the Coordinating Site.

Concerns have been made under the heading "approval with the recommendation." In this scenario, the clinical team is obligated

to transmit the CONEP recommendations, together with all of the relevant updated papers, to all sites so that they may be submitted to the CEPS. Before the research can begin at each location, each CEP is required to go through the adjustments and provide their approval on them.

If questions are raised when the status is "Pending," the clinical team is required to give the suggestions, together with all of the appropriate updated papers, to the Coordinating Site alone. These will then be sent to the Coordinating CEP. After the replies have been approved by the coordinating CEP, they are sent to the CONEP for evaluation. Following the acceptance of the study by CONEP, all remaining sites and their respective CEPS are required to obtain the revised papers that have been authorized for the purpose of review and local permission before the research may begin at any site.[18]

Comitê de Ética em Pesquisa (CEP), which translates directly from Portuguese to "Committee of Ethics in Research," are local ethics committees that are registered with CONEP (the central committee). They are able to evaluate and sanction clinical tests that are carried out at an establishment.

a. Every firm participating in the clinical study has to have compiled a list of the necessary papers and information.

b. The sponsor and the study locations are the sources of these papers and the information they contain. It's possible that these papers will include sample versions of the necessary forms, documentation, and statements for the research. In addition to that, they include assertions relating to facts about broad studies. One of the initial three research locations is chosen at random to serve as the Coordinating Site. Once this decision has been made, the CEP of the selected site becomes the Coordinating CEP. Any and all documents must be presented in Portuguese, and any document that has been translated into Portuguese must be supported by the appropriate certificate of translation.

Agência Nacional de Vigilância Sanitária (ANVISA): This is the Brazilian Regulatory Agency. This group is responsible for reviewing all technical aspects and issuing the Import License for a clinical trial. Two types of dossiers are reviewed by ANVISA:

a. Processo de Anuência (Consent Process): The main application dossier for initial submission. This dossier will receive a unique specific number from ANVISA to be used for all updates.[19,20]

b. Processo de Inclusão de Centros (Inclusion Centers Process): The dossier for adding sites when every site other than the one submitted in the Processo de Anuência. This document will carry the same number as the one previously assigned.

Documentation required

ANVISA would rather have all of the material included in its entirety inside the dossiers. However, it is allowed to submit the dossier with some of the material still missing, and then to update the remaining papers as they become available in the future. There will be responses provided to meet each of the questions that ANVISA poses.

Several documents submitted are briefly described below:

1. Brazilian Informed Consent Form (ICF) template that must be translated into Portuguese and adapted to the local government. There are three different types of ICF that one may find:

Master ICF is the primary document that is submitted.Revised ICF is done whenever the changes affect any local requirement.Revisions to site-specific ICF are any revisions to a site-specific ICF.The process of importing, which involves submitting paperwork relating to the request for an import license. This document contains any recent revisions to the list of goods that are eligible for importation. It includes all of the material pertaining to the research drugs (such as Certificate of Analysis, BSE Certificates, and documents). This request is valid for the whole duration of the clinical study, which is one year, as well as for numerous shipments. In the event that the duration of the clinical study or the quantities required g too beyond the conditions that were allowed, an extension must be done in order to meet the additional requirements.[20]

Check the master labels of all of the research medications and supplies to make sure they have all of the necessary information. These labels are written in English as well as their Portuguese version. Both languages are supported.

Any study-related announcements or advertisements that will be sent out to the sites.

The ICF's Confidentiality and Data Handling section lay forth the necessary precautions to take while dealing with sensitive information. When an individual is injured during the course of the study, the Sponsor is responsible for paying medical expenses not covered by insurance.

The protocol has been updated to reflect these changes. Each CEP had to sign off on these changes before they could be implemented, and then they had to let ANVISA know about it. Requesting CONEP's blessing is optional yet possible.

Safety report must be done according to local requirements. This document is received from the Sponsor in both English and Portuguese.

Progress and annual reports are prepared and submitted following local requirements. The study staff must submit an interim report to its CEP every six months.

The notice of the end of the trial is comparable to the progress reports and annual reports submitted to ANVISA by the sites.

Reports trials are only created and sent to ANVISA if the sponsor specifically requests them to do so.

Approval process

In most cases, the process of obtaining regulatory clearance involves going through two separate ethical assessments. These are known as the institutional CEP and the CONEP. The multicentre research center study protocol is sent to CONEP for consideration once it has been submitted by the Coordinating Ethics Committee (EC), and approval would apply to all locations. The protocol, the ICF, the investigator's brochure, Power of Attorney, a letter from the Coordinating EC stating that the protocol has been accepted, and any other papers that have been presented to the Coordinating EC are required for submission to CONEP.

