Pharmaceuticals Export Promotion Council of India

(Set up by Ministry of Commerce & Industry, Government of India)

REGULATORY & MARKET PROFILE OF BRAZIL

Demography

SL. No	Parameter	Description
1	Region	South America
2	Country	Brazil
3	Capital	Brasilia
4	Population	207,353,391(July 2017 est.)
5	Population growth rate (%)	0.73%(2017 est.)
6	GDP (purchasing power parity)	$3.24 trillion(2017 est.)
7	GDP - real growth rate (%)	1% (2017 est.)
8	GDP - per capita (PPP)	$15,600(2017 est.)
9	Epidemiology	Ischemic Heart diseases, Cardiovascular Diseases, Alzheimer disease Lower respiratory tract infections and COPD Diabetes etc
10	Population below poverty line	4.2%
11	Age structure (%)	0-14 years: 22.33%
		15-24 years: 16.36%
		25-54 years: 43.86%
		55-64 Years: 9.12%
		65 Years and above 8.33%
Source: CIA World Fact Book updated to July 2017		

Introduction:

The Brazilian authorities will continue to place downward price pressures on medicines, resulting in profit declines for drug makers. Brazil's pharmaceutical market will provide an increasingly challenging operating environment for drug makers, with schemes like the productive development partnership programme designed to control prices and boost local capacity. However, on balance, multinational drug makers will continue to see Brazil as a major opportunity for expansion.

Pharma market was of the size $ 20.87billion in 2017 after negatively growing by 3%.

Latest Updates:

- The Pharmaceutical Researchers and Manufacturers of America (PhRMA) 2018 submission for the United States Trade Representative (USTR)'s Special 301 Report continues to recommend that Brazil be placed on the priority watch list due to Brazil's market access barriers and intellectual property concerns.
- In January 2018, Biocon and Mylan's biosimilar trastuzumab was approved by ANVISA. Trastuzumab will be marketed in Brazil by Libbs Farmaceutica for the treatment of overexpressing HER2-positive metastatic breast cancer, HER2-positive early stage breast cancer and HER2-positive advanced gastric cancer.
- In January 2017, the Brazilian Ministry of Health published a list of 52 high-cost imported medicines that are targets for a productive development partnership (PDP).
- In December 2016, Sanofi committed to investing USD210mn in its Brazilian distribution operations through to 2020. As part of the scheme, the company opened a distribution centre in São Paulo run by DHL, the operations specialist.

Strengths:

- Brazil's pharmaceutical market is one the fastest growing markets in Latin America and has enjoyed steady growth since 2004 and the largest in Latin America
- The government has moved to align the drug regulatory environment with international standards, including significant intellectual property (IP) reforms carried out in recent years.
- The local Biotechnology is developing rapidly giving opportunities to international companies.

Threats:

- Government policy has been biased towards local drug producers, and the government itself is a major producer as well as consumer of medicines, particularly vaccines, presenting conflicting government interests.
- Trade and production of counterfeit medicines remain significant problems.

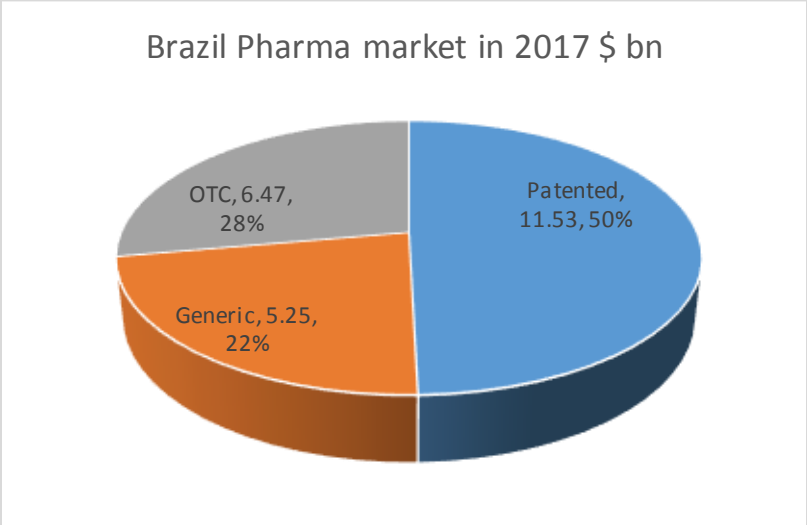
Opportunities:

- Rise in the market share of generic drugs
- Continued resistance to further improvements in IP and draft proposals to ban secondary use/polymorph patents

Market Summary:

	2016	2017	2018	2019	2020	2021	2022
Pharma sales in $ bn	21.5	20.87	24	25	26.6	26.9	30.7
Growth		-3	15	4.17	6.4	1.13	14.2
Source: BMI							

Brazil has traditionally been Latin America's largest pharmaceutical market. A peculiarity of the domestic pharmaceutical market is the relatively low price of medicines in comparison to other large markets in the Americas. By 2022, Brazilian Pharma market is expected to touch $ 31 bn.



The fastest growing drug sector in Brazil is bioequivalent generics, a trend that shows no signs of abating. While generic products represent a large proportion of domestic consumption in volume terms, by value they account for 30% of total prescription drug sales and 22% of total drug expenditure. There are about 550 pharmaceutical firms in Brazil, and the leading local producers include **Aché/Biosintética**, **Neo- Quimíca**, **Teuto**, **Medley**, **Eurofarma**, **Libbs**, **EMS-Sigma**, **Laboratório Cristália**, **Biolab Sanus**, **União Farmacêutica** and **Vallé**. Industry investments previously focused on generic drugs but they are increasingly shifting towards exports and generic versions of biological products.

Generic Market:

Brazil's generic drug sector is the largest in Latin America. It was valued at $ 5.25 billion. Forecast show it is likely to touch $ 6.5 bn by 2022 with a cagr of 4.5%

ProGenericos, the Brazilian Association of Generic Drug Manufacturers, has announced that the number of generic drugs approved between January and May of 2015 could equal volume of generics approved throughout the full year of 2014, underscoring continued commercial opportunities for generic drugmakers in the Latin American country. This will drive the consumption of generic drugs in Brazil, particularly within the public sector which maintains a strong preference for prescriptions of generic drugs and provides pharmaceutical access to over 90% of Brazil's population.

This is mainly due to cost containment and also devaluation of its currency. As out of- pocket spending accounts for the majority of the country's healthcare expenditure, Brazilians are willing to consume low-cost generic medicines. The government is aiming to support the generic drug sector so it can provide affordable, effective drugs to reduce the financial burden on local citizens and boost the country's economy. Local companies have become very competitive through sector consolidation, the government's favourable public purchase policy and cheap loans, as well as the mOswaldo Cruz Foundation (Fiocruz)'s knowledge and technology transfer partnership deals with multinational drugmakers. There will be further drug pricing pressure from the government and competition in Brazil's generic drug market sector.

Variations in Regional Demand

Consumption of generic drugs by volume show that the south east region accounts for the highest proportion of the total generic medicines market with 65.6%. Market shares in other regions are registered at 15.5% in the south, 11.4% in the north east, 4.8% in the west central and 2.7% in the north. This is largely due to demographic factors that have a major bearing on the consumption of pharmaceuticals, such as population size, which also shows large variations. The south east hosts 42.5% of the total population, the south 15.3%, the northeast 28.0%, the west central 6.8% and the north 7.5%. Based on these figures, consumption of generic products is most concentrated in the south east, while substantial under-consumption is evident in the north east and north.

Over 50 % of the doctor community have less faith in generics available in the country due to their lack of confidence in Brazilian bioequivalence standards.

Of the 2,792 generics registered in Brazil, 89% originate in the country. There are only 300 imported generic medicines, of which almost two-thirds are of Indian origin.

Pharma Trade

Brazil's reliance on imported medicines will remain, ensuring the country's negative trade balance through to 2021.

Forecast show Brazil's import trade will grow from USD6.9bn in 2017 to USD11.4bn by 2022, with a CAGR of 10.6%. Brazil's top pharmaceutical import partners in 2015 included US (USD1.3bn), Germany (USD1.1bn), Switzerland (USD643mn) and the UK (USD423mn).

