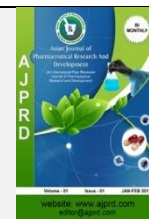


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Review Article

## Regulatory outlook from concept to commercialization of Biosimilars in Brazil market

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### ABSTRACT

Biological products or biopharmaceuticals are medicinal products derived from living organism systems and manufactured by using modern biotechnology that differ widely from the conventional synthetic drugs. They are much larger and more complex molecules with inherent diversity; hence, different manufacturers cannot produce identical biological products, even with the same type of host expression system and equivalent technologies. Thus, biologics manufactured and marketed after patent expiration are usually referred to as biosimilars. Biosimilars endeavor to copy the original technology leading to the production of innovative biotechnological medicines to obtain a product which is similar to the reference product. These products reported to improve the treatment landscape for multiple diseases, particularly in the areas of oncology, blood disorders, rheumatology, endocrinology and are becoming choice of treatment regimen due to policy push by governments for its affordability without comprising on quality, safety and efficacy. Pharmaceutical exports from Brazil increased by around 41% between 2009 and 2013, touching a high of U.S. \$1.516 billion. The valuation of Brazilian pharma markets has shown double digit growth in the past decade. Between 2012 and 2015, market valuations have increased from U.S. \$25.2 billion to U.S. \$35.3 billion.

Biosimilarity is based on a comprehensive comparability exercise wherein unavoidable clinical differences are evaluated and must meet equivalence or non-inferiority criteria. Biosimilars need to comply with different regulatory requirements for market authorization in different sites. There are several other related issues that need to be defined by the national authorities, such as interchangeability, labeling and prescribing information. The Brazilian health surveillance agency shadows the key principles established by the World Health Organization for the assessment of biosimilarity. However, the regulations also widen the gap by having standalone application pathway that does not require the usual comparability exercise with the reference product, originating non-biosimilar copies. Interchangeability and the use of nonproprietary names are not regulated. The objective of this manuscript is to explore the Brazilian Regulatory outlook from concept to commercialization of Biosimilars.

**Keywords:** Biosimilar; Biologics; ANVISA; Brazil.

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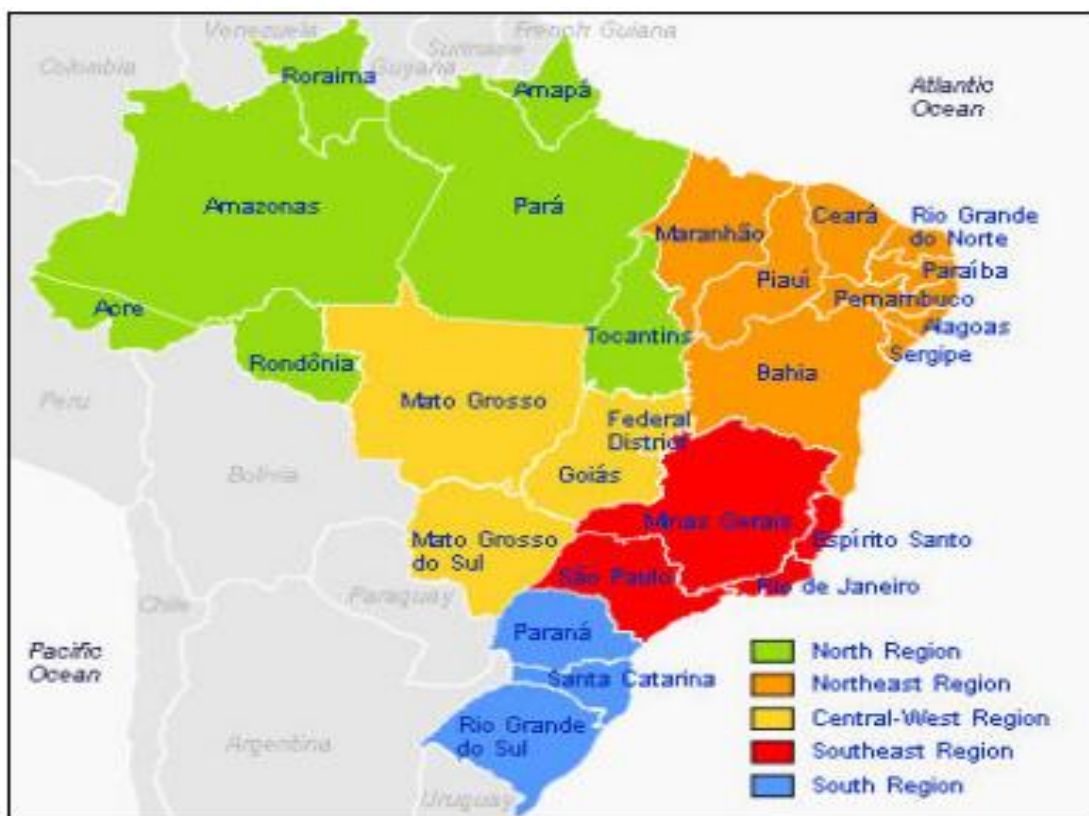
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### INTRODUCTION