The Coordination of Clinical Research with Drugs and Biological Products (COPEC) and the Coordination of Clinical Research with Devices and Food (COPEA) are two distinct departments that are part of ANVISA. These departments are responsible for coordinating clinical research on drugs and devices respectively. Instead of evaluating each study individually, ANVISA looks at the clinical dossier that accompanies drug development. In the case of specific clinical protocols, a straightforward submission package is necessary whenever trials of phase I, phase II, or phase III are to be carried out in Brazil. On the other hand, for phase IV, all that is required is a notice to ANVISA. According to their instructions, the examination of the dossier by ANVISA might take anywhere from ninety to one hundred and eighty days before the research can be started.[21]

Import

When the CTA is approved by ANVIA, this will also serve as permission for the importation of the pharmaceuticals into Brazil. At the clearing, you will be required to provide a copy of the Special Bulletin, often known as an approval certificate. In addition to the certificate of approval, the following items are required to be submitted:

- A copy of the document of delegation of responsibility for importation must be provided with each shipment of goods that is imported by a body that is not the holder of the DDCM;
- Anticipated duration of clinical trial.
- Proof that the goods are economically viable for importation, as well as documentation of the international transport contract.[23]
- ANVISA's Resolution No. 9/2015 governs not only the paperwork requirements for import, but also the shipping containers that are used to import medications. This is in addition to the documentation requirements for import. The following information is required to be included on the containers: SB number or Document for Importing Product(s) that are currently under investigation by the DDCM and to which the investigational product is subject.
- The amount of material that was imported.
- Instructions on how to properly maintain the conditions of storage, including temperature, humidity, and light.
- Information on the presentation of the product, including its physical shape or its pharmacological form.[24]
- Information on the validity of the product and, if appropriate, the medical device; and,
- The number of the lot or the serial number.

Quality

During the process of characterization of the product, the comparability route mandates the following requirements in order to prove that the follow-on biology is of sufficient quality:

- A side-by-side comparison with the biological product that serves as the comparator.
- Product-related substances (variants), primary and higher-order structures, post-translational modifications, biological activity, purity and impurities, and immunochemical properties.
- The primary structure has to be exactly the same as the comparator.
- Clinical assessment in order to complete the clinical comparability exercise, a step-by-step process is required:
- Studies of the pharmacokinetics and pharmacodynamics of the drug, followed by key clinical trials.
- It's possible that clinical effectiveness trials may be required.
- One essential factor to take into account is how to choose a susceptible group as well as appropriate endpoints. The selection process ought to make it easy to identify any potential discrepancies between the items.
- It is required to conduct comparative immunogenicity research.
- Equivalence is recommended for the design of the research; however, non-inferiority might be utilized instead if it can be substantiated.

Indications extrapolated to their full extent[25]

In Brazil, it is possible to acquire permission for indications in which the follow-on biological has not been tested; nevertheless, in order to do so, it is necessary to satisfy the following criteria:

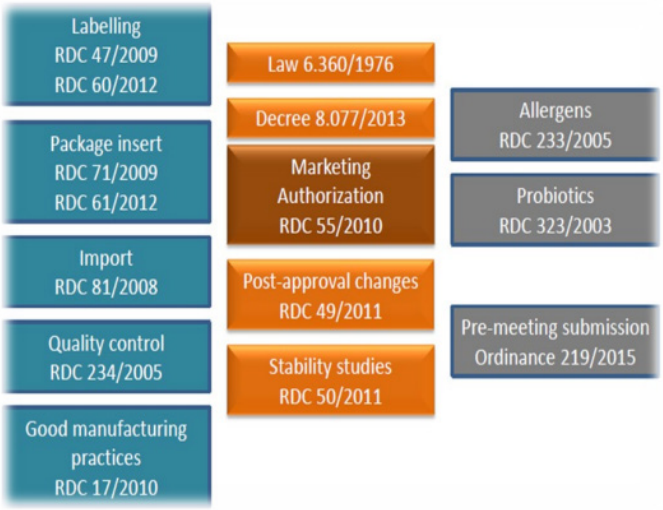
- It is necessary to make use of a sensitive test model that is able to identify any possible differences that may exist between the biosimilar and the comparator.
- There must be no difference in the mode of action and/or the receptor(s) that are engaged.

- The immunogenicity and the safety of the substance need to be well described.

