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Understanding Biologics and Biosimilars in Brazil

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In Brazil, only new biological products and biological products (including biosimilars) registered with the National Agency of Sanitary Surveillance (ANVISA) and manufactured or imported by companies authorized by the Federal government and licensed by the state government may be sold and distributed. ANVISA's responsibilities include overseeing the development, manufacturing and marketing of products and services that are subject to sanitary surveillance and controls relating to matters at ports, airports and borders.

In order to understand the approval process for biologics and biosimilars in Brazil, it is important to understand how certain terms are used by the ANVISA and other governmental agencies. Important terms include:

1. A "biological product" is a biological that is not new or is known and contains a molecule with known biological activity that is already registered in Brazil (namely, with ANVISA) and has undergone all stages of manufacturing (namely, formulation, bottling, lyophilization, labeling, packaging, storage, quality control and release of the biological product batch for use). The following are considered to be "biological products":

a. Vaccines;

b. Hyper-immune serums (which are defined as whole or fragmented heterologous, purified immunoglobulins, obtained from the plasma of hyper-immunized animals with toxic substances that originated from animals, microorganisms or viruses);

c. Hemoderivatives (which are defined as pharmaceutical products obtained from human plasma, subjected to industrialization processes and standardization to provide quality, stability, activity and specificity);

d. Biodrugs which are classified into:

i. Drugs obtained from biological fluids or tissues of animal origin; and

ii. Drugs obtained by biotechnological procedures;

e. Monoclonal antibodies; and

f. Drugs containing live, attenuated or dead microorganisms.

2. A “new biological product” is a biological product containing molecules with known biological activity that are not registered in Brazil (namely, with ANVISA) and that have undergone all stages of manufacturing (namely, formulation, bottling, lyophilization, labeling, packaging, storage, quality control and release of the new biological drug batch for use).

3. A “comparer biological product” is a biological product already registered with ANVISA based on submission of a complete dossier and that has already been sold in Brazil.

4. A “complete dossier” is the full set of documents submitted to ANVISA to demonstrate the attributes of quality, safety and efficacy of a biological product. The dossier is made up of the full characterization of the product and detailed description of the production process, demonstrating the consistency in the manufacturing of the drug in addition to the substantial evidence of clinical safety and efficacy demonstrated through nonclinical and clinical studies (phases I, II, and III).

Registration of new biological products or biological products

To register a new biological product or a biological product, an applicant company (applicant) must file a registration application (which must be submitted in Portuguese with one copy of the entire application being provided on a CD-ROM in a pdf format). Any documents included in a foreign language must be translated.

Specifically, an applicant is required to submit the following documents:

1. Registration application forms – fp1 and fp2;

2. An original copy of proof of payment of the health surveillance inspection fee;

3. A declaration of the economic capacity of the applicant;

4. A copy of applicant’s business license and/or health permit;

5. A copy of applicant’s business authorization certificate/form or its publication in the federal official gazette;

6. A copy of an updated technical responsibility certificate issued by a regional pharmacy board evidencing that the manufacturer has assistance from a pharmacist in charge (who is qualified for such a purpose);

7. Technical justification for the biological product’s registration;

8. A copy of the good manufacturing practices certificate (GMPC) issued by ANVISA for all manufacturers of the active ingredient, bulk biological product, biological product in its primary packaging and the finished biological product, diluent and adjuvant;

9. A copy of the GMPC issued by the competent health authority in the country where the manufacturer of the active ingredient, bulk biological product, biological product in its primary packaging and the finished product, diluent and adjuvant is located;

10. A history of the biological product registration status in other countries, where applicable;

11. A copy of proof of registration in the country of origin of the biological product, issued by the respective competent health authority;

12. A copy of the package insert approved by the health authority in the country of origin, accompanied by a sworn translation;

13. The package insert and primary and secondary package models as required by the legislation currently in effect;

14. Updated pharmacoviligance data, as required by the legislation currently in effect, obtained from clinical studies and product sales, when applicable;

15. Barcodes (or other identification) and safety mechanisms to enable tracing of the biological product as required by the legislation currently in effect;

