REGULATORY TECHNICALITIES FOR DRUG PRODUCT REGISTRATION IN BRAZIL

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REVIEW ARTICLE

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ABSTRACT

Brazilians are demanding better healthcare and modern medicines, presenting significant opportunities for foreign investment. In Brazil, medicinal product registration is an extensive process. To do business in Brazil is not without its challenges. Accessing the Brazilian healthcare market can be a major headache for many medium and small companies without the resources and market knowledge to handle this highly regulated, technical, fragmented and sometimes corrupt process. The Active Pharmaceutical Ingredient and excipients should be informed with their DCB (Common Brazilian Denomination) number and administration, specifications, leaflets/labels, precautions, and relevant information regarding the drug products must be submitted in Portuguese language in a dossier. The registration process for medicine takes more than a year. In Latin America, Brazil, Argentina, and Chile are countries which provide encouragement for generic product registration by discounting the registration fees for generics. Regardless of the challenges and qualms, Brazil's diverse population of nearly 200 million people, their geographic location in America Latina and off course its emerging economy have proven to be enticing and promising as a profitable market for many drug makers.

Keywords: DRA, Brazil, South America, Drug Registration, ROW, ANVISA, Generic Drug.

INTRODUCTION

Over 200 million of population and 8th position in world's largest prescription drug markets, Brazil at present is the major target for big investments and outstanding expectations from large pharmaceutical markets. ANVISA is regarded as the strongest and most predominant agency in Latin America and also been used as reference globally.

In addition, pharmaceutical companies from developed countries whose market are based on loan repayments and companies which are saturated with registering most their products to other export markets as well in a crisis, registering their drug product in Brazil will give them promising strategy. The only annoyance is for non-Brazilian, the drug registration process seems to become more confusing, time-consuming and much complex which actually not without some fact.

Instead of traditional way in which majority of national regulatory agencies follows to provide guidance through guidelines, in Brazil instruction or guidance for pharmaceutical industries are based on legal and hierarchical structure which may consist of decrees, resolutions, ordinances or laws and established acts and does not described in guidance document. (1)

Young Agency and the Breakdown with Past

In 1976, the National Secretariat of Health Surveillance (SNVS) was formed to protect consumer health all the way through regulations to uphold the quality of such products as food, cosmetics, disinfecting products and medications. To bear out these actions, some regulations concerning the guidelines for making up and registration of drugs were promulgated. For example, Law 5991/73, regulated by Decree 54170/74, determines the sanitary control of the drug trade, drugs and active pharmaceutical ingredients, and Law 6360/76, regulated by Decree 74170/77, controls the production of medicines.

Therefore, in the 1970s-1980s, drug registration was based only on the regulations that required general technical, safety and efficacy information without detailing documentation which should be submitted for approval process. SNVS used to grant drug registration within a period of six months.

The National Sanitary Surveillance Agency (ANVISA) was established on of 26 January 1999 (Law No. 9,782/99).[7]ANVISA's statutory role is to protect public health by regulating the production and marketing authorization of pharmaceuticals, food, sanitizers, cosmetics, medical devices, smoking products and so on.

The ANVISA's work led to the publication of many enactment and resolutions in 2003, such as Resolution 136/2003 for the registration of new medicines, which are still being used today. Industries with old registrations had to adapt their documentation to these new regulations during the renewal process (every five years). Many of these, particularly Brazilian traditional drugs that had been registered since long time, were impacted so greatly that industries lost the drug product authorization during renewal or decided to terminate them. As a result, the Brazilian drug market presently is composed primarily of generics (core business of national companies) and new drugs developed by the multinationals. (2)

Drug product registration categories

For registration of drug in Brazil, ANVISA classifies products in the following categories:

1. Medicinal Products: Medicines for human use with their active ingredients and other substances.
2. Pharmaceutical Raw Materials: Drug substances or Raw materials which later to be use in medicines may termed as excipients.
3. Health Product and Medical devices: Equipment and device used in Hospitals including Medical, Dental or Hemotherapy centers and those intended for laboratory and image diagnosis.