Scottish businesses and research institutions reported that the Brazil pharmaceuticals market is the sixth largest economy in the world, and recent forecasts suggest that it is likely to reach the fifth position in the coming years; naturally, this sheer market size has cemented the crucial importance of the country in the overall operations of all pharmaceutical companies with global ambitions. The largest life-science market in Latin America and a platform used by overseas companies to penetrate the Latin America market. Brazil has a \$26bn

pharmaceutical market and a \$4.6bn medical device market both showing strong annual growth of 12 and 16%, respectively. As such, Brazil offers tremendous opportunities for imports, corporate partnerships, and research collaborations not only in the above mentioned life-science markets but also in a range of others including animal health and agribusiness where Brazil is a world leader<sup>1</sup>

Before, explaining on Brazil market, it is critical to discuss about socio demographic aspects. Brazil is the fifth largest country in terms of both land area and population, with 8.51 million sq. kilometers. The details are tabulated below in Table 1<sup>2</sup>;



**Figure 1: Demographic and macroeconomic indicators**

**Table 1: Demographics of Brazil**

Official Name	Federative Republic of Brazil
Languages Spoken	Portuguese
Is Landlocked	No
Latitude/Longitude	-10-55
Currencies Used	Brazil Real
Demonym	Brazilian
Capital	Brasilia
Top cities of Brazil	Sao Paulo, Rio de Janeiro, Salvador, Fortaleza, Belo Horizonte, etc.

The pharmaceuticals market in Brazil will be projected to touch close to \$60 billion by 2020. The growth of the market will be driven by the healthcare industry in Brazil, which is undergoing profound transformation and experiencing new business dynamics, making the domestic market one of the most promising and it is by no means an easy market, but it is unequivocally a highly attractive market in the world<sup>3</sup>. According to another report, Brazil's pharma market is the sixth largest market in the world in terms of sales revenue. Half of the sales come from prescription drugs, over-the-counter drugs take a 27% share, and generic drugs have the remaining 23%. The generic drug segment was the main driver behind the decade-long growth of pharma industry in Brazil, with its market sales tripling between 2009 and 2013.

Pharmaceutical exports from Brazil increased by around 41% between 2009 and 2013, touching a high of U.S. \$1.516 billion. The valuation of Brazilian pharma markets has shown double digit growth in the past decade. Between 2012 and 2015, market valuations have increased from U.S. \$25.2 billion to U.S. \$35.3 billion<sup>4</sup>.

Brazil has potential to become an important destination for state of art infrastructure R&D and expertise in biopharma. In Brazil, Regulatory approvals for the import of drugs,

approval of new drugs and clinical trials, meetings with stakeholders, approval of certain licences is governed by the ANVISA. For biologics and similar biologics, ANVISA being the apex national regulatory authority that evaluates safety, efficacy and quality of drugs in the country. ANVISA released series of similar biologics guidelines, these guidelines are applicable for Similar Biologics to be developed in Brazil or imported into the country for marketing authorization.

The National Health Surveillance Agency commonly known as ANVISA (Agência Nacional de Vigilância Sanitária) is the food and drug regulatory agency in Brazil. ANVISA was created in 1999 and is linked to the Ministry of Health.

Brazilian regulatory agency that is responsible for the approval and supervision of food, cosmetics, tobacco, pharmaceuticals, health services, and medical devices, among others. To keep pace and up to date with international regulatory requirements, as well as ensuring that the Brazilian context is included in the process of preparing the international references that will guide health regulation worldwide, ANVISA participates in the main forums for discussion and regulation of products and services subject to health regulation.