Regulatory regime:

The basis for market regulation is Law No. 6360/76, which has been updated on several occasions since its introduction. Pharmacovigilance in Brazil is considered as fairly well-developed in comparison with many emerging markets, with standards largely comparable to those in developed markets. A programme for the modernisation of ANVISA's management framework was presented by the agency's president, Dirceu Raposo de Mello, at the 27th Forum of Planalto in August 2010. Since then, ANVISA has established eight categories for the registration of medicines. These include new medicines, generic medicines, similar medicines, botanic medicines, biological & biotechnological medicines, parenteral medicines in bulk, homeopathic medicines and medicines that do not need registration.

To obtain product registration, the manufacturer, importer or merchant must have either an 'Operating Authorisation' or a 'Special Operating Authorisation' issued by the MoH, a prior condition of which is an 'Operating Licence'. Companies must be established locally to obtain an 'Operating Licence' and an 'Operating Authorisation'. Only locally established companies can apply for product registration

ANVISA has recently implemented compulsory certification of GMP guidelines for international Drug makers exporting to Brazil, and the implementation of a recall system, which allows the immediate Withdrawal of products that have quality variations or are under suspicion.
Foreign suppliers are also required to have a technical representative in Brazil to deal with matters relating to drug safety. It is also important to note that Brazilian legislation does not recognise companies that are dedicated exclusively to the commercialisation of drugs on behalf of third parties.

Generics Regulation:

In 1999, Brazil introduced generic regulation with Decree 3,181, which regulated Law 9,787. The new legislation required the generic name to be used on the packaging of all drugs. The government also published an initial list of 100 reference products to be used in equivalence testing. Under Resolution No. 41/2000, bioequivalence tests for registration were introduced.

Generics imported into Brazil up to June 30 2003, whose bioequivalence tests had been undertaken overseas, would need a comparative dissolution testing, the international drug reference and the national drug reference.

Since June 30 2003, bioequivalence tests have only been accepted for referenced drugs approved and marketed in Brazil. In order to speed up the bioequivalence test process, manufacturers can send the relevant documentation to the Management Unit of Generics (Unidade de Gerencia de Medicamentos Genericos) in Sao Paulo.

The SUS (Sistema Unico de saude, A publicly funded health care system) must give preference to generics when making purchases for the sector, even when prices are comparable. SUS prescriptions must use the Brazilian Common Denomination (DCB) or INN in the private sector.

Pharmacists are able to make generic substitutions unless expressly forbidden by the prescriber. Pharmacies are required to clearly display a list of all the generics which have received market approval as a reference for consumers. Resolution No. 84/2002 reassured issues of generic quality and substitution, rescinding Resolution No. 391/1999.
ANVISA's Resolution No. 134/2003 obliges producers of similar drugs to present bioavailability tests for product renewal. The first deadline for this was December 1 2004, when 130 products were cancelled. The remainder will be tested at their first and second renewals, the process finishing in 2014. As many similar drugs might not comply with the resolution, the generic sector is expected to increase.

Policy:

The Brazilian government is keen to support the development of the domestic pharmaceutical industry.

Public procurement of goods produced outside South America, including pharmaceuticals, is set to decrease as a result of a new law that has recently come into force – Lei No. 12.349/2010 – which amends the bidding law Lei de Licitação No 8.666/93. The new legislation grants preference in public tenders to goods and services provided by domestic or foreign companies installed within the Mercosur economic block, even if their prices exceed those offered by foreign firms by up to 25%.

The government's industrial policy is to foster domestic generic production of essential medicines, in particular vaccines and insulin as well as ARVs (HIV/AIDS), and it has invested substantial sums to boost local production technology and capacity.

67% of its imports during 2010 were from USA (23%), Rest from Switzerland, Germany, France and Ireland showing high dependency on patented drugs.

Brazilian govt. did not hesitate to exercise compulsory licensing to help their large HIV patient population.26% of Brazilian population suffers from either hypertension or Diabetes. Generic suppliers, be it domestic or foreign origin has a high chance of business from this sector.

Government Favours Local Firms

To encourage the development of the local pharmaceuticals industry, domestically manufactured medicines in Brazil will be purchased at a 25% price premium (compared to imported medicines) through the SistemaÚnico de Saúde (SUS). There are 78 drugs and 44 biopharmaceuticals on the list. Additionally, various margins will be applied to different drugs: imported finished drugs (8%),locally produced medicines (20%) and biopharmaceuticals (25%).The federal government and state governments will invest BRL1bn (US$550mn) each to cover the margin difference and support the domestic manufacturing program.