16. A copy of the national, international or internal compendium of the applicant with a description of the finished biological product’s specifications;

17. Additional information according to the legislation in effect on transmissible spongiform encephalopathy control, when applicable;

18. A technical report (discussed in more detail below);

19. A therapeutic experimentation report; and

20. A pharmacovigilance report.

The technical report that must be submitted must contain the following information:

1. The name and address of the manufacturer and the cell bank storage location;

2. The name and address of all manufacturers of the active ingredient, bulk biological product, biological product in its primary packaging and the finished biological product, diluent and adjuvant;

3. The name and address of the party that issued the finished product batch release

certificate;

4. The following general data on the biological product:

a. Dosage form presentation;

b. A full description of the formula of the biological product, with all its components specified by the corresponding technical names and synonyms according to the Brazilian common denomination or international common denomination or, in its absence, a denomination of the chemical abstracts services, including the units of measurement used;

c. The functions performed by each substance in the formula;

d. The route(s) of administration;

e. Directions for use, when applicable;

f. Indications, purpose or intended use;

g. Contraindications;

h. Side effects;

i. Adverse reactions;

j. Restrictions or cares to be considered;

k. Precautions or warnings;

l. Drug and food interactions;

m. Change in the lab tests;

n. Signs, symptoms and conduct (in cases of overdose);

o. Expiration date;

p. Preservation/storage care;

q. Preservation/storage temperature;

r. Transportation temperature;

s. Specifications regarding the primary and secondary packaging material; and

t. Codes or conventions used by the applicant to identify the active ingredient batches, bulk biological product, the biological product in its primary packaging and finished biological product;

5. A history of the development of the biological product, including a description of the purpose for each batch produced (namely, for use in stability studies or preclinical or clinical studies);

6. Information on the various stages of manufacturing, including:

a. A summarized production protocol in the form of a flowchart that identifies the controls in the process;

b. A list of the main equipment used in the manufacturing;

c. A detailed description of all stages of manufacturing of the biological product, diluent and adjuvant;

d. Identification and justification for the selection of the critical stages of the manufacturing process;

e. A description of the controls in place and a justification for the determination of these specifications;

f. A scale of production in all manufacturing stages indicating the minimum and maximum size of the industrial batch to be produced for sale;

g. A description and justification for the changes made in the production process during the development of the finished biological product;

h. A validated report of the procedures used to remove and/or eliminate viruses, when applicable;

i. A validated report of the critical stages of the manufacturing process; and

j. Validation and justification for any reprocesses;

7. Information on quality control, including:

a. A description of all quality control tests conducted (including all tests conducted on the active ingredient to the final product);

b. A description of the reference standards used;

c. Validation of the analytical methodologies used as required by the health legislation currently in effect; and

d. A reference and justification for each specification determined in the quality control tests;

8. A description of the storage requirements for the active ingredient, bulk biological product, intermediary biological product, biological product in its primary packaging and the finished biological product, diluent and adjuvant;

9. A description for recipients and storage forms for the active ingredient, bulk biological product, intermediary biological product, biological product in its primary packaging and the finished biological product, diluent and adjuvant and the conditions to be maintained to assure the biological product quality;

10. Transport chain validation, including:

a. Operation and performance qualifications of the boxes to be used for transport and validated transport procedures for the active ingredient, bulk biological product, intermediary biological product, biological product in its primary packaging and the finished biological product, diluent and adjuvant; and

b. Operation and performance qualifications of the boxes to be used to transport the finished biological product in the national territory;

11. A description of the solutions, components and culture mediums used to manufacture the biological product;

12. Information on the excipients, including:

a. A description of the physical, chemical, microbiological properties and other quality control information;

b. The specification of each excipient;

c. A description of the possible chemical interactions of each excipient with the active ingredient; and

d. A study demonstrating the efficacy of any preservatives used (for any biological product that contains a preservative in the final formula);

13. A report detailing the stability studies (including the protocol) conducted according to the health legislation currently in effect;