REGISTRATION APPLICATION

New Medicine Product/ Innovator Drug:

This includes Branded Medicines that have patent protection and its efficacy, safety and quality are scientifically proven and can be identified by its brand.

Generic Product: (Branded Generics)

Medicines that are similar to a reference product or originator drug with which it is intended to be exchangeable, generic products can only be produced after the expiry or refusal of patent protection and other exclusivities, with its efficacy, safety and quality having been scientifically proven, and named in accordance with the Common Brazilian Name Listing (DCB) or the Common International Name Listing (DCI).

Similar Product: (Non-Branded Generics)

A product containing the same active principle or principles in the similar concentration with the same pharmaceutical form, means of administration, dosage and therapeutic or diagnostic indication as the reference medicine registered with the Regulatory Agency. (3)

Clone product

When an applicant wishes to get approval of Similar Product for which its Generic Product is already approved or vice versa, in that case clone application can be submitted. Also in case when registered Innovator drug applicant wants to approve its Generic Product/Similar Product clone application is submitted.

Documents required for Submission of Application

In Brazil registration dossier made up of Legal documents, Quality documents, Degradation profile and identification & qualification of degradation products, finished product stability studies, Dissolution method development report, Bioequivalence study & Bio waiver study. Required data for each application may differ, depending on submission type such as a new medicine, similar/generic product or clone product. However all the required data more or less similar to CTD structure.

Dossier requirements to be submitted from local agent of foreign company includes Technical Report on the product, informing the components of the formula, instructions, directions, cautions, etc.

Label sample, brochures, pertinent information about the products, all translated into **Portuguese**; If a medical equipment, all documents showing product safety, country of origin, detailed schematic diagram or technical drawing of the equipment's inner parts and user manual, have to be presented for registration. (4)

Registration requirements for administrative documents

For Legal documents an applicant must submit the Application form issued by the Brazilian Ministry of Health, together with a comprehensive table of contents and information regarding the medicine to be registered, eg, Name and Composition of the drug; dispensing requirements; proposed shelf life. Besides this there are several legal documents which need to be attached. These include:

- Proof of registration fee payment: Original copy of the machine stamped bank slip
- Manufacturing site certificate of API supplier and manufacturer issued by ANVISA
- Documents issued by the certification authority stating the technical responsibility of the distributor/manufacturer
- Copy of the notification protocol of pilot batch production
- Business license ("Alvará de Funcionamento") issued by the State authority to the manufacturer's distributor.
- Operating Permit ("Autorização de Funcionamento"), issued by the Federal authority to the manufacturer's distributor.
- In case of products not clearly mentioned in the Brazilian law, it is mandatory to demonstrate its efficacy and safety.
- Copy of the legal Distributor Agreement document, by which the manufacturer authorizes its distributor to trade and distribute the products.
- Information on the regulatory status of medicine in other countries (Imported products) with respective registration dates
- Original legalized Certificate of a Pharmaceutical Product (CPP) from the Brazil embassy in WHO Format
- Free sale certificate, Good Manufacturing Practice (GMP) certificate.
- Documentary evidence of the medicine's registration and marketing in the country of origin (where the manufacturer is located) with its respective registration numbers and dates (Product should be registered in domestic market licensed by state FDA from same site).
- Two samples of finished product in its original container. For Combination – Maximum 3 is allowed for oral or injectable preparations. Four combinations are allowed only if the fourth ingredient is caffeine. (5)

Registration requirements for Technical documents

Quality documents vastly include Active Pharmaceutical Ingredient information, Formulation development details, Quality control of raw material, finished product manufacturing and quality control, Degradation profile, Packaging material description and Finished product stability studies. In case of drug registration in Brazil there are several documents required additionally than general technical documents.

Specific registration documentation and required tests to be performed are as follows:

DCB (Common Brazilian Denomination) number has to be mentioned for each ingredient used in the formulation.