The government is also focusing on the transfer of technology between private and public pharmaceutical companies via the Productive Partnerships for Development (PDP) initiative. There are 29 PDP programmes for the production of 30 finished medicines, involving 32 drug makers (10 public and 22 private domestic and foreign companies). It is estimated that savings generated from the PDP projects will create annual savings of BRL400mn (US$220mn).
Furthermore, the Ministry of Health aims to save BRL1.7bn(US$0.93bn) a year from increased domestic production of medicines and via aggressive negotiations with multinational drug makers through centralized purchasing procedures.
Multinational pharmaceutical companies to increase their direct exposure to the Brazilian market through local manufacturing plants and direct sales forces, are likely to exploit the price premium on locally produced medicines. The administration is also encouraging multinational drug company collaboration with local drug companies – pushing for the sharing of technology and intellectual property rights – to produce drugs locally, therefore protecting revenue streams.

Local Generic Industry

Brazil's growth potential in the pharmaceutical sector provides considerable opportunities for revenue expansion. However, the government measures to expand access to medicines will benefit mostly domestic generic drugmakers, a perceived bias that is increasingly being realised. Critics feel it is imperative that multinational pharmaceutical firms invest in local production capabilities in order to maintain their share of the market. There are around 80 local manufacturers capable of producing more than 2,600 products to treat over 90% of known diseases. Brazilian firms, such as EMS-Sigma, Eurofarma, Medley, Aché-Biosintética and Cimed, have ongoing production modernisation programmes valued at some BRL1bn (USD468mn). Investment reportedly totalled around USD400mn between 1999 and 2006, illustrating not only an expansion of capacity, but also the repositioning of product lines in favour of genuine generic products. Of the total generic drugs registered in Brazil, approximately 80% originate in the country. The presence of 300 imported generic medicines does indicate room for foreign competition, but we note that almost two-thirds of these are of Indian origin,

Issues& Suggestions:

1) Presently all the samples irrespective of quantity are required to be sent only by Cargo. Hence the industry is inconvenienced whenever smaller quantities are required to be sent. Permission / authorisation for sending samples of small quantity (say up to 500g) in courier mode instead of compulsion to receive only in cargo mode would be of great relief.

2) Generally large companies have multiple manufacturing sites. Many a times same API is manufactured in different but GMP approved(As per the guidelines of the importing regulatory agency) sites. Usually international agency accept same API being manufactured at multiple approved sites. BRAZIL, ANVISA's approval associates product with the manufacturing site and in case of manufacturing being conducted at multiple sites, each and every site has to undergo the process of GMP approval for that product separately. This is time consuming and expensive.

3) GMP issued by the agency is valid only for two years.

4) Simplification of procedures on trans-shipment of Reefer containers to dry ports.

5) Importers in Brazil are required to obtain import permission for every consignment. Our members have reported incidences where, they had to wait to dispatch the goods for unusual lengths of time after raising the invoice on receipt of indents from their exporting partners in Brazil, as; they could not obtain import permission/license. This blocks their capital as the stocks invoiced are lying idle in their warehouses.

6) Fee associated with port utilization charges is one of the highest and import delays within the country makes it even more difficult for exporters. This also makes investors to think again.

7) High electricity charges add to high fixed expenses and deters some of the investors.

8) Brazil's labour market is very rigid and difficult to deal with and international study rates Brazil 9th among 17 countries in LAC region while assessing labour risk index.

Statistics

India's Exports:

India's Pharmaceutical exports to BRAZIL $ Million						
Category	**2015-16**	**2016-17**	**2017-18**	**GR%**	**contbn%**	**Contbn to**
BULK DRUGS AND DRUG INTERMED	115.56	127.69	139.19	9.00	36.27	38.75
DRUG FORMULATIONS AND BIOLO	173.14	161.16	197.54	22.58	51.48	31.29
AYUSH	0.01	0.00	0.04	3627.39	0.01	2.85
Herbal Products	1.00	1.19	1.66	38.81	0.43	19.42
Surgicals	8.11	12.00	15.78	31.47	4.11	49.25
Vaccines	28.35	35.32	29.52	-16.43	7.69	28.73
Total	326.17	337.37	383.72	13.74	100.00	33.81

India's exports to Brazil is growing much faster than Brazil's generic market suggesting improvement of India's market share.