14. Information on contaminants and impurities, including:

a. A characterization of the contaminants and impurities;

b. A description of the processes used to reduce/remove impurities that originate from the biological product breakdown or from the manufacturing process;

c. Justification for any impurity specifications in the finished product; and

d. A safety evaluation of adventitious agents from the starting materials of biological origin; and

15. The primary and secondary packaging description and specifications.

Routes for approval for new biological products and biological products in Brazil

There are two routes by which a biological product registration may be filed:

1. Individual development route (used for new biological products and biological products); or

2. Comparability route (used for biological products, namely, biosimilars).

Individual Development Route

An applicant can seek regulatory approval for a new biological product or a biological product pursuant to the “individual development route.” Under the “individual development route,” not only must an applicant present all of the above information, but the applicant must provide a full report of all nonclinical studies as well and the complete protocols and reports of clinical studies (namely, phase I, II and III studies). Additionally, if available, data from phase IV clinical studies should be presented. An applicant submitting a new biological product or biological product registration application under this route must submit sufficient information and data (through nonclinical and clinical studies) to demonstrate the quality, safety and efficacy of the new biological product or biological product.

With respect to the nonclinical studies, the extent of these studies may be reduced depending on the complexity and the level of characterization of the molecule and the extent of the characterization of the biological product’s impurity level, toxicity potential and therapeutic index. Regarding clinical studies, phase I, II and III studies are required with phase III studies being absolutely mandatory. Clinical studies may be conducted in or outside Brazil. For clinical studies conducted outside of Brazil, the studies must be approved by the health authority in the country where the clinical research was conducted (such as by the FDA, EMA, etc). For clinical studies conducted within Brazil the following approvals must be obtained prior to the commencement of any study:

1. Ethical approvals must be obtained from the clinical ethics committee (CEP) and the National Commission for Ethics in Research (CONEP) of each coordinating site (Brazil does not have any institutional review boards); and

2. Clinical protocol approvals must be obtained from ANVISA {ANVISA’s approval is required because it is responsible for issuing an import license for the biological product as well as an official approval document (known as the “Special Communicate” which is a single document

which contains the approval of the clinical protocol as well as ANVISA's official approval)}.

Brazil does not require that the phase I and II studies be comparative; however, phase III studies must be comparative when an application is for a new biological product (except in the case of hemoderivatives, vaccines and biological products having an oncology indication).

Comparability Route (Biosimilars)

An applicant can seek regulatory approval for a biological product pursuant to the "comparability route." The "comparability route" is a regulatory route that an applicant can use to obtain registration for a biological product by demonstrating comparability in terms of quality, efficacy and safety between a biological product and a "comparer biological product."

When an applicant files a biological product registration application under this route, not only must the applicant present all of the above information (namely, the detailed application and technical report), but must also submit the following documents:

1. A report with data on the biological product, including the following, mandatory information:

a. A description of the analytical techniques used to detect any potential differences between the biological product and the comparer biological product; and

b. Data on the biological, physical and chemical characterizations related to the quality attributes of the biological product;

2. A declaration providing the name of the comparer biological product;

3. A declaration with evidence demonstrating that the same comparer biological product was used during the biological product's development studies;

4. Information on the expression system used to manufacture the biological product and the comparer biological product;

5. A comparison of the molecules comprising the biological product and the comparer biological product;

6. Reports on the comparative analysis between the main active ingredients, whenever required;

7. A report containing a detailed description of head-to-head comparability tests, with an indication of the capacity of the tests to detect differences in the quality attributes between the biological product and the comparer biological product;

8. Reports of the comparative stability studies that have been generated in accelerated and under stress conditions according to the legislation in effect;

9. A report containing a description of the differences observed in the purity and impurity

profile between the biological product and the comparer biological product;

10. An evaluation of the contaminants and impurities identified in the biological product and a discussion of their potential impact on the quality, safety and efficacy of the biological product;

11. An analytical characterization of the biological product and the comparer biological product;

12. Results of comparative biological tests to determine the level of comparability between the biological product and the comparer biological product; and

13. A conclusive report, including a demonstration of comparability, containing sufficient information to predict if the differences detected in the quality attributes result in an adverse impact on the safety and efficacy of a biological product.

