Review Article

Comparability Pathway for the Approval of Similar Biologics with Respect to Reference Biologics in Europe and Brazil

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ABSTRACT

The regulatory environment for biologics is continuously evolving, because they are ensuring the targeted therapies for many dreadful diseases. But the high cost of biologics has made the European Union to go for the biosimilar development for the first time after the expiration of patents. The strict requirements by the European Medicines Agency (EMA) guaranteed the highest quality standards. These biosimilars are complex in nature and difficult to characterize because they are extracted from the living sources and requires modern biotechnological methods that differ widely from the conventional drugs. The biosimilarity will be assessed based on the comparability studies where there should not be any traces of clinical differences in terms of quality, safety and efficacy. While the Brazil focused mainly on reducing the cost of biosimilar which are essential in treating many rare and specific diseases which lead to the PPD concept for the sake of the public health care system. Two regulatory pathways are emerged for the biosimilars in Brazil in which the molecules that were licensed through the comparability pathway are only considered as biosimilars. The present article summarizes the development process, regulatory perspectives of biosimilars and related issues that may occur due to interchangeability, extrapolation and International non-proprietary names in EMA, ANVISA and also mentioned about the benefits and purpose of Brazil National Health Surveillance Agency (ANVISA) Partnership for productive development (PPD) concept.

Key words: Biologics, biosimilars, EMA, ANVISA, comparability, International non-proprietary name Partnership for productive development.

INTRODUCTION

A Biologic is a large protein based therapeutic (monoclonal antibodies and recombinant proteins) which will be made by using a unique cell lines and is more complex in structure and in functioning. These are produced using the proprietary cell banks optimized for manufacturing. The molecular size of the biologics is 1,000 times more than that of the chemical drugs and has highly complex structures including protein folding. Biologics plays an important role in terms of active therapy. There are several issues associated with the development and manufacturing processes of complex large molecular biologics as opposed to small molecule drugs. The treatment with biologics is expensive and it places a substantial financial burden on the health care system. In addition, these high costs restrict the availability and accessibility of such drugs to only those who can afford them. Some countries, such as Australia, have responded to these high costs by restricting the administration of the biologics to only indication that receive reimbursement through their pharmaceutical benefits scheme. Nevertheless, problems such as formulary inclusions, drug availability and patient out of pocket

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costs still access to biological treatment in several developing and even some developed countries remains limited. However, the imminent expiry of patents and the limited accessibility of biologics provided a major opportunity for another branch of medicine- biosimilars.[1] A Biosimilar is also a protein based therapeutic that is highly similar to the reference biologics with no clinical differences in safety, efficacy, quality characteristics or biological activity and they are not identical to the reference biologic as they are developed using the different cell lines and also the different manufacturing and purification processes. The manufacturing process for biologics has been drastically changed over the time in particular areas like scaling up of the process, improving efficiency, or modernization when equipment needs to be updated or replaced.[2] To make changes in the manufacturing process without involving the companies to conduct a new clinical development program, regulators introduced the comparability concept to establish pre and post change products similar to permit ongoing marketing under the same product label.[3] The similar biologics approach is more difficult to characterize than chemically derived medicinal products, because of its complex nature, its difficult extraction and then clinical and regulatory experience should be gained. The concept of similar biological medicinal product can be applicable to any biological medicinal product. However, practically the success of such development will depend on the ability to characterize and the extent to which it achieves similar nature of the reference product.[4] As the biological drugs are produced by the living cells which are very complex and such complex molecules are typically expensive to develop and also requires advanced manufacturing and production processes. The biosimilars can be developed only after the patent expiry of the originator biologics. Recombinant proteins are highly complex at a molecular level which involves cloning, selection of a suitable cell line, fermentation, purification and formulation. Along with this, the therapeutic properties of the recombinant proteins depend on each step of manufacturing process and the ultimate result will be having a unique product which may have a distinctive safety and efficacy profile hence it can be called as biosimilar instead of biogeneric and the prepared biosimilar is only similar not identical to original biologics. A biosimilar is a biologic medicine which is similar but not identical to the original biologic medicine and it is not possible to develop the exact copy of the biologic medicine because for the development, the cell lines are unique to a given manufacturer.[5]

Advantages

1. The operating profit margin of traditional generic drugs is roughly 20%, but depending on the biosimilar product, profit margins have the potential to be somewhat higher, as much as 30%.
2. The treatment cost for biosimilars is lesser than innovator biological drug.
3. They have less market risk than reference product because of no investment in phase I-II of clinical trials
4. There is tremendous demand in the market as many biological products are going off-patent.

