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Journal of Pharma Research

Journal of Pharma Research
Available online through
www.jprinfo.com

Review Article
ISSN: 2319-5622

A Nostalgic Approach on Brazilian Regulatory Guidelines: ANVISA

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Received on: 06-05-2015; Revised and Accepted on: 16-05-2015

ABSTRACT

This retrospective study provides the regulatory guidelines for product registration and conduction of clinical trial as per ANVISA. In addition to the required registration documents and fees; the Brazilian Health Surveillance Agency (ANVISA) requires GMP certifications for each product imported into Brazil. Brazilian Health Surveillance Agency (ANVISA) requires GMP certifications for each product imported into Brazil. ANVISA has been conducting inspections of finished dose (FD) manufacturers for some time and began to require registration of active ingredient manufacturers in recent years. ANVISA has been conducting inspections of finished dose (FD) manufacturers for some time and began to require registration of active ingredient manufacturers in recent years. Currently, ANVISA is conducting inspections of companies that are manufacturing APIs on the list of priority products established by the health authority and, earlier this year, asked companies to delay certification requests for products not included on this list. ANVISA is responsible for drug registration and licenses to pharmaceutical laboratories and to other companies inside the pharmaceutical production flow. ANVISA is also responsible for establishing regulations applicable to clinical trials and drug pricing, which is carried out by the Chamber of Drug Market Regulation (CMED).Together with states and municipalities, the agency inspects factories, monitors the quality of drugs, exercises post-marketing surveillance, takes pharmacovigilance actions, and regulates drug promotion and marketing. Moreover, ANVISA is in charge of analyzing patent requests related to pharmaceutical processes and products, in partnership with the National Industrial Property Institute.

Key words: *ANVISA, Chamber of Drug Market Regulation, GMP, API, Brazilian Health Surveillance Agency.*

INTRODUCTION

Among Latin American countries, Brazil has the largest market share with an estimated worth of $25 billion. In addition to the required registration documents and fees; the Currently, ANVISA is conducting inspections of companies that are manufacturing APIs on the list of priority products established by the health authority and, earlier this year, asked companies to delay certification requests for products not included on this list.

ANVISA has conducted inspections in a number of countries with almost half of successfully inspected sites being located in China and India combined, and the remainder coming from European, Latin American and rest of world sources. To meet increasing oversight demands, ANVISA published a list of state and local authorities that cooperate with the national authority to conduct inspections within Brazil. Similarly, COFEPRIS announced that GMP certificates from a number of regulatory authorities will be recognized in Mexico [1].

Product regulation requires a balance between protecting public health through an extensive evaluation of a particular product and promoting public health by making needed products available without un due delay [2]. The registration procedure is different in every region. Some will follow the ICH guidelines, WHO guidelines for the registration of the drug product .But some region have the country specific guidelines for the registration of the FPP. Drug regulatory affairs in pharma industries have mandated two types of dossier namely CTD (Common Technical Dossier) and ACTD (Asean Common Technical Dossier) [3]. ANVISA means *"Agencia Nacional de Vigilancia Sanitaria".*This abbreviation is in Portuguese language. In English, it means "National Health Surveillance Agency" or sometimes it is written as "*Brazilian Health Surveillance Agency*". ANVISA was created in 1999 Linked to the Ministry of Health,

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ANVISA is financially autonomous and independently administered [4]. Its activities involve the setting of standards and rules, together with inspection and health surveillance enforcement. ANVISA's work led to publication of many ordinances and resolutions in 2003, e.g., Resolution 136/2003 for the registration of new medicines, which are still been used today. Companies with old registrations had to adapt their documentation to these new laws during the renewal process (which is every five years). The Brazilian drug market currently is composed primarily of generics (the core business of national companies) and new drugs developed by multinationals [5]. Brazil's pharmaceutical market is the 11th largest in the world and second in Latin America after Mexico since the devaluation of 2001[6]. Brazil's market is clearly a key market to drive the global development of any pharmaceutical company with international ambitions and may have located regional headquarters in the country. The regulatory framework is considerably improved and makes Brazil a preferred gateway to other Latin American markets. Product registration in Brazil is a laborious exercise, and is to be requested by the local Brazilian based office of the foreign company or its distributor in Brazil. The registration is valid for 5 years and can be renewed continuously for the same period. Law must complete the registration process within 90 days after the registration is requested, or denied. For registration purposes, ANVISA classifies the products in various categories [7].