ANVISA's participation in bilateral, regional and international negotiations and regulatory convergence initiatives promotes the use existing international tools to assist the Agency in its role of regulating, monitoring and supervising products subject to health regulation. These activities aim at avoiding duplication of efforts and making the better use of available resources, with a focus not only on health protection and promotion, but also on the national economic development. ANVISA is also an important player in Brazilian technical cooperation efforts. Technical cooperation in health regulation is an effective instrument for strengthening the regulatory capacities of all parties involved, promoting the exchange of experiences and the use of best regulatory practices carried out by different health authorities.

These are some of the main recent international achievements by ANVISA<sup>5</sup>:

**2016:** Becomes a member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)

**2015:** Controls performed by ANVISA for pharmaceutical ingredients are recognized as equivalent to those of the

European Community. Becomes member of International Cooperation on Cosmetics Regulation (ICCR)

**2012:** Co-founds the International Medical Device Regulators Forum (IMDRF)

**2010:** Meets all the necessary criteria to be recognized as a Regulatory Authority of Regional Reference (NRA) by the Pan American Health Organization (PAHO)

The Brazilian Health Regulatory Agency (ANVISA) is a nodal agency linked to the Ministry of Health, part of the Brazilian National Health System (SUS) as the coordinator of the Brazilian Health Regulatory System (SNVS), present throughout the national territory.

ANVISA role is to promote the protection of the population's health by executing sanitary control of the production, marketing and use of products and services subject to health regulation, including related environments, processes, ingredients and technologies, as well as the control in ports, airports and borders<sup>5</sup>. In Brazil Research and Commercialization of Biotech product and Similar Biologics Governed as per the Law 6.360/1976, Decree 8.077/2013 and RDC n° 55/2010 (as amended from time to time) details are mentioned in below table 2:

**Table 2:** Regulatory legislation and Guidelines in Brazil

<b>REGULATORY AGENCIES</b>	ANVISA: Agência Nacional de Vigilância Sanitária or The National Health Surveillance Agency, Ministry of Health Brazilian National Health System (SUS) Brazilian Health Regulatory System (SNVS) CMED-(Câmara de Regulação do Mercado de Medicamentos) The Medication Market Regulation Chamber is the inter-ministerial body responsible for the economic regulation of the drug market in Brazil CONEP-The National Commission for Research Ethics
<b>LICENSE APPROVING AUTHORITIES</b>	Director
<b>Pharmaceutical Laws And Regulations/ Guidelines</b>	RDC 55/2010-MAA RDC 50/2011-Stability RDC 49/2011-PAC RDC 46/2000-Blood products RDC 47/2009 and RDC 60/2012- Labelling RDC 71/2009 and RDC 61/2012- Package insert RDC 81/2008-Import RDC 234/2005- Quality control RDC 17/2010-GMP Comparability guidelines Guidelines for elaboration of Clinical study reports-Biological products Guidelines for Non-clinical study Heparin development by comparability Guidelines for Non-clinical study –Interferon Alpha development by comparability Guidelines for transport qualification of biological products GCP Guidelines.

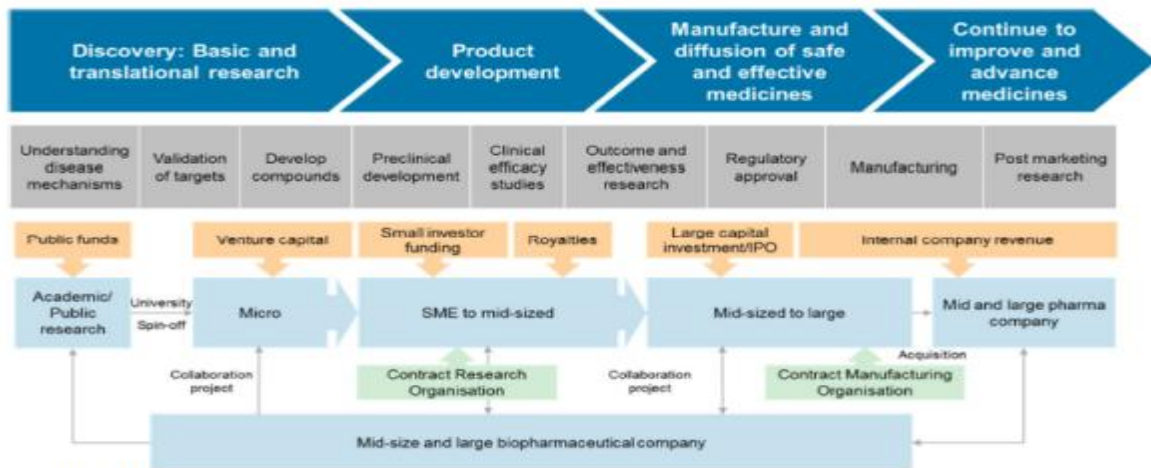
### Biologics:

A biologic medicine is a large molecule typically derived from living cells and used in the treatment, diagnosis or prevention of disease. These are produced by using biotechnology procedures like r-DNA technology. Biologic medicines include therapeutic proteins, DNA vaccines, monoclonal antibodies and fusion proteins. Biologics are

distinct from small molecule drugs in that they are larger, and are far more structurally complex agents. Biologic medicines are often 200 to 1,000 times the size of a small molecule drug. They are also highly sensitive, making them more difficult to characterize and produce. Due to both their size and sensitivity, biologic medicines are almost always injected into a patient's body<sup>6</sup>.



**Product Life cycle:**

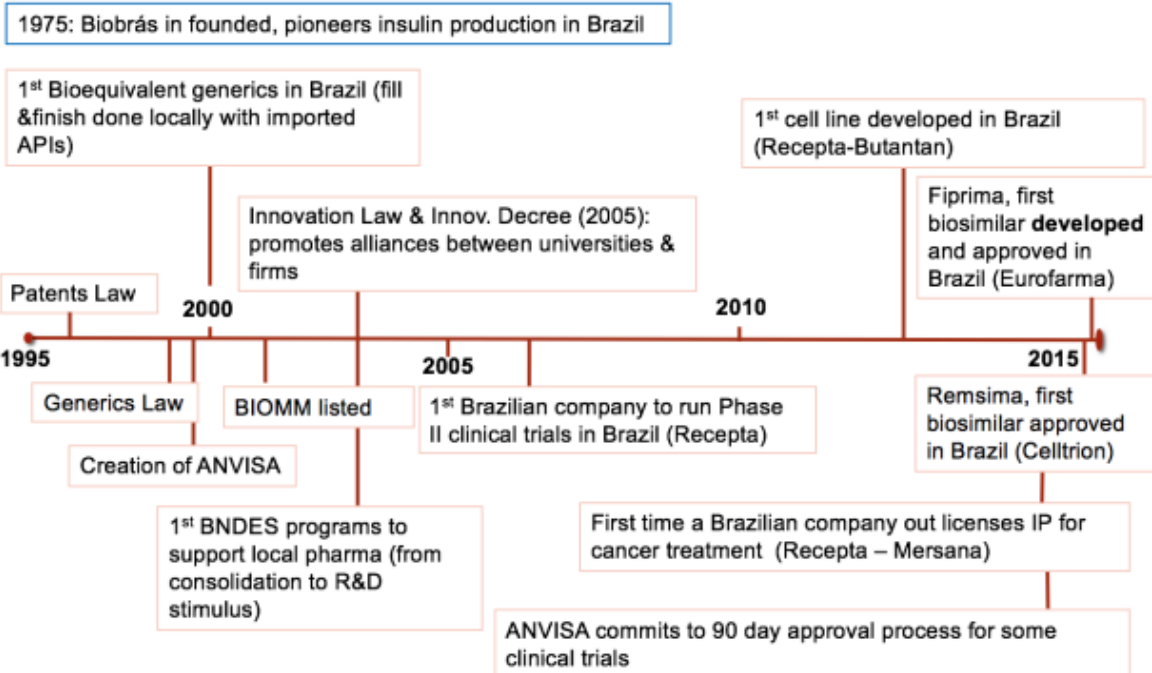


Source: CRA, 2014

**Figure 2:** Biopharmaceutical lifecycle and its value chain<sup>7</sup>

The biopharmaceutical industry’s unique, multidisciplinary and science-based structure makes it difficult to apply any one analytical framework when examining the actors that comprise it. As depicted in above figure, it takes a complex knowledge-based ecosystem to develop and bring a biopharma product to market. Because product cycles are so lengthy, the industry requires a supportive and stable institutional framework. For this reason, the biopharmaceutical industry has tended to flourish in countries and regions that can offer a solid enabling

environment. Because science-based innovation requires the exchange of tacit knowledge, the industry has developed into regional clusters. In addition to the range of capabilities and collaborations required at each stage, the figure illustrates the importance of public funds and venture capital to the success of an industry where profits, while sizeable, often take many years to materialize. A recent study estimated that the cost of developing a biotech drug today from initial research to market approval is \$2.6 billion dollars.