Differences between generics and the biosimilars

However, because of the greater complexity in the bio production of biologics, the biosimilars cannot be considered as generics which are identical to the reference products and then they can be considered as biosimilars. These biosimilars also differs from chemical drugs in molecular properties. Generic drugs can be approved through abbreviated new drug application (ANDA). The generic drugs should exhibit same dosage and strength and should have the safety and efficacy which should be equivalent to that of branded drugs. It is not possible to meet the exact standards for the evaluation of biosimilars. The chemical drugs are easy to reproduce and specify by mass spectroscopy and other techniques in which there is a lack of appropriate investigative tools to define the composite structure of large proteins.[6] The major differences between generics and the Biosimilars are shown in Table 1.[7]

Regulatory guidelines for biosimilars in Europe

European guidelines

The European Union was the first to develop a biosimilar approval pathway because of the earlier expiration of patents for biotechnologically derived products in European countries. The EU started the legislation for biosimilars in 2004 and developed the regulatory approval pathway in 2005 and then the first biosimilar was approved in 2006. Sandoz's recombinant human growth hormone, Omnitrope (reference product is Pfizer's Genotropin) was the first biosimilar launched in Europe in 2006. There are nine classes of biosimilars approved in Europe

- Recombinant erythropoietin
- Recombinant granulocyte colony-stimulating factors (G-CSFs)
- Recombinant human insulin
- Recombinant human growth hormone (GH)
- Recombinant follicle-stimulating hormone (FSH)
- Recombinant parathyroid hormone (PTH)

Table 1: Comparison of Generics and Biosimilars[6]

Specifics	Generics	Biosimilar
Product characteristics	Molecular weight is low	Molecular weight is high
	Physiochemical properties are well known Chemically highly pure compounds	Physiochemical properties are complex Chemically complex compounds which are not easy to purify
	Generics are usually non-antigenic	Biosimilars product may be antigenic in nature
	Stability is more than Biosimilars	Stability is less than generics
	They are stored at room temperature	They are required cold chain for storage
Manufacturing aspects	They are produced by chemical synthesis	They are produced biotechnologically from living cells
	They are less sensitive to changes in production process	They are very sensitive to production process change and stringent conditions are required
	Production process is easy and highly reproducible	Production process is complex and reproducibility is tough to achieve
	Purification is simple and well established	Purification is complex and time consuming process
Clinical process	Generics is required only Phase I clinical studies	They are required broad clinical studies including phase I, II, III studies
	The development cost is less and limited to 5m$	The development cost is high as compared to generic about 80-120 m$
	The time required for approval process is short	They are needed in depth Pharmacovigilance and periodic safety updates after launch
Regulation requirement	They are required to exhibit bioequivalence as a reference drug	They are required to ensure similarity as an innovator product

- Fusion protein (TNF inhibitor)
- Monoclonal antibodies (mAbs)
- Low molecular weight heparins

According to the European Medicines Agency (EMA) a biosimilar medicine is a biological medicine that is developed to be similar to an original biological medicine (the reference medicine). Biosimilars are not same as generics, which have simpler chemical structures and are considered to be identical to their reference medicines.[8]

Biosimilars regulatory evolutionary environment in the Europe

The EU started the concept paper on the development of a guideline on the comparability of biotechnology-derived products in 1998 as well as the idea of similar biological medicinal product was started by the EU and introduced into the EU legislation in 2001 (Directive 2001/83/EC; is a legal act of the EU). The Annex 1 was incorporated into the Directive in 2003 to make the process for marketing authorization and also made clear procedures for preparing biosimilar medicinal products.[9,10] In addition to the pharmaceutical, chemical, biological data the bioequivalence and the bioavailability data also should be provided to demonstrate the biosimilarity. Taking into consideration of the specific characteristic of each individual medicinal product the additional data like toxicological and other non-clinical and clinical data will be determined on the case-by-case basis. In 2004 the Directive is further revised which allowed the full development of biosimilars before the original biologics patent gets expired.

The Committee for Medicinal Products for Human Use (CHMP), the Biotechnology Working Party and the Working party on similar biological medicinal products worked together and released specific guidelines to deal with all the aspects of the development, production, testing and regulation of biosimilar medicines. The EMA issued biosimilar guideline in 2005. The following year two more guidelines regarding quality, clinical and non-clinical issues relating to the development of biosimilars was updated and also the product specific guidelines and guidance on the assessment of immunogenicity are also available.[11]

Other forms of biosimilars

Multiple classes of biologics has been created due to more time gap of patents for original biologic products, in addition to biosimilars

Non comparable Biologics: These types of biosimilars do not meet the requirements of comparability studies to the original biologics and also don't show the biosimilarity to the reference biologics, as stipulated by

the relevant bodies like European Medicines Agency (EMA), World health organization (WHO).