ANVISA in Brazil: [8]

With its 191 million inhabitants, Brazil is currently the world's eighth largest prescriptiondrug market and has been the target of large investments and significant expectationsfrom big pharmaceutical companies.Registering drugs in Brazil has been a promising strategy for companies from developedcountries whose pharmaceutical markets, often governed by repayments, already aresaturated and in crisis.These days, the Brazilian National Health Surveillance Agency, ANVISA, is recognizedas the strongest and most influential agency in Latin America and also has been used asa reference around the globe.

Fig. 1: Geographical Indication of Brazil

Anvisa's Mission: [10]

"To protect and promote health, ensuring the hygiene and safety of products and services and taking part in developing access to it."

Values: Transparency, Knowledge (as a springboard for action), Cooperation

Vision: To be an agent for transformation of the decentralized sanitary surveillance system, within a network, holding a distinct position, legitimized by the population, as regulator and promoter of social well-being.

Responsibilities: ANVISA is responsible for

- Monitoring drug prices
- Prices of medical devices
- Control and inspection of smoking products
- Technical support in granting of patents by the National Institute of Industrial Property.
- Protection of the health of the population by exercising sanitary control over production
- Marketing of products and services subject to sanitary surveillance, controlling ports, airports and borders
- Linked to the Brazilian Ministry of Foreign Affairs and foreign institutions over matters concerning international aspects of sanitary surveillance.

Registration of Company in Brazil:

Product registration in Brazil is a lengthy task. Only companies with local operations have standing to apply for registration of medical products. Depending on the product, the registration may be valid from two to five years and can be renewed continuously for the same period. In the case of pharmaceutical drugs, one must inform the active and inactive ingredients. Instructions, directions, cautions, labels, brochures, and pertinent information about the products must be translated into Portuguese. The product registration process often takes more than one year. If the process takes longer than three months, importers and producers are allowed to use a protocol number provided by the Brazilian authorities to distribute their products in Brazil.

Only countries that offer incentives for the registration of generics/copies/similars are Argentina, Brazil and Chile. These three countries discount the registration application fee for generic drugs and in addition Brazil offers a shorter evaluation time for generic and similar products. The cost of registering a product is $27,000 as on March, 2005. According to the Brazilian legislation, the production, manufacturing, imports, exports and sales of any medical, pharmaceuticals and cosmetics products can only be handled by authorized companies, registered with the ANVISA - National Sanitary Vigilance Agency, an agency of the Brazilian Ministry of Health. Manufacturers have to disclose to the local authorities, through their agents (local distributors), the quantitative and qualitative formula of their products, which should be patented in Brazil before the product is introduced into the market, and at the time of registration. This has to be described on the registration document.

Setting up new companies is relatively easy and inexpensive in Brazil. There are four steps to launch business viz. procedures required to establish a business, the associated time and cost, and the minimum capital requirement. Entrepreneurs can expect to go through 17 steps to launch a business over 152 days on average, at a cost equal to 11.7 per cent of gross national income (GNI) per capita. There is no minimum deposit requirement to obtain a business registration number, compared with the regional average of 28.9 per cent of GNI and OECD average of 44.1 per cent of GNI.

Regulatory Issues:

In the early 1990s, the market for pharmaceuticals in Brazil was slackening. In the mid-1990s, it was realized that drug prices had risen substantially and some control was needed to be reintroduced.