Forced Degradation Study (FDS) resolution

Resolution RDC-53/15, which was first adopted in 2015, outlined the particular parameters that need to be met in order to carry out forced degradation studies for product registration and post-approval adjustments. In addition to the guidelines made by the ICH, it describes the reporting, identification, and certification of degrading products (Tattersall *et al.* 2016). In addition, a guideline with regard to this subject was published (Guia 04/2015). In essence, what is being asked for in this resolution is:[25]

- If the degradation products' concentrations are higher than a qualifying limit, then safety investigations are required for them.
- An analysis of the particular forced degradation circumstances has been carried out and is afterward reported in a report.
- It is important to take into account the deterioration that occurred as a consequence of manufacture and storage.



- It is necessary to determine and explain the mass balance.

This resolution also includes a request that the research on forced degradation is documented in a report that outlines the particular standards that must be met. A number of businesses are concerned about this matter since ANVISA mandates that the proposed resolution be implemented not only for the submission of the new medicine but also for certain post-approval alteration requests. In order for the pharmaceutical sector to comply with these standards and support authorized medications, which may be supported by a vast body of historical data, considerable effort would be required.

Current Regulatory Acts Concerning Biological Products

CONCLUSION

The ideas reflected in the World Health Organization's rules and standards for the evaluation of similar biotherapeutic products are reflected in the Brazilian Regulatory Agency's 2010 order for licensing biosimilars. Nonetheless, it has several contentious alterations, such as the terminology (rebranding the copies as produto biológico to avoid the word biosimilar) and the addition of an additional pathway of approval that is not based on the comparability exercise. The comparability exercise and subsequent designation of licensed copies of biologic drugs as biosimilars have been generally positively accepted by regulatory agencies and the academic community. Biosimilars have paved the way for cheaper alternatives to biological drugs. As a result of their complexity, biosimilars' potential problems cannot be predicted with any accuracy. To ensure the safe delivery of biosimilars to patients, pharmacovigilance studies should be conducted after product approval to detect any potential side effects. However, the existing rule in Brazil leaves this decision to physicians. Brazil's philosophy of partnerships for product development has many benefits, the quickest way to acquire biosimilars is probably the most significant. Perhaps ANVISA will see fit to update its rules and incorporate this term into them. Since it is widely acknowledged that several critical concerns about biosimilars require definition by national authorities, we place special emphasis on the necessity for legislation on the issues of labeling, extrapolation, and interchangeability. We fear that the lack of a government stance on these matters poses a threat to medical professionals' capacity to perform safely and effectively, as well as patients' health. Biosimilar development supported by adequate regulation can reduce healthcare expenditures without compromising patient safety or clinical efficacy.

ACKNOWLEDGEMENT

This study was supported by JSS College of Pharmacy, Mysuru. We thank our colleagues from the Regulatory Affairs department who provided insight and expertise that greatly assisted the study, although they may not agree with all of the conclusions of this paper. First of all, no words to express gratitude to my Parents for their love, affection, encouragement, and support throughout my course, which helped me a lot to complete my work. We would also like to show our gratitude to Dr. Balamuralidhara V. Associate Professor and Head of the Department of Pharmaceutics, JSS College of Pharmacy, Mysuru for sharing their pearls of wisdom with us during the course of this research, and we thank 3 reviewers for their insights. We are also immensely grateful to Ms. Gowthami K R. Ph.D. Research Scholar for the comments on an earlier version of the manuscript, although any errors are

our own and should not tarnish the reputations of these esteemed persons.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ANVISA: National Agency for Health Surveillance (Agencia Nacional de Vigilancia Sanitaria); **DNA:** Deoxyribonucleic Acid; **RDC:** Resolution of the Collegiate Board; **WHO:** World Health Organization; **CMC:** Chemistry Manufacturing Control; **CMED:** Chamber of Drug Market Regulation; **EC:** Ethics Committee; **INPI:** National Institute of Industrial Property; **CONEP:** National Committee of Ethics in Research; **CEP:** Committee of Ethics in Research; **COPEC:** Co-ordination of Clinical Research with Medicines and Biological Products; **ICF:** Informed Consent Form; **COPEA:** Clinical Research with Devices and Food; **CTA:** Clinical Trial Applications; **DDCM:** Drug Clinical Development Dossier; **FDS:** Forced Degradation Study.

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Cite this article: Deeksha KS, Veeranna B, Ravindra GK. Analyzing Biosimilars in Brazil: Comprehensive Specifications of the Regulatory System. Indian J of Pharmaceutical Education and Research. 2023;57(3s):s499-s506.