Biobetters: These types of products are superior to the originator biologics with a greater stability and with better performing indicators. They are considered as the improved version of originators (example: Improved patient adherence to therapy) such that they can neither be an originator nor a biosimilar, but a novel category of products. In many areas the biosimilars also referred as follow-on pharmaceuticals, subsequent entry biologics and biocomparables.[12]

Development of biosimilars

Clinical trials for biosimilars can be started at any time irrespective of patent expiry and the application can be filed only after eight years of data exclusivity and the approval will be only after the ten years of exclusivity. The clinical development of the biosimilars should be completed atleast two years prior to the expiry of patent. But the approval and the launching of biosimilar would be only after the expiry of the patent of originator biologics and approval time usually ranges from 12-20 months. The development process starts with the selection of the reference biologics and that product should be registered in that country where the approval of biosimilar is required. The reference product with a different country registration can be used with bridging data comparing biosimilar and out-side country registered reference product used in comparability exercise. Then the development begins with the comparison of the quality evaluation characteristics between biosimilar and the reference biologic. However, if it shows the similarity this can lead to the reduction of the non-clinical and clinical data needed for the approval. The step wise approach given below;

Analytical, quality comparison/ characterization

- Manufacturing process
- Product characterization
- Structural and physiochemical properties
- Biological activity
- Immunological properties
- Purity and impurities
- Stability
- Quality comparability study

Non-clinical studies (comparative)

- *In vitro* studies
- *In vivo* studies

Clinical studies (comparative)

- Pharmacokinetic (PK) studies
- Pharmacodynamics (PD) studies
- Confirmatory safety and efficacy studies
- Safety and immunogenicity data[13]

List of critical Manufacturing factors for biosimilars

Non- clinical data (in vitro and in vivo)

- Bioanalytical evaluation
- Pharmacokinetic studies
- Pharmacodynamic studies
- Toxicological studies

Clinical data

- Demonstration of pharmacokinetic profile
- Clinical equivalence

Safety

- Comparative safety data
- Immunogenicity study
- Risk management plan
- Pharmacovigilance
- Data extrapolation[1]

Basic regulatory requirements for granting approval of Biosimilars by European Medicines Agency (EMA)

High analytical similarity

- Same amino acid sequence and folding.
- Highly similar analytical profiles based on highly sensitive methods.
- Same set of glycans, comparable levels of functionally relevant glycans.
- Comparable or lower levels of non-glycan variants (N- and C- terminal variants, aggregates, deamidation, oxidation), all minor differences clinically not relevant.
- Comparable stability profiles.
- Closely matching functionalities for all relevant mechanisms of action.
- High purity, in other words, extremely low levels of contaminants from cell line and process.

Confirmation of biosimilarity in a PK/PD study and/ or clinical study

- Comparable human PK and PD profiles.
- Comparable efficacy, safety and immunogenicity in a sensitive indication (large effect size, adequately immunocompetent population).

Extrapolation of indications based on the totality of the evidence

- High similarity is a key, especially regarding functionalities (potentially) relevant to the mechanisms of action in the difference indications.
- Must be scientifically evaluated and is granted or rejected by the regulators separately for each indication.[14]

Steps in the development of Biosimilars through the stepwise comparability with the reference product

First step – Quality Comparability (Physiochemical and biological comparability)

- Comparison of the physiochemical and biological quality attributes which includes purity and this can be done through different analytical methods and therefore it is impossible for the biosimilar product to characterize all the aspects of a reference product
- Whether there is any occurrence of significant differences in the analyses in the modified development process. There will be a need of continuous modification in every step that are required for the European Medicines Agency until the product generated has a profile that matches the profile of the reference product

Second step – Non- Clinical Comparability (Comparative non-clinical studies)

- The Non-clinical trials i.e., Animal studies are required before the initiation of clinical studies in the humans. The Non- clinical trials for the biosimilars starts with the different *in vitro* tests and in exceptional cases as per the EU guidelines the studies will be done in the animals.
- The studies will begin with an analytical studies and *in-vitro* pharmaco-toxicological studies and then based on the results the decision will be made whether any *in-vivo* studies in animals are required or not. If it is required then the PK / PD studies and safety studies will be conducted based on the three principles (replacement, refinement, reduction)

Third step – Clinical comparability (comparative clinical studies)

- The need of clinical studies for biosimilars is not required as much it is needed for the new active substance, but the comparison is more appropriate for the biosimilars i.e., comparison of clinical performance, nature, characteristics and intended use of biosimilar to that of the reference product. The closer the profile of the biosimilar and reference products and the higher the similarity which has been demonstrated through appropriate studies like comparative quality, biological and receptor binding assays and *in vitro* studies. The attainment of biosimilarity in clinical trials helps to confirm the efficacy and the safety profiles between the biosimilar and the reference product and the comparison of the immunogenicity is also a part of the clinical safety data.[15]