Brazil comes under climatic zone IVb, stability studies to be conducted as 30°C ± 2°C & 75% ±5% RH for long term study and for accelerated

stability study 40°C ± 2°C & 75% ±5% RH for 12 and 6 months, respectively, in case if stability batch fails here, study can be done for 30°C ±2°C & 65% ±5% RH.

As per ANVISA guideline method validation should be performed by three-time independent sampling at manufacturing sites and results to be attached in triplicate manner for both API and finished product. Following to this in Batch analysis part Identification test must be performed for each container of raw materials of all batches including API and excipients both. Three copies of Certificate of Analysis for drug substance from supplier and product manufacturer and finished product Certificate of Analysis signed by authority with name and date in block letters.

Final yield of any finished product batch must not be less than 90%.

In AMV, reference standard has to be used, and if not available then working standard with its characterization is required. Linearity has to be performed in triplicate for each level in Analytical Method Validation.

For a drug product stability study of finished product for each strength in the primary pack for three batches are required as per ICH climatic Zone IVb for Accelerated and Long term stability study. Release and shelf life specification for at least three stability batches should be tested for polymorphic form to confirm that there is no change in polymorphic form stated by ANVISA.

While submitting Pharmaceutical development report, there will need to attach a dissolution development report as ANVISA guidelines. In compatibility part control strategy and Product Lifecycle Management and Continual Improvement are added. As per RDC 31/2010 of Pharmaceutical equivalence studies by ANVISA Comparative Dissolution Profile has to be performed. Photo stability study for the API and finished product also performed for at least three batches. (6)

Registration requirements for clinical study reports

Clinical study reports are to be submitted in Module 5, Brazilian guidelines states that study to be performed after possible results of equivalence and dissolution profile comparison and bioequivalence study must conducted at centers certified by ANVISA with Brazil reference drug. (7)

Registration time & fees

In all Latin American countries drug approval duration is much simpler than developed countries except Brazil, Chile and Cuba. Also, the charges of registering a product are less in these countries. Furthermore, Brazil also motivates for the registration of generics and similar medicines by discounting the registration application fee for generic drugs.

Time and Tariff for registering a pharmaceutical drug in Brazil for New medicine/Originator drug is 12-14 months and in case of Generic drug it is 6-8 months, fees required for Originator drug and Generic drug is 2700 USD-27000 USD depending on size of manufacturer and 2000 USD respectively. In case of similar product, it is around 7000 USD and time required is 8-12 months.

Retail Price: if the product is already available in other markets, then seller/marketer has to submit retail price of product to consumer. If product is nowhere registered, and first time registered in Brazil, then applicator has to submit the Proposed retail cost of new drug product. (4)

Drug Labeling

In Brazil similar requirements apply to prescription drug and OTC formulations. During registration process, drug label for registering drug should be submitted and preclearance is required as part of the procedure. Product label should not contain any designs, figures, geographical name, symbols or other indications that may mislead indicated on label or in advertisements. Additionally, any modification on the medicine label after registration is actionable leads to cancellation of the registration.