The new agency is responsible for overseeing pharmaceuticals, as well as medical equipment, cosmetics and hospital services. The agency also has the additional responsibility for authorizing products on the market, as well as the licensing of manufacturers. TRIPS allow the government to grant licenses allowing the country to manufacture generic versions of patented drugs. Brazil's intellectual property law allows the government to break patents in a health emergency or if it decides prices are exorbitant [13].

ANVISA'S Product Registration Dossier:

The marketing authorization dossier of a medicinal product-Product Registration Dossier (PRD) should be submitted to the Brazilian Health Authority in Portuguese.

A brief overview of the Brazilian regulations shows that the dossier is structured in two main parts.

- Compilation of all administrative data, including specific requirements for imported products.
- Technical reports, including quality, nonclinical and clinical information, presenting Similarities to the Modules 2, 3, 4, and 5 of the CTD dossier [14].

Types of Product Registration:

For registration purposes, ANVISA classifies products in the following categories (Law 9.782/99):

1. Medicine Products (Drugs): for human use, their active substances and other inputs.
2. Pharmaceutical Raw Materials: drugs or raw materials to be used in medicines.
3. Health Product: Medical-hospital, Odontological and Hemotherapic equipment and materials and those intended for laboratory and image diagnosis.

Drugs Classifications:

- **New Medicine Product:** Innovative product that has patent protection whose efficiency, safety and quality have been scientifically proven and identified by its brand.
- **Similar product:** A product which contains the same active principle or principles in the same concentration with the same pharmaceutical form, manner of administration, posology and therapeutic, preventive or diagnostic indication as the reference medication registered with the Agency.
- **Generic Product**: Medication similar to a reference product or innovative product with which it is intended to be exchangeable, generally produced after the expiry or waiver of patent protection or other exclusive rights, 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).

Documentation Needed for Registration:

- The followings are the basic documents required from the local agent of the foreign company for the registration of products in Brazil.
- Application form obtained from the Brazilian Ministry of Health.
- Original copy of the machine stamped bank slip, which serves as proof of registration fee payment.
- Trade Permit ("Alvará de Funcionamento") issued by the State authority to the manufacturer's distributor.
- Same type of document ("Autorização de Funcionamento"), issued by the Federal authority to the manufacturer's distributor.
- Document showing the technical responsibility of the distributor/ manufacturer, issued by the certification entity.
- 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;

- For products not clearly mentioned in the Brazilian law, it is mandatory to provide information about their utilization in order to demonstrate its efficacy and safety;
- Copy of the registration granted to the products at the country of origin (or copy of the Free Sale Certificate);
- Copy of legal document, by which the manufacturer authorizes its distributor to trade and distribute the products.
- If a medical equipment, all documents showing product safety, country of origin, detailed (exploded view) of the equipment's inner parts and user manual, have to be presented for registration [13].

Dossier requirements for submission to Regulatory bodies: [15]

- Dossiers to be submitted in Local Language
- CPP / WHO GMP / Manufacturing license
- Free Sale Certificate
- Letter of Authorization / Power of Attorney
- Legalization of administrative documents from the embassy
- API Technical package (Brazil, Mexico)
- Specification and methods
- COA of API and Excipients from vendors
- Manufacturing procedure and controls
- Executed Batch manufacturing records / Batch Numbering system.
- Stability data on three batches- Stability conditions -as per zone definations.