Data required for the Marketing Authorization application to be presented to the European Medicines Agency (EMA)

For the biotechnologically derived product which requires Marketing Authorization in the Europe will be assessed through a centralized procedure by evaluating the data in the registration Dossier. If the data submitted is satisfied in all the aspects, then the Biosimilar product will get the opportunity to market their product in the European Union. The following data should be submitted for the marketing authorization of the biosimilar product in European Union

1. Quality data
2. Non-clinical data
3. Clinical data
4. Pharmacovigilance

The results that are obtained from the above trials of the biosimilar product which are comparable to that of the reference product should be submitted for the purpose of the marketing of their biosimilar product in the European Union. Thenthe summary of the data and the assessment regarding the medicinal product, known as the European public assessment report (EPAR) will be made available to the public. The EPAR is compiled by the European Medicines Agency and is published on its website after issuance of the Marketing authorization by the European Commission.

Extrapolation

Extrapolation, which is the endorsement of the biosimilar for clinical indications of the reference product without the need to conduct clinical trials, for those indications, is an important element for the biosimilarity concept. If the manifestation of the biosimilar comparability has been achieved in all the aspects then extrapolation to other indications of the reference product will be acceptable but should be scientifically justified. According to the EMA requirements, the following indications must be satisfied for the purpose of extrapolation

1. The mechanism of action of the reference product must be same across all the indications required for the extrapolation,

2. The equivalence and the clinical comparative studies should be performed in the most sensitive therapeutic indications,
3. The most sensitive indication must be able to produce appropriate difference in terms of efficacy, tolerability and immunogenicity parameters.[16]

If the above data is unclear, the safety and efficacy which is confirmed only in one indication would be relevant to other indication and then the additional data will be required.[17] The major problem is that the active substance itself has more receptor sites, so it is difficult to detect the differences in all the relevant aspects of efficacy, safety, PD parameters and functional assays which might have the impact on the pharmacological action of the molecule. The extrapolation will be acceptable in the EU only if the data regarding safety and efficacy of the biosimilar and also any differences is justified.[18]

Interchangeability, switching and automatic substitution and its related issues

It is important for the physician to know when the product has been switched from original biologic to biosimilar, biosimilar to originator and biosimilar to biosimilar. The decision of changing will be done by the physician based on the information through the SmPC (summary of product characteristics and EPAR (European Public Assessment Report) with no loss in efficacy and safety. Sometimes, due to the complex nature of biosimilars even small differences like manufacturing impurities could trigger the immune reactions and also the effectiveness of a given medicine in patients may be altered if the product is changed during a period of treatment due to differences from its reference product.[19] The interchangeability may affect the Pharmacovigilance and also generates confusion between biosimilars and originators during the post marketing surveillance. So the decision for interchangeability left with each member state in EU because the EU does not have the specific authority to select interchangeability. The substitution refers to the practice which was allowed by law requiring pharmacists to dispense the less costly biosimilar in place of the preferred biologic medicine without the prior authorization of the prescriber.[20] The European Union recognized that this substitution issue is outside of its legal authority, so it remained silent as the rules are different across the national market, so the Individual EU member states considered the substitution as an optional.

Pharmacovigilance and risk management plan

The possibility of adverse events is unpredictable in case of biologics and at the time of marketing approval the safety information about the product is limited. Due to its complex nature, the manufacturing process and facilities of the biosimilar and the originator biologics will not be identical and the biosimilars manufacturers differ from the originators. Moreover, immunogenic potential, as noted previously, may be fundamental to patient, product and treatment duration. So, prior to the administration of biosimilars to the patients it was suggested to assess the risk of immunogenic reactions and alsocontinuous batch-by-batch surveillance of all the biosimilars through the patient health records should be justified. So, post marketing monitoring of clinical safety for biosimilars should be considered more appropriate along with all the medicinal products for the patient safety.[21]

The applicant should submit the risk management plan at the time of application for product licensure. The main aim of the plan is to ease potential risks which are associated with the biosimilar product.[22] The risk management plan in accordance with EU legislation should include

- Safety specifications
- Pharmacovigilance plan
- Evaluation of the need for risk minimization activities (routine Vs additional risk minimization activities)
- Risk minimization plan
- Summary of the EU- RMP
- Contact person details[23]

Nomenclature

Each product bears two names brand name and the International non-proprietary name. To prevent the confusion between the biosimilars and the biologics, a specific nomenclature is needed to distinguish them but the International non-proprietary name (INN) should not be used as the only option for the identification. Claiming only the non-proprietary name for the biosimilar will be difficult to attribute adverse events to a particular product. So, using the same brand name or the INN plus the brand name or some other unique identifier should be suggested to discriminate the biosimilar.[24] In 2012, the European Commission issued the directive 2012/52/EU which permitted to use the same non-proprietary name that was used by the originator to the follow on biologics. Along with this the batch number and manufacturer identification should be notified to the regulatory authority to ensure proper traceability.