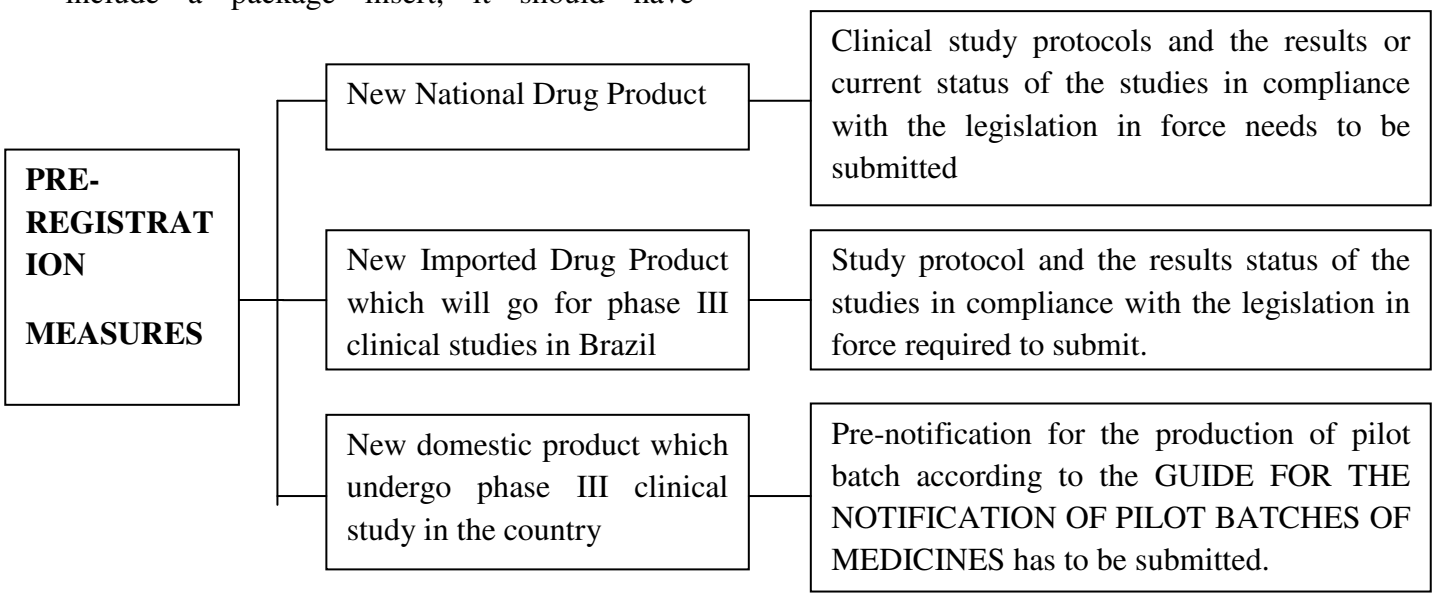
The details which should be printed on package label includes Name of formulation (Generic/ Trademark), Pharmaceutical form, Number of