Source: Authors, based on interviews with industry representatives

**Figure 3:** Evolution of Biologics in Brazil<sup>7</sup>

**Clinical trial requirements in Brazil (8):** To conduct the clinical trials in Brazil the documents has to be submitted as per the below mentioned table; As per the LawNo9.782, ResolutionNo9, and Ord650/2014, the Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária) (ANVISA) is the regulatory authority responsible for clinical trial oversight, approval, and inspections in Brazil. ANVISA grants permission for clinical trials to be conducted in Brazil in

accordance with the provisions of ResolutionNo466, ResolutionNo9, and Ord650/2014.

ANVISA is attached to the Ministry of Health (MOH), which grants it authority to regulate food and drug laws in Brazil. Ord650/2014 states that the agency is ruled by a Collegiate Board of Directors composed of five (5) members, and it oversees five (5) directorates. In addition, ANVISA also has two (2) main offices: the Advisory Council and the Ombudsman office. The Advisory Council

monitors the Collegiate Board's activities and responds to public inquiries, and the Ombudsman serves as an independent body for the public to directly communicate any complaints.

As delineated in Ord650/2014, within ANVISA's directorate framework, the General Management of Medicines (Gerência-Geral de Medicamentos e ProdutosBiológicos (GGMED) operates within the General Managers of Organizational Processes (Gerências-Gerais

de ProcessosOrganizacionais) to manage drug registration. It also oversees the Office of Clinical Research Coordination on Drugs and Biologicals (Coordenação de PesquisaClínicaemMedicamentos e ProdutosBiológicos (COPEC)), which is housed within the Office of Efficacy and Safety Evaluation Management (Gerência de Avaliação de Segurança e Eficácia (GESEF). COPEC is responsible for the analysis and registration of new drugs and clinical trial protocols.