Cost reduction pathway

Although Europe has led the way in the development of biosimilar markets, a 2012 study found that information about biosimilar pricing and reimbursement policies in member states was sparse. While actual sale price (paid after quality or volume discounts, or both, received by purchases, such as state and compulsory insurers) are typically confidential, list prices in the retail sector remain high.

Currently there are more than 150 reference products for biosimilars to emulate, including about 40 with sales in the block buster (more than $1billion per year) revenue range. Even 10 percent of this market could be enough for biosimilars to be profitable. With biosimilars as marketing opportunities, it makes sense for companies to outsource their development if it can be demonstrated cost effective.[25]

The development and production costs of biosimilars limit not only the number contenders on the market but also the scope for competitive pricing. Thus, although the price of a generic that fall to 20% of the originator, the list prices of biosimilars in the European Union seem unlikely to fall more than 30 percent below those of the reference goods. Although these discounts can seem small when compared with generics, they represent significant savings for payers and patients from the much higher prices of biomedicines. For example, a 30 percent discount on a treatment with an undiscounted $50,000 annual cost represents an annual savings of nearly $16,000. Hospital based pharmacists may therefore be well- favorable for financial reasons; hospitals have become competitor strategic targets. Hospitals may also be retail market for chronic therapies because, after discharge, patients and prescribers are often unwilling to move drugs started at the hospital. Thus, originator biologics manufacturers must avoid engaging in anticompetitive behavior, hospitals may be penalized for choosing a biosimilar by refusing them discounts on other goods still under patent. Today ahead of biosimilar competition, certain originator biological manufacturers decrease their prices before the expiry of the patent, as in the case of erythropoietin's. They also support strict reporting criteria for hidden monetary costs associated with the use of biosimilars and advocate. But these hidden costs- supposedly due to effectiveness and safety problems are mainly based on the conflation of biosimilar characteristics licensed in the European Union and copy biologics sold outside the European union.[21]

Regulatory guidelines for biosimilars in Brazil

The regulatory authority for the new biologics and the biosimilars in Brazil is Brazil National Health Surveillance Agency (ANVISA). In Brazil, the expiration of patents made the government to start the idea of the development of the biosimilar drugs and all the patents of medical components are made under the Intellectual property code-CPI/96 which introduced the concepts of patents in pipeline and patents under revalidation. The government in Brazil expanded the politics of the biotechnology development; through a decree 6.041 in 2007 which made the companies to reduce the cost of the medicaments for the biosimilar molecule production. In 12 may 2008, the executive group of the health complex (GECIS) was implemented for the analysis of highlighting the deficiencies and limitations related to technology development of new drugs.[26]

In 2010, a resolution (Collegiate board Resolution) RDC number 55/2010 was passed by the Agencia Nacional de Vigilancia Sanitaria for creating new regulatory pathways for the new biologics and the biosimilars. The same resolution mentioned about the nomenclature of biosimilars which named the biosimilars as "Biologic products" and the reference products as "New Biologics". Two pathways were emerged for the biosimilars one was "Comparability pathway" and the other was "Individual pathway". The Individual pathway fit for the less biotherapeutics like pegylated interferon's and low molecular weight heparin and the requirements like dossier, quality issues, clinical study data are less essential relative to the comparative pathway. Apart from the requirements the extrapolation of indications is not acceptable in the individual pathway. The comparative pathway is more appropriate and it requires comparative phase I, II and III trials to that of the originator biological product. This pathway suits for the biotherapeutics with more complex molecules such as monoclonal antibodies. The molecules that were licensed through the comparability pathway are only considered as biosimilars and the clear discrimination about the pathways was mentioned in the Table 2.[27] In 2011, the ANVISA issued four guidelines and also the regulations for registration and post registration have been released for biosimilars However in 2012, the new guidelines were published specifically for the production of the monoclonal antibodies

Brazilian Partnership for Productive Development (PPDs)

The programme between public pharmaceutical companies or Government and private technology holders, either national or international which aims for the transfer of the technology for the local production of the strategic drugs and then to reduce the costs of the

Table 2: Summary of ANVISA (National Health Surviellance Agency) requirements for each Biosimilar approval pathway[27]