Brazil Regulatory Drug Approval Process: [16]

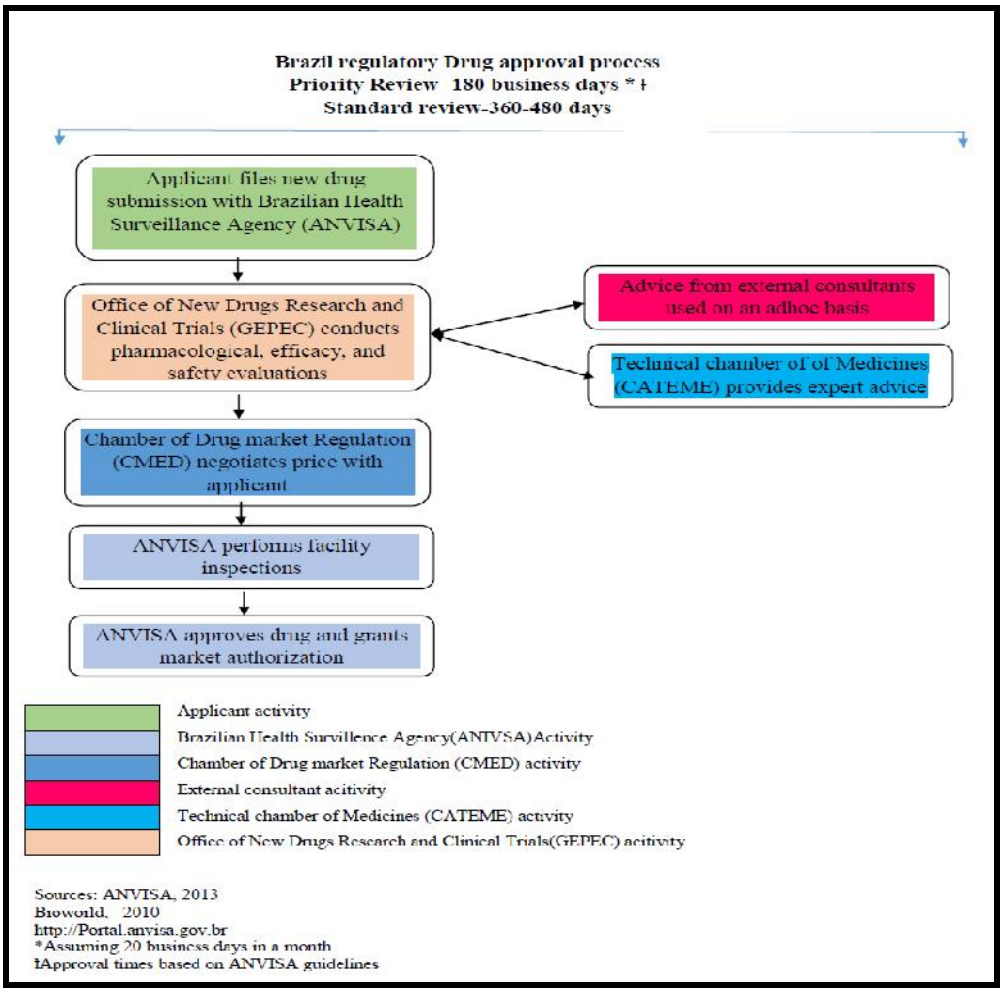


Fig. 2: Brazil Regulatory Process

Registration of New Drug:

Registration procedure of new drug is divided in mainly 3 parts as follows

Pre-registration measures:

- Protocol for clinical study

Registration:

- Documents to be submitted
- Protocol for the new drug
- Protocol for import of new drug

Post-registration:

- Alteration in Registration, Renewal of Registration

Thus, these three parts can be considered similar to IND, NDA and Supplementary NDA as per US FDA.

Pre-registration measures:

- In case of a new national drug product, the protocols of the clinical studies and the results or current status of the studies in compliance with the legislation in force has to be submitted.
- In case of a new imported drug product that will undergo phase III clinical studies in Brazil, the study protocol and the results or current status of the studies in compliance with the legislation in force has to be submitted.
- Whenever phase III will take place with a new product manufactured in the country, pre-notification for the production of pilot batch according to the GUIDE FOR THE NOTIFICATION OF PILOT BATCHES OF MEDICINES has to be submitted.