**Table 3:** Regulatory submission process in Brazil

Language restrictions	<p>All documents must be submitted in Portuguese. Applications submitted to CONEP/CEP should be accompanied by the original untranslated documents as well.</p> <p>Translating all documents into Portuguese can take 2-4 weeks.</p> <p>In 2011 it was estimated that costs can range from \$3000 to \$6000 for translations to be done.</p>
Submission Sequence	<p>Approval is required by the Institutional ethics committee (known as Comitê de ÉticaemPesquisas in Brazil or "CEP" prior to ANVISA. While under Resolution No. 9/2015, foreign sponsor initiated studies must still be approved by the national ethics committee, CONEP, ANVISA's decision is no longer dependent upon CONEPs.</p> <p>Multi-site studies should obtain EC approval from the coordinating center's CEP first, and then CONEP and ANVISA can be submitted in parallel. Study conduct at other sites must obtain local (CEP) approval before the study can begin there but CONEP-ANVISA submissions can proceed without them.</p>
Additional submissions	<p><b>Import:</b></p> <p>ANVISA's approval of the CTA will also act as approval for importing the drugs into Brazil. A copy of the Special Bulletin (approval certificate) must be presented at clearance. The following documents must be presented along with the approval certificate:</p> <ul style="list-style-type: none"> <li>• For imports made by a body other than the holder of the DDCM, a copy of the document of delegation of responsibilities for importation;</li> <li>• Anticipated duration of clinical trial</li> <li>• Documentation of international transport contract and proof of viability of the product for import</li> <li>• In addition to the documentation requirements for import, ANVISA through Resolution No. 9/2015 also regulates the shipping containers used to import the drugs. The containers must include the following information:</li> <li>• SB number or Document for Importing Product(s) under investigation by the DDCM to which the investigational product is subject</li> <li>• Amount of imported material</li> <li>• Information on special care for storage, such as temperature, humidity, and light</li> <li>• Information on physical form or pharmaceutical form referring to presentation of the product;</li> <li>• Information of the validity of the product, and where applicable, the medical device; and</li> <li>• Lot number or serial number</li> </ul> <p><b>Amendments to the DDCM:</b></p> <p>Substantial amendments (modifications) made to the DDCM must be filed with ANVISA and approved before implementation. Substantial amendments should be submitted in the form of an amendment attached to the protocol.</p> <p>The following are considered substantial amendments:</p> <ul style="list-style-type: none"> <li>▪ Inclusion of clinical study protocol(s) not previously established in the initial development plan</li> <li>▪ Alterations that potentially impact quality or safety of the investigational product, active comparator or placebo</li> </ul> <p>All other amendments should be submitted to ANVISA as part of the Safety Update Report, which is submitted annually to ANVISA.</p> <p><b>Amendments to the Protocol:</b></p> <p>All amendments to the protocol must be submitted to ANVISA. Substantial amendments must be submitted to ANVISA in the form of an amendment attached to the protocol and await approval before implementation; the approval timeline for amendments is the same as for approval, 180 days for biologic products, Phase 1 and 2 trials; 90 days for all others.</p> <p>Substantial amendments are those which</p> <ul style="list-style-type: none"> <li>▪ Change the clinical trial protocol which affects the safety or physical or mental integrity of the participants</li> <li>▪ Change the scientific value of the trial protocol</li> </ul> <p>All other amendments to the protocol must be submitted to ANVISA as part of the annual report.</p> <p><b>Early Termination:</b></p> <p>Early terminations must be submitted to ANVISA within 15 days; for a temporary suspension as an immediate safety measure, ANVISA must be notified within 7 days. The appropriate technical and scientific justifications must be noted, as well as the follow-up plan for clinical trial participants. If the sponsor wishes to resume the study a request for re-activation as well as justifications for the trial to be restarted must be submitted to ANVISA.</p> <p><b>Annual Reports:</b></p> <p>Sponsors must submit annual monitoring reports to ANVISA within 60 days from the beginning of the trial. The information, listed below, should only be from Brazilian centers, and submitted in tabulated form:</p> <ul style="list-style-type: none"> <li>▪ Title of the clinical trial</li> <li>▪ Protocol code</li> </ul>

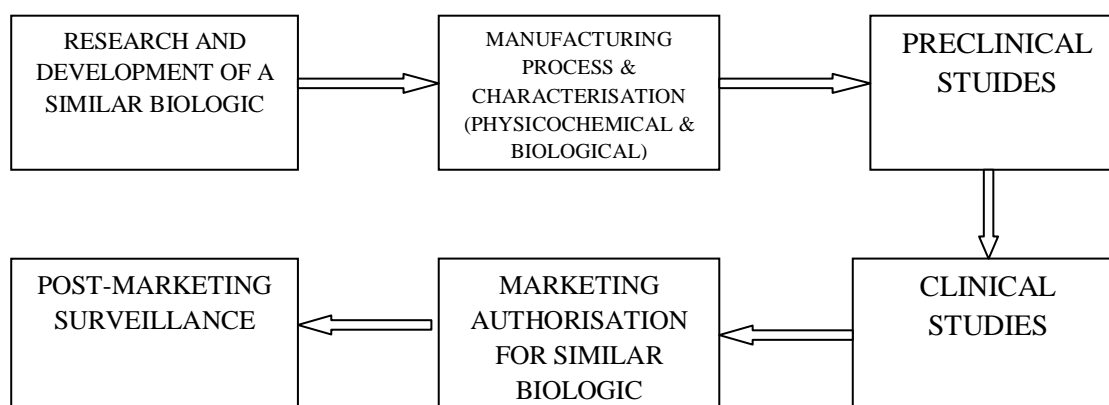
	<ul style="list-style-type: none"> <li>▪ Status of participants recruited for the clinical trial</li> <li>▪ Breakdown of the number of participants recruited by the center</li> <li>▪ The number and description of the deviations and protocol violations by the center; and</li> <li>▪ Description of all adverse events occurring at the center during this period, identifying the trial participants with the codes used in the Case Report Form adopted in the clinical trial protocol</li> </ul> <p><b>Final Reports:</b></p> <p>Final reports must be submitted to ANVISA within 12 months after the end date of the trial and include the following information:</p> <ul style="list-style-type: none"> <li>▪ Title of the trial</li> <li>▪ Protocol code</li> <li>▪ Breakdown of the number of participants recruited removed from the clinical trial</li> <li>▪ Description of patients included in each statistical analysis and those who were excluded from the analysis of efficacy</li> <li>▪ Demographic description of participants recruited for the trial</li> <li>▪ Statistical analysis</li> <li>▪ Number and description of protocol deviations and violations</li> <li>▪ All adverse events and laboratory abnormalities with causality assessment, occurring in participants</li> <li>▪ The results obtained in the measurement of outcomes for each participant in the clinical trial and</li> <li>▪ The rationale for early termination of development in Brazil or anywhere else in the world, if applicable</li> </ul>
Fees	<p>Clinical trial approval fees paid to ANVISA are referred to as Sanitary Surveillance Inspection Fees (“TFVS”). The TFVS are generated during the application process by use of a union recruitment code or “GRU”. The value is generated based on the subject (such as approval of an application) and the size of the company. The company size is determined based on the economic capacity of the company (and any subsidiaries) as measured by its gross annual turnover;</p> <p>ANVISA's table of current rates of TFVS, (in Portuguese only) is set from the Interministerial Portfolio MF-MS 45/2017 of January 30 2017. The fees for clinical trial approval, based on company type, are as follows (all the monetary figures are Brazilian Reals/as of August 14, 2017, the conversion rate was \$3.1 USD to \$1 Brazilian Real):</p> <p>Group 1 – Large (exceeding 50 million Reals): R \$19,677.00</p> <p>Group 2 – Large (equal or less than 50 million Reals): R \$16,725.45</p> <p>Group 3 – Medium (equal or less than 20 million Reals): R\$ 13,773.90</p> <p>Group 4 - Medium (equal or less than 6 million Reals: R \$7,870.00</p> <p>Small (equal or less than R \$3,600,000.00 and more than to R \$360,000: R \$1,967.70</p> <p>Micro (equal or less than \$360,000 R: 983.85 Brazilian Real</p> <p>It is unclear whether or not the CEPs/CONEP charge fees for CTA review.</p>
Insurance requirements	Local insurance broker is required.
Referenced Documents	Resolution No. 9/2015

### Procedure for Marketing Authorisation of Biosimilars in Brazil<sup>9,10</sup>:

The development of a similar biologic involves a stepwise approach of optimizing the production process, comparability exercise for characterization of the product (physicochemical as well as biological) followed by pre-clinical and/or clinical studies.

To develop a biosimilar, the manufacturer will need to first identify a marketed biologic product to serve as the reference biologic product. Then a detailed characterization of the reference biologic product will be performed. The information obtained from the characterization of the reference biologic product will be utilized to direct the process development of the biosimilar product and comparative testing to demonstrate bioequivalence between the biosimilar product and the reference biologic product.

### Development phase



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



In 2010, Brazil introduced regulations to precisely address and establish specific pathways to grant licence for follow-on biological products using a comparability pathway. The Brazilian regulations (RDC 55/2010) are based on different regulations and guidelines from around the world, including the WHO Similar Biological Product Guidelines. These guidelines follow the same scientific principles as the WHO guidelines but contain some differences due to the specific needs of Brazil.

According to Resolution–RDC 55/2010 there are two pathways exist for non-originator biologicals – a comparability pathway and a stand-alone pathway.

The two pathways have different requirements for the amount of data required for the registration of dossier, refer below Figure.

Parameters	New biological product	Biological product	
		Comparability	Stand-alone
CMC data	Required	Comparative	According to standards
Preclinical studies	Required	Comparative	Can be reduced
Clinical studies phase I (and II)	Required	Comparative	When needed, no need to be comparative
Clinical studies phase III	Required	Comparative	Comparative, with exceptions
Immunogenicity studies	Required	Comparative	Required
Comparator product	No	Yes	Not specified
Pharmacovigilance	Required	Required	Required
Extrapolation of indications	N/A	Possible	Not possible

↑  
Follow-on biological

Figure 5: Regulatory pathways for registration of biological products by ANVISA

ANVISA: Agência Nacional de Vigilância Sanitária; CMC: chemistry, manufacturing and controls; N/A: not applicable.

**Stand-alone pathway**-The stand-alone pathway is used in instances where a non-originator biological cannot be compared to the originator product. With this pathway the applicant must submit a summary of the preclinical and clinical studies performed on the non-originator biological product. The scope of the preclinical studies may be reduced and phase I/II studies can be exempt. Phase III studies are mandatory, with exceptions, and must be compared to 'non-inferiority', 'equivalence' or 'superiority' to the new biological product (originator biological)

**Comparability pathway**-The comparability pathway outlines an approach in which the follow-on biological is compared to the reference product in terms of quality and available data. This pathway closely resembles that of the WHO Similar Biological Product Guidelines.

A comparative dossier containing preclinical and clinical studies is necessary to demonstrate comparability between the products. Non-clinical and clinical data can be reduced. The pathway also allows for extrapolation of therapeutic indications between the follow-on biological and the reference product.

#### Quality

In order to demonstrate the quality of the follow-on

biological the comparability pathway demands the following during characterization of the product:

- Head-to-head comparison with the comparator biological product.
- Primary and higher-order structure, post-translational modifications, biological activity, purity and impurities, product-related substances (variants), and immunochemical properties.
- Primary structure must be identical to the comparator.
- Clinical evaluation the clinical comparability exercise requires a stepwise procedure:
  - Pharmacokinetic (PK) and pharmacodynamic (PD) studies followed by pivotal clinical trials.
  - Clinical efficacy studies could be required:
  - The selection of a sensitive population and adequate endpoints is a critical consideration. Selection should allow the detection of possible differences between the products.
  - Comparative immunogenicity study is necessary.
  - For the design of the studies equivalence is preferable, but non-inferiority can be used, if justified.

#### Extrapolation of indications

In Brazil, it is possible to receive approval for indications in which the follow-on biological has not been tested, but the following criteria must be met:

- A sensitive test model has to be used, which has to be able to detect potential differences between the biosimilar and the comparator.
- The mechanism of action and/or involved receptor(s) must be the same.
- Safety and immunogenicity have to be sufficiently characterized.

### General considerations

Finally, an application for approval of a follow-on biological in Brazil has to take into consideration the following requirements:

- The pharmaceutical dosage form and the route of administration should be the same as those of the comparator
- For licensing of a biosimilar it is mandatory to present a risk management plan.

As mentioned earlier in Brazil, there are two pathways: (i) a complete technical and scientific registration dossier including clinical and non-clinical data; or (ii) comparability, in which case the product is registered upon comparison of its efficacy and safety attributes with a comparator product, which is a product already registered at ANVISA. Also, the registration process of biological products under the comparability pathway by following the instructions laid down in the guidelines approved by ANVISA and, currently, ANVISA has approved the guidelines for the registration of the alpha interferon and heparin.

Once the data is submitted to ANVISA in the above format, ANVISA Biological division reviews and if gets satisfied, approves a similar biologic for marketing. For both registration pathways, in case of imported products, the biological product must have been registered in the country of manufacturing for further approval by ANVISA.

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Once registered with ANVISA, a biological product can only be put up for sale in the domestic market after its price is stipulated by the Medication Chamber (CMED), based on preset criteria; for a biological product with proven therapeutic gains, for instance the sales price cannot be higher than its price list effective in a basket of countries selected by CMED. During marketing phase, if any queries or complaints or changes were found this is to be reported to authority immediately in the Post-Marketing Phase.

### CONCLUSION

In the present scenario, Brazil has stringent and at par regulatory requirements for approval of a new drug. Pharmaceutical product approval process should be seen as a critical milestone in ensuring access to safe and effective drugs in order to protect the public health and facilitate healthy growth of pharmaceutical firms.

The directive for licensing biosimilars published by the Brazilian Regulatory Agency in 2010 is in line with the principles mentioned on the WHO norms and standards for the evaluation of similar bio therapeutic products. ANVISA now is a member country of ICH organization, it is expected to be more harmonization activities with ICH. Designating approved copies of biologic products as biosimilars after the comparability exercise has been well explained in the regulations. ANVISA may find an opportunity to revise its regulation and also adopt expression on omission of standalone pathway. It has been generally recognized that many important issues associated with biosimilars need to be defined by the national authorities in future amendments; we therefore emphasize regulatory approval process in Brazil shall be evolved to make at par with regulated market for biosimilars from development to commercialization like regulated market such as USFDA to accelerate the early grant of biosimilars to market with ensuring access to safe and effective drugs.