All studies in a development program where registration is sought for a biological product through the comparability route must be of a comparative nature. Also, a biological product may not be considered to be comparable if the analytical procedures used are not sufficient to point out any relevant differences that could impact the safety and efficacy of the biological product and/or the relationship between specific quality attributes, safety and efficacy have not been established.

In addition to providing all of the above information, an applicant must also submit complete reports of nonclinical studies. The nonclinical studies must be comparative and designed to detect significant differences between the biological product and the comparer biological product. Specifically, an applicant must submit reports of the following *in vivo* nonclinical studies:

1. Relevant pharmacodynamic studies for the therapeutic indication intended; and

2. Cumulative toxicity studies (including at least one repeated dose), including a characterization of the parameters of toxicity kinetics conducted in a relevant animal species.

In addition to the nonclinical studies, an applicant must submit reports of the following clinical studies (including the protocols):

1. Pharmacokinetic studies;

2. Pharmacodynamic studies; and

3. Pivotal clinical safety and efficacy studies (namely, Phase III studies).

The pharmacodynamic and pharmacokinetic clinical studies can be combined provided that the

pharmacokinetic/pharmacodynamic relationship is characterized. However, any comparative clinical studies must demonstrate the comparability in terms of the safety and efficacy profiles between the biological product and the comparer biological product. Moreover, the design and comparability margins of any safety and efficacy studies must be statistically and clinically supported. Finally, data from a phase IV study must also be submitted if available.

Biosimilars approved in Brazil

Approximately 187 biosimilar applications have been approved by ANVISA. Examples of some of the biosimilars that have been approved and registered (namely, received marketing authorization by ANVISA) include:

1. Somatropin (a growth hormone) which is marketed by Sandoz Do Brasil Indústria Farmacêutica LTDA, Merck S/A, Laboratorios Pfizer LTDA, Laboratório Químico Farmacêutico Bergamo LTDA Bergamo LTDA, Biosintética Farmacêutica LTDA, Novo Nordisk Farmacêutica Do Brasil LTDA and Aspen Pharma Indústria Farmacêutica LTDA;

2. Filgrastim (a granulocyte colony-stimulatory factor) which is marketed by Produtos Roche Químicos e Farmacêuticos S.A, Laboratório Químico Farmacêutico Bergamo LTDA, Blausiegel Indústria e Comércio LTDA, Dr. Reddys Farmacêutica Do Brasil LTDA, Teva Farmacêutica LTDA, and Biosintética Farmacêutica LTDA;

3. Enoxaprin (a low molecular weight heparin) which is marketed by EUROFARMA Laboratórios S/A, Instituto Biochimico Indústrua Farmacêutica LTDA, Cristália Produtos Químicos Farmacêuticos LTDA, Sanofi-Aventis Farmacêutica LTDA, Blausiegel Indústria e Comércio LTDA and Aspen Pharma Indústria Farmacêutica LTDA;

4. Etanercept (a fusion protein) which is marketed by Wyeth Indústria Farmacêutica LTDA; and

5. Recombinant erythropoietin (a hormone) which is marketed by Biosintética Farmacêutica LTDA and Chron Epigen Indústria e Comércio LTDA.

Availability of regulatory/data exclusivity for biologics in Brazil

Brazilian law does not provide for specific periods (or “periods of non-reliance”) during which third parties are prohibited from obtaining registration (namely, marketing approval) for a biological product (biosimilar) from ANVISA by referring to an originator’s data for a comparer biological product. According to Law nº 10,603, data/regulatory exclusivity periods in Brazil are only available for pharmaceutical products relating to veterinarian use, fertilizers, agrochemicals, their components and the like. Therefore, Brazilian law does not provide any regulatory/data exclusivity periods for new pharmaceuticals (small molecules) or new biological products (biologics) for human use.

Thus, in practice, ANVISA will register any generic drug (such as a branded or non-branded small molecule) or biological product (biosimilar) for human use anytime after the registration of a new drug or new biological product (biologic). The only option available for an originator to try and secure regulatory/data exclusivity for its new drug or biologic would be by filing a lawsuit against ANVISA.

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