Registration:

Documents to be submitted:

- Registration petition forms
- Proof of payment of Sanitary Surveillance Inspection

- Copy of the company's Operation License
- Technical Responsibility Certificate by the Regional Pharmacy Council
- Copy of the notification protocol of pilot batch production
- Good Manufacturing Practices certificate (GMP) emitted by ANVISA

Protocol for the new drug:

- General data: package insert text, label etc…
- Expiry date by Stability studies
- All Toxicity study reports
- Clinical trial data with statistical treatments
- For Combination - Maximum 3 is allowed for oral or injectable preparations. Four Combinations are allowed only if the fourth ingredient is caffeine.
- Physico-Chemical parameters of drug
- Synthesis route (all reagent, solvent, condition)
- Pharmacodynamic parameters
- Pharmacokinetic parameters
- Production Report(Batch size ,methods and equipments used)
- Q.C. of raw material and finished products

Protocol for the import of new drug:

- GMP of importing country or Inspection by ANVISA.
- Documentation is allowed in Portuguese, English or Spanish language.
- Label, Package Insert must be in Portuguese (Brazilian) language
- Official Documents like certificates given by importing country, if it is in foreign language that must be translated with Legal translator only.
- In some cases, applicator wants to import Bulk drug from foreign and then Pack the product in Brazil. In such cases, Expiry Date must be counted from Manufacturing date in foreign, and not the packaging date in Brazil
- Additionally all document should be submitted in CD

Post-registration measures:

- Any registration changes shall follow the procedures specified in the GUIDE FOR MAKING POST-REGISTRATION ALTERATIONS AND INCLUSIONS IN MEDICINES.
- ANVISA may undertake a control analysis of commercialized batches in official laboratories in order to monitor the quality and conformity of the drug with the drug registered.

Whenever necessary, ANVISA may request that the companies train their technicians in order to enable them to undertake this monitoring.

Harmonization of already registered drugs:

- ANVISA had introduced some modification in Registration procedures and Documents after 1st December 2004.
- Drugs Registered before this date, has to submit information or data or documents related to drug, for harmonization with Newer Registered drug products.

Table No. 1: Harmonization of already registered drugs

S. No.	Registration EXEMPTED for…	Registration REQUIRED for…
1	Simple drug product (Single Ingredient)	Simple or Compound (2 or more Ingredient)
2	Without trademark or brand name	With trademark and brand name
3	Manufacturing as per Brazilian Homeopathic Pharmacopoeia	whose formulation is composed of substances of verified therapeutic action described in the homeopathic drug product literature, official compendia, clinical studies or indexed journals and manufacturing procedures are as per Brazilian Homeopathic Pharmacopoeia
4	Or in official compendia recognized by ANVISA	

Table No. 2: GITE List of specified therapeutic group and indications

S. No.	Specified Therapeutic Groups and Indications
1	Drugs described in GITE can be sold OTC
2	Parentrals can't sold OTC (can not sell without Prescription)
3	Drugs not listed in GITE can not sell without PRESCRIPTION.
4	Any NEW DRUG, not to be sold under GITE
5	If New Drug has minimum 5 years experience in USA or European market (with FDA or EMEA approval), and if it comes under GITE list, applicator may request to classify it as OTC product.

Classification of *in vitro* diagnostic product into 4 classes as follows…

Table No. 3: *In-Vitro* Diagnostic Product

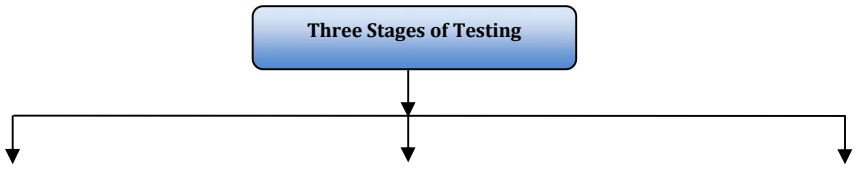
Group A	Materials, devices, accessories & inputs for support of *in vitro* diagnostic products.
Group B	For diagnosis of non-transmissible diseases.
Group C	For diagnosis of infectious-contagious diseases, except those classified in Group D.
Group D	For diagnosis of infectious-contagious diseases, sexually transmissible diseases or diseases spread by blood and blood products, as well as identification of blood groups, transfusion or preparation of blood products.