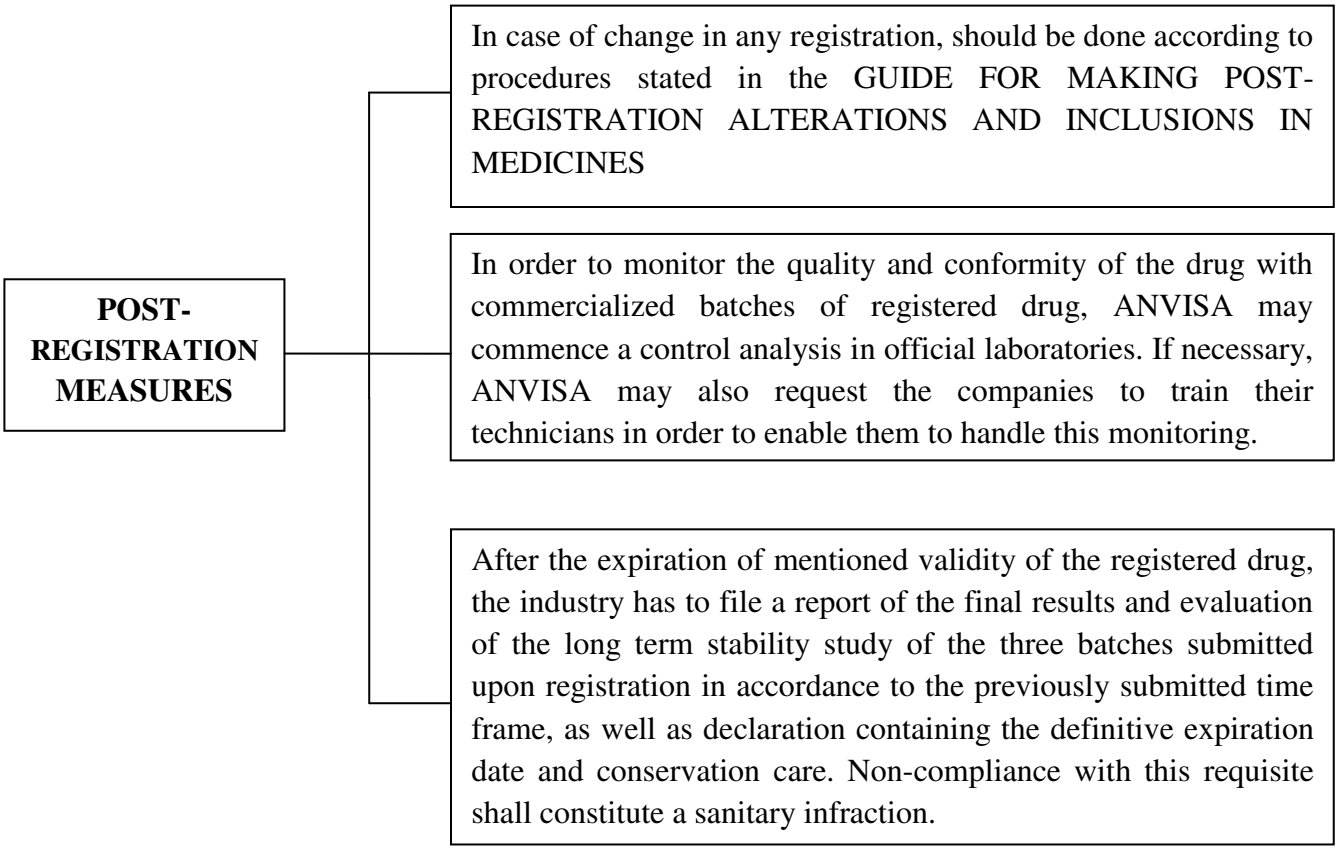
units packed, Active Ingredients, Quantitative composition formula of product, Details of manufacturer, Responsible pharmacist, Date of issue and product license number, Manufacturing and expiry date, Batch number, in case of prescription medicine "Prescription only" indications, Storage, Side effects and Precautions (if applicable).

It is not compulsory to include Pack inserts for all the products, but in case company wants to include a package insert, it should have approved well in advance. Pack inserts/Leaflets are generally physician-oriented. After approval changes in inserts must be submitted for assessment along with its technical justification for the suggested change. (8)

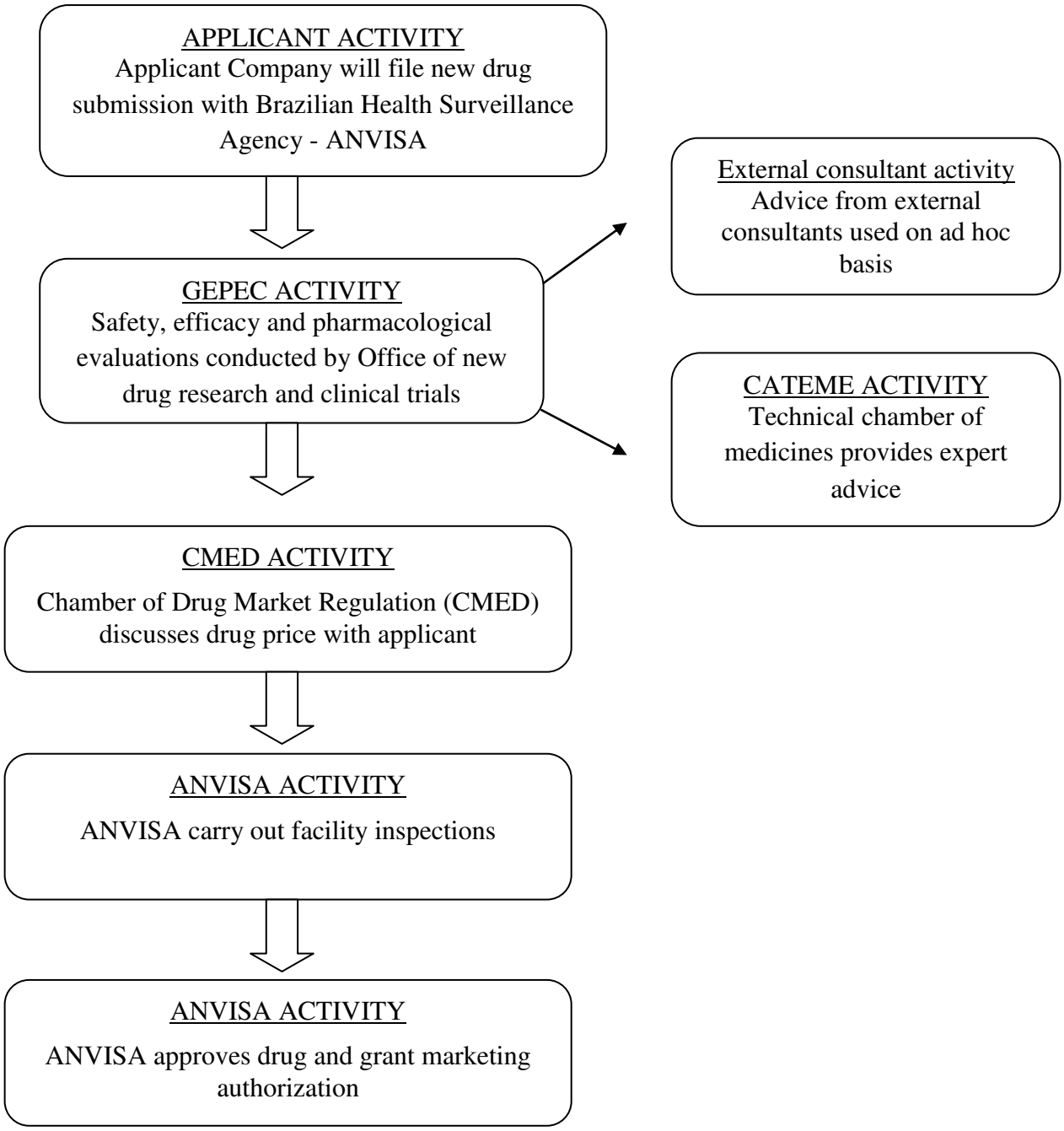
Language used in product final packing (on blister & carton) must be Portuguese with Braille embossing.

Registration Procedure: (Pre / Post Registration Measures) (9)





Dossier Evaluation Process (10):



Regulatory Challenges for Drug Registration in Brazil

Though submission format is CTD, ANVISA has many complex and country specific requirements for drug product registration in administrative part as well as in quality part. Certificate of Pharmaceutical Product (CoPP) submitted must be legalized from Brazil embassy. For API supplier and manufacturer both the manufacturing site should be inspected and certified by ANVISA.

Product to be submitted should be registered in the domestic market from the same site (product license from local FDA). As per ANVISA guideline, identification test should have performed by testing the samples of raw material from each container of API and excipient both.

In case API claims any polymorphic form, then the stability of the finished product and API has tested for X-Ray Powder Diffraction pattern. Release specification and shelf life specification of at least three stability batches should be tested for polymorphic form to confirm that there is no change in polymorphic form.

ANVISA guideline states Analytical Method Validation should performed for API and finished product at manufacturing unit only. The Dissolution Development Report should be additionally attached in product development section as Brazil guideline.

For generic drug registration, the applicant has to send samples to Brazilian authority for Pharmaceutical equivalence. Comparative dissolution profile to be performed with Brazil reference drug as per RDC 31/2010 (ANVISA guidelines) at Brazil Laboratory for testing. After passing the tests Analytical method validation and Bioequivalence study conducted must be in centers certified by ANVISA, moreover the price should not be more than 65% of the price of the corresponding reference drug. ANVISA also suggest performing photo stability study of API as well as finished product required to be performed as per Brazil resolution for all strength of three batches.

Stability study of finished product in the primary pack for three batches is required in ICH climatic zone IV b with Accelerated and Long term study. If applicable, Genotoxic impurity study by API supplier should be done.

Besides this Linearity, Accuracy and photo stability data should provide in triplicate. Requires three copies of Certificate of Analysis from API supplier and finished product manufacturer signed by an authority with a name in block letters & date. Validation study for ANVISA must perform on manufacturing site. For assay study it is mandatory use 5 points between 80 and 120% and performed in triplicate. Degradation products having results higher than the identification threshold and lower than the qualification threshold should be identified, RDC 58 data (i.e., their chemical structure must be known) Characterization tests data for working standard used needs to attach. Pharmaceutical equivalence study and comparative Dissolution profile study have to be performed in REBLAS (ANVISA approved analytical laboratories). Bioequivalence study to be performed in ANVISA approved laboratory as per recommendation provided by ANVISA in BE lists only after positive results of PE/CDP study.

Also Bioequivalence Study (BE study) must be performed using same batch samples and if the product is commercial then samples must have collected from Brazil market. BE study has to be performed again for site addition, variation of products with the Modified drug release profile. For finished product samples required to send with registration dossier requires import permit to send Brazil. Certificate of Analysis should be signed by Authority with name in Capital letters & date.

In addition to these, the ANVISA website (www.anvisa.gov.br) primarily published in Portuguese and also not contains all the updated laws and condensed guidelines for easy reference. Sometimes only selected parts of a law are repealed, while others continue to exist. Thus, one has to keep themselves constantly updated through the National Official Gazette, where laws, decrees and resolutions are published, or through private corporations that give regulatory guidance. The prepared dossier and documents should translate into Portuguese and filed physically in the capital of Brazilian, Brasilia, which again increases overall complexity of the dossier. Many workers and technical staff of ANVISA return to their hometown because they did not acclimatize well to a new city and that leads to dramatically increase in the drug review process and may take up to 2 years to take final judgment, which considerably impact on applicant company's business cases. Along with these ANVISA uses comparative criterion for allocating drug prices, by that price should not be more than the lowest price of that drug sold in countries such as Australia, Canada, France, Greece, Italy, New Zealand, Portugal, Spain and US or more than the manufacturer's price in the product's manufacturing country. By that companies may decide not to commercialize the registered medicine if non-competitive price is assigned. (2)

CONCLUSION

Brazil is the World's 8th largest pharmaceutical market, has a population of around 200 Million and it stood as a major target and outstanding expectations. However, being one of the largest market, Brazil has a both Pros and Cons of its own. At times it can be very difficult for the applicant to register a product in Brazil. There is an increasing trend of profit from Brazil amongst the semi regulated countries; moreover, by discounting the registration application fee for generic drugs, it motivates the registration of drugs in Brazil.

Most of the pharmaceutical industries in Brazil are based on legal and hierarchical structure which consists of decrees, resolutions, ordinances or laws and established acts which makes it more difficult for a pharmaceutical company to set up its own manufacturing unit. There is a lack of guidelines to set up these units. For exporting to drugs to Brazil it is very difficult as it takes around couple of years for registration and the language is Portuguese for all communication which further hinders the process. Earlier the registration was difficult as there was no website, but recently ANVISA has established the website which helps in the registration process (however it was first published in Portuguese language).

Despite of the challenges and hindrance, and non-uniformity in the structured registration, Brazil is still one of the biggest pharmaceutical market and has the potential to give good outcomes in the pharmaceutical market.

DISCLAIMER

The views and opinions expressed in this article are those of the author and do not reflect or represent the views of the company the author works for in any manner.

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CONFILCTS OF INTEREST

The authors declare that there are no conflicts of interest.

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