Brazil's Imports:

Top Ten Importing Partners of Brazil $ Million						
Rank	Country	2014	2015	2016	Gr%	Share%
1	USA	1525.17	1313.85	1265.28	-3.70	19.86
2	Germany	1402.36	1108.06	1024.77	-7.52	16.08
3	Switzerland	820.12	643.09	531.37	-17.37	8.34
4	United Kingdom	282.91	422.89	410.00	-3.05	6.43
5	Belgium	343.28	323.07	362.19	12.11	5.68
6	France	487.30	331.34	342.48	3.36	5.38
7	Canada	75.92	147.92	324.80	119.58	5.10
8	Italy	463.51	296.61	297.31	0.23	4.67
9	Ireland	306.07	258.83	234.37	-9.45	3.68
10	India	225.47	247.14	218.45	-11.61	3.43
	World	7409.21	6446.31	6371.40	-1.16	100.00
Source: UN comtrade						

REGISTRATION AND LICENSING REQUIREMENTS

➢ Regulatory Authority	:	**ANVISA - Agencia nacional de Vigilancia Sanitaria (National Health Surveillance Agency)**
➢ Website of regulatory Authority	:	http://portal.anvisa.gov.br/english
➢ Fees for Drug Registration	:	USD 2000
➢ Normal time taken for registration	:	3 yrs
➢ Registration Requirement [Dossier Format]	:	Non-CTD
➢ Whether plant inspection is mandatory	:	Yes BE need to be done with Brazil Innovator product.
➢ Barrier in product Registration		BE studies need to be done with Brazil Innovator product.
➢ Requirement of Local agent/ Subsidiary	:	Subsidiary is Required to operate locally

About the ANVISA:

The Brazilian Health Regulatory Agency (Anvisa) is an autarchy linked to the Ministry of Health, part of the Brazilian National Health System (SUS) as the coordinator of the Brazilian Health Regulatory System (SNVS), present throughout the national territory.

Anvisa's role it to promote the protection of the population's health by executing sanitary control of the production, marketing and use of products and services subject to health regulation, including related environments, processes, ingredients and technologies, as well as the control in ports, airports and borders.

Scope of action:

- Market authorization for products prior to its manufacturing, market exposure or delivery to consumers
- Inspections to ensure manufacturing quality; products' post-market and post-use activities (monitoring, oversight, complaints' receipt, etc.)
- Oversight to enforce compliance with sanitary regulations

- Control of the import, export and circulation of ingredients and goods subject to health regulation
- Health regulation actions in services for outpatient care (routine or emergency) and hospitalization; diagnostic support and therapeutic services that entail the incorporation of new technologies
- Coordination of special programs to monitor the quality of regulated products and services
- Control actions in ports, airports and borders, to ensure the sanitary control of facilities, services and means of transportation, products' import and the protection of travelers' health
- Adoption of preemptive and control measures for outbreaks, epidemics and public health emergencies

How to Apply for Registration at Anvisa?

The registration request must be made by the interested company through the Petitioning System , following the steps below:

1st STEP - REGISTRATION

The Company Registration is the first step to have access to the Petitioning System and should be used to register private companies that provide products or services regulated by Anvisa and to register users with a representation link with these companies.

STEP 2 - CHANGE OF THE COMPANY'S PORT (optional)

The companies should then promote the change, if necessary, of the Company Port, which will determine the amount of the fees to be paid by the interested party.

STEP 3 - REQUEST

Before accessing the Requesting System it is recommended that the interested party identify the Subject Code related to their request, since it is from this code that the entire transaction of the request will develop.

During the process, the interested party will be guided to the type of petition of the chosen Subject Code.

STEP 4 - FEES

At the end of the petition process, the Union Recruitment Guide (GRU) will be generated to pay the Sanitary Surveillance Inspection Fee (TFVS) related to the chosen subject. The amount of the fee is determined by Interministerial Ordinance No. 701, of August 31, 2015.

5th STEP - PROTOCOL

After payment of the GRU, the interested party must gather all the requested documentation, according to the *checklist* of thechosen Subject Code and file with Anvisa, either in person or by mail.

The documents forwarded to Anvisa by