GMP:

As per the latest updates of "**GMP Guide for Pharmaceutical Industry**" approved by WHO's World Health Assembly – WHA.

- For Import of Drug in Brazil from country which is not included in MERCOSUL group requires Inspection of Drug Manufacturing unit by ANVISA.
- MERCOSUL = Mercado Commun del Sul means "*South Common Market*" includes Argentina, Brazil, Chile, Paraguay & Uruguay (Group of Countries of South America)
- All documents should be submitted in Portuguese language and Certified by the Brazilian Consulate, of the Country, where the Drug for Importation in Brazil is manufactured
- GMP Certificate is valid up to 1 year only.

BA/BE Guidelines:



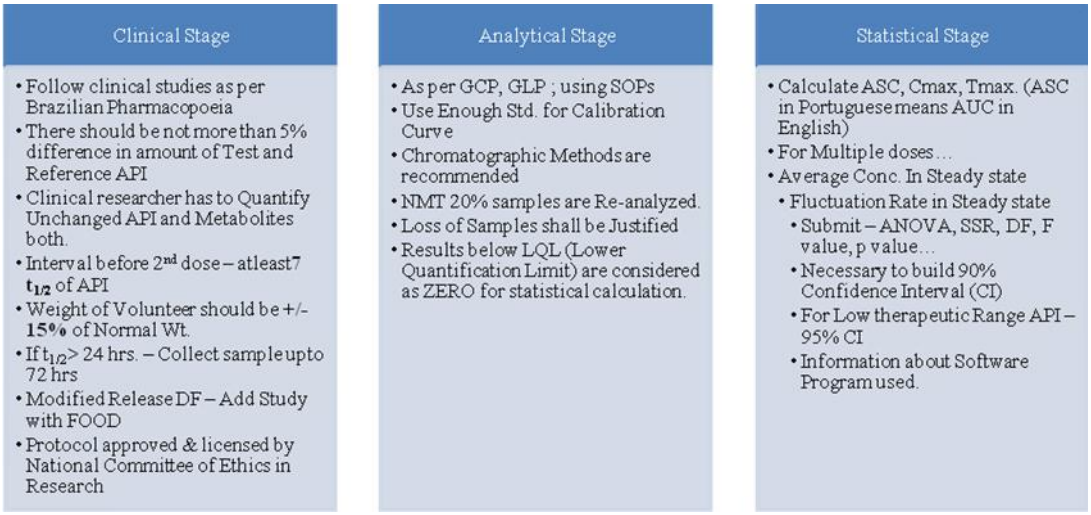


Fig. 3: BA/BE Guidelines

BA-BE Good Practice manual:

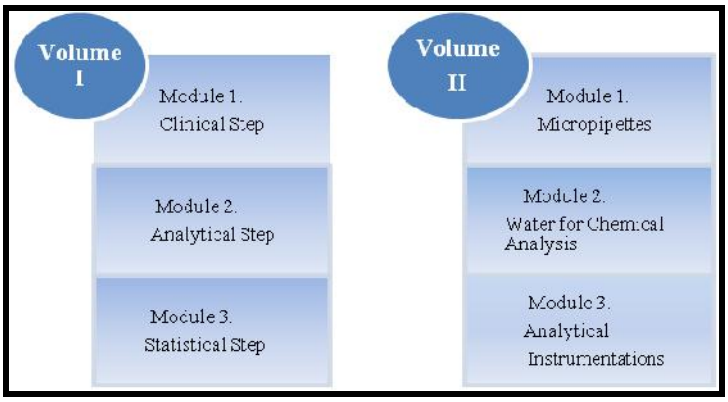


Fig. 4: BA – BE Good Practice Manual

Brazilian Regulatory Organizational Chart on Clinical Trials: [12]