Data Requirements	New Biologic products	Biologic product (follow on)	
		Comparability (Biosimilar)	Individual Development (non-Biosimialr)
Chemistry, manufacturing and controls documentation	Required	Comparative	According to Developing standards
Preclinical studies	Required	Comparative	Comparative data with exceptions
Phase -I clinical studies	Required	Comparative	Requirements may be waived and may not be comparative
Phase- II clinical studies	Required	Comparative	Requirements may be wiaved and may not be comparative
Phase -III clinical studies	Required	Comparative	Comparative data with exceptions
Extrapolation of indications	Not applicable	Possible(with conditions)	Not applicable

products for the sake of the public health care system SUS (Unique Health System) is the main concept of the Partnership for productive development (PPD) in Brazil and this proposal for the PPD was developed by the patent holder and the public pharmaceutical company which was presented to the competent department of the Ministry of Health. To establish PPD, the private company should receive a contract from the government. The process begins with a call for proposals for specific products by the government and this followed by the establishment of the partnership with the public laboratory by the private companies. After this partnership an application should be submitted and then the government provides a contract. In order to know the tricks of the biologics the private company again needs to team up with an international partner along with the public laboratory. In the beginning years of the PPD concept, the international company produces the drug and supplies it to the government through the private company in Brazil and the public laboratory. To take over the manufacturing and commercialization of the biosimilar by the private companies the international partner need to complete the technology transfer. The private company is responsible for all the financial requirements for creating the manufacturing plant and transferring the technology within the Brazil. The PPDs concept not only meant for encouraging the growth of the biotechnology industry but also protects the country form the supply shortages. For the public organization in Brazil, to have an access in technology and support required to manufacture the biologic, the Ministry of Health will buy the product directly from the Manufacturer, as part of the Development of the PPD project, including registration with ANVISA. The first Acquisition takes place only after the technology transfer contract is done between the technology holder and the pharmaceutical company. This seems that PPDs gained to offer opportunity for the Government and private companies and by this the biotechnological development flow has been established which is allowing for potential cost reduction and self-sufficient production. Apart from this the exclusive sales rights have been ensured during the period of technology transfer.[28]

Apart from the rapid growth in emerging market, the company which has been contracted by the government will be having a major regulatory advantage. The main advantage of the PPD is that you get priority review which fastens the review and approval and this PPD programme also provides an opportunity to have an annual meeting with the Technical Regulatory committee (CTR), which monitors the progress of PPD, timelines, technology transfer and its regulatory activities. After the approval of the project the PPD provides the partnership with a simplified registration procedure to lead to a quicker acquisition of the biosimilar by the Ministry of Health. Therefore, the PPD program is a double win for the development of country's technology and improvement of patient's health care.[29]

Regulatory process for Biosimilars in Brazil

The regulatory timeline in ANVISA is known to be 8.6 months longer when compared to the other agencies like FDA. The first biosimilar approved by the comparative development pathway and the only monoclonal antibody in the field of Rheumatology is the biosimilar Infliximab, Remsima (reference product) which was approved in all the indications of the original biologic product. The evaluation of the regulatory process of biosimilars starts with the analytical and Non-clinical comparison of structural and *in vitro* functional characteristics as well as *in vivo* ani-

mal studies including the assessments of toxicity. If the biosimilar gets approved in the above steps then clinical tests are required to demonstrate the equivalence in terms of efficacy, safety and immunogenicity.[30] The development process of the biosimilar is clearly mentioned in the Figure 1.

The marketing approval of the follow-on biological products in Brazil can be obtained either by individual development route or by comparability route. In the individual route, the applicant must submit the reports of the preclinical and clinical trials and also the results of the phase III clinical trial must be comparative. In the comparative route the applicant must prove that the product is comparative to the reference product by submitting the report which provides the comparative analysis of both the products in all the stages of development (manufacturing of molecule, comparison of product stability, purity, impurity profile). Along with this there is a need to submit even the reports of non-clinical trial reports like pharmacokinetic studies, Pharmacodynamics studies and essential studies regarding safety and efficacy. A dossier should be prepared to register the biosimilar indicating that it meets all the standards that provide the quality, safety and efficacy for the market approval.[31] Once registered with the ANVISA, the biosimilar can go for sale in the market only after its price has been predetermined by the Medication Chamber (CMED).[32]

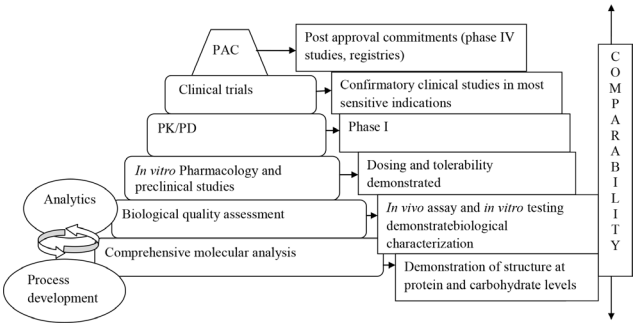

Figure 1: Biosimilar Development Process.

Non-proprietary names and Interchangeability in Brazil

In Brazil there is no discrimination on non-proprietary names for biosimilars and reference product and also says that this differentiation is needed to provide an opportunity for the physician to decide which product to be dispensed. Brazil considered that the interchangeability has not been defined by a regulatory agency and left the gap in this matter. The ANVISA recently stated that interchangeability is more directly related to clinical practice than to regulatory status and also mentioned that medical evaluation is the essential part in case of interchangeability and substitution but the multiple exchanges between the product is not acceptable as the traceability and the monitoring of use will be very difficult. Therefore, the current regulation left this decision to payers or physicians.[33] The comparison between main features of biosimilars in Brazil and Europe was shown in the Table 3 and the list of approved biosimilars in Europe and Brazil was shown in Table 4.

Table 3: Comparison of Main features of Biosimilars in Brazilian regulations with respect to European Union

Feature	Brazil	Europe
Denomination	*Producto Biologico* / Biologic product	Biosimilar or follow on Biologics
Regulatory pathways	Two pathways comparative and individual (standalone)	Only by comparability
Primary source of regulation	Resolution of board of directors of ANVISA	EMA guidelines were developed after directives approved by the European parliament
Reference product	Required in comparative pathway and not required in individual pathway	Well defined and required in all cases
Non- clinical and clinical studies	In individual pathway, A unique comparator is not required	Detailed guidance Same reference is required inall the comparisons
Biosimilarity	Not defined and not required in individual pathway	Defined and required for the approval of the Biosimilar
Interchangeability	Not regulated	Only regulated by member states
Extrapolation among indications	Possible with defined criteria	
Non-proprietary names	No rule ;same names for reference and all biosimilars	Possible disambiguation through manufacturer identification
Data exclusivity	No data exclusivity	Yes

**Producto biologico* refers to the whole class or only the copies, depending on the context; ANVISA, National Health surveillance Agency in Brazil;EMA, European Medicines Agency

Table 4: List of approved biosimilars		
EMA approved biosimilars		
Product name	**Authorization date**	**Manufacturer/Company name**
Abasaglar (previously Abasria)	9 Sep 2014	Eli Lilly / Boehringer Ingelheim
Abseamed	28 Aug 2007	MediceArzneimittel Putter
Accofil	18 Sep 2014	Accord Healthcare
Amgevita	22 Mar 2017	Amgen
Benepali	14 Jan 2016	Samsung Bioepis
Bemfola	24 Mar 2014	Finox Biotech
Binocrit	28 Aug2007	Sandoz
Biograstin	15 Sep 2008 Withdrawn on 22 Dec 2016	CT Arzneimittel
Blitzima	13 Jul 2017	Celltrion
Cyltezo	10 Nov 2017	Boehringer Ingelheim
Epoetin alfa Hexal	28 Aug 2007	Hexal
Erelzi	27 Jun 2017	Sandoz
Filgrastim Hexal	6 Feb 2009	Hexal
Filgrastim ratiopharm	15 Sep 2008 Withdrawn on 20 Apr 2011	Ratiopharm
Flixabi	26 May 2016	Samsung Bioepis
Fulphila	CHMP positive opinion 20 Sep 2018	Mylan
Grastofil	18 Oct 2013	Apotex
Halimatoz	26 Jul 2018	Sandoz
Hefiya	26 Jul 2018	Sandoz
Hulio	17 Sep 2018	Mylan/Fujifilm Kyowa Kirin Biologics
Hyrimoz	26 Jul 2018	Sandoz
Herzuma	9 Feb 2018	Celltrion Healthcare
Imraldi	24 Aug 2017	Samsung Bioepis
Inflectra	10 Sep 2013	Hospira
Inhixa	15 Sep 2016	Techdow Europe
Insulin lispro Sanofi	19 Jul 2017	Sanofi-Aventis
Kanjinti	16 May 2018	Amgen/Allergan
Lusduna	4 Jan 2017	Merck(MSD)
Movymia	11 Jan 2017	StadaArzneimittel
Mvasi	15 Jan 2018	Amgen
Nivestim	8 Jan 2010	Hospira (Pfizer)
Ogivri	CHMP positive opinion 18 Oct 2018	Biocon/Mylan
Omnitrope	12 Apr 2006	Sandoz
Ontruzant	15 Nov 2007	Samsung Bioepis
Ovaleap	27 Sep 2013	Teva Pharma
Pelgraz	CHMP positive opinion on 26 Jul 2018	Accord Healthcare
Pelmeg	23 Nov 2018	Cinfa Biotech/Mundipharma
Ratiograstim	15 Sep 2008	Ratiopharm
Remsima	10 Sep 2013	Celltrion
Retacrit	18 Dec 2007	Hospira
Ritemvia	13 Jul 2017	Celltrion
Ritzena(previously Tuxella)	13 Jul 2017	Celltrion
Rixathon	19 Jun 2017	Sandoz
Riximyo	15 Jun 2017	Sandoz

continued...

Table 4: Cont'd.		
Semglee	28 Mar 2018	Mylan
Silapo	18 Dec 2007	StadaArzneimittel
Solymbic	22 Mar 2017	Amgen
Somatropin Biopartners	9 Sep 2013 Withdrawn on 1 Dec 2017	Bio Partners
Terrosa	4 Jan 2017	Gedeon Richter
Tevagrastim	15 Sep 2008	Teva Generics
Thorinane	15 Sep 2016	Teva Generics
Trazimera	26 Jul 2018	Pfizer
Truxima	17 Feb 2017	Celltrion
Udenyca	20 Sep2018	ERA Consulting (Coherus Biosciences)
Valtropin	24 Apr 2006 Withdrawn on 10 May 2012	Bio Partners
Zarzio	6 Feb 2009	Sandoz
Zessly	24 Mar 2018	Sandoz
Ziextenzo	27 Nov 2018	Sandoz
Brazil approved biosimilar		
Remsima	2016	Hospira
Ontruzant	December 2017	Samsung Bioepis

CONCLUSION

The biosimilars has provided a pathway for the cost reduction of the biological products. The complications regarding biosimilars are unpredictable due to their complex nature. So the Pharmacovigilance studies play a crucial role after the approval of the product which can identify the adverse events and it was suggested to assess the risk of immunogenic reactions prior to the administration of biosimilars to the patients for the safety purpose. The European Union considered the issues like interchangeability, automatic substitution as an optional and left the decision to the each member state whereas the current regulation of the Brazil left this decision to physicians. While the partnership for productive development concept of Brazil has the major advantage and also provides the partnership with a simplified registration procedure for the quicker acquisition of the biosimilars.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ANVISA: Brazil National Health Surveillance Agency; **EMA:** European Medicines Agency; **PPD:** Partnership for productive development; **ANDA:** Abbreviated new drug application; **EU:** European Union; **CHMP:** The Committee for Medicinal Products for Human Use; **WHO:** World health organization; **PK:** Pharmacokinetic studies; **PD:** Pharmacodynamics studies; **EPAR:** European public assessment report; **SmPC:** Summary of product characteristics; **INN:** International non-proprietary name; **RDC:** Collegiate board Resolution; **SUS:** Unique Health System; **CTR:** Technical Regulatory committee; **CMED:** Medication Chamber.

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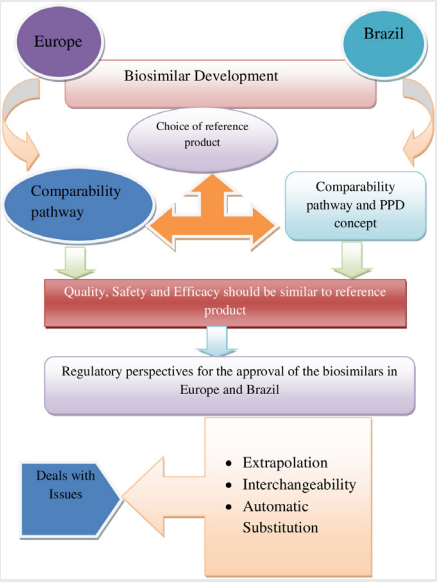
PICTORIAL ABSTRACT



SUMMARY

The biosimilars has provided a pathway for the cost reduction of the biological products. The complications regarding biosimilars are unpredictable due to their complex nature. The regulatory environment for biologics is continuously evolving, because they are ensuring the targeted therapies for many dreadful diseases. But the high cost of biologics has made the European Union to go for the biosimilar development for the first time after the expiration of patents. The strict requirements by the European Medicines Agency (EMA) guaranteed the highest quality standards. While the Brazil focused mainly on reducing the cost of biosimilar which are essential in treating many rare and specific diseases which lead to the PPD concept for the sake of the public health care system. Two regulatory pathways are emerged for the biosimilars in Brazil in which the molecules that were licensed through the comparability pathway are only considered as biosimilars.

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