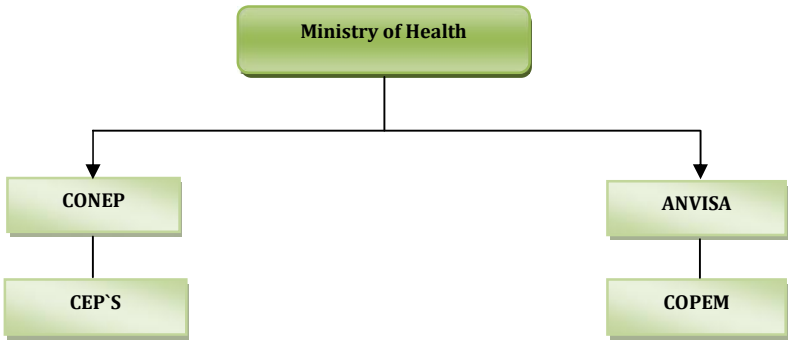


Fig. 5: Brazilian Regulatory Organizational Chart on Clinical Trials-CONEP-National Commision on Research Ethics,CEP'S-Clinical Research Center ethics Committee, COPEM-Coordination of Research and clinical trials and new drugs

Any company wanting to conduct clinical trials in Brazil will need to prepare some key initial documents, namely the protocol, informed consent form (ICF), investigator's brochure (IB), program of activities (POA), protocol approval letter from an IRB of the origin country, and insurance applicable to the Brazilian sites [15].

There are three steps for clinical trials, and they involve the local ethics committee (EC), CONEP (National commission on research ethics), and ANVISA. The processes related to CONEP and ANVISA run in parallel for a part of the overall process.

Drug Labeling: [17]

Brazilian labeling requirements are the same for over-the-counter (OTC) and prescription drugs. As a general rule, neither labeling nor advertisements may include geographic names, symbols, figures, designs, or other indications that might be misleading.

In addition, any unauthorized modification of the label is punishable by cancellation of the registration. Preclearance of labeling is required as part of the registration procedure.

The package label must include the following:

Table No. 4: Drug Labelling

Drug Labeling
• Name of product (trademark or generic)
• Pharmaceutical form
• Number of units in package
• Active ingredients
• Complete formula of the product with quantitative composition
• Name and address of manufacturer
• Responsible pharmacist
• License number and date of issue
• Batch number
• Expiration date and date of manufacture
• Storage instructions
• For prescription products, statement that it is supplied on prescription only
• Indications
• Side effects &
• Precautions, if any.

Recommendations for important requirements in Brazil: [15]
Requirement: PE (Pharmaceutical equivalent study to be performed in Brazil).

Recommendations: ANVISA to accept the Pharmaceutical equivalent study generated by the Manufacturer as the facility and lab is inspected by the ANVISA.

Benefits: Time.

CONCLUSION

The health care industry in Brazil is undergoing profound transformations and experiencing new business dynamics, making the domestic market one of the most promising and attractive in the world, despite being extremely complex. In 2010, health care expenditures in Brazil totalled US$ 193.09 billion, according to the World Bank and the World Health Organization (WHO). Of this total, 47% of the revenues came from the public sector, through SUS, and the other 53% from the private sector. Expected to become the fourth biggest global pharmaceutical market by 2016, Brazil currently leads the Latin American region , and is the second largest only to China among emerging markets. The country's rapidly growing middle class (presently 120m strong), low national debt, improved business regulations and government's expansion of health care have enticed pharmaceutical companies to go West (or indeed south).

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How to cite this article:

J. Balasubramanian et al.,: A Nostalgic Approach on Brazilian Regulatory Guidelines: ANVISA, J. Pharm. Res., 2015; 4(5): 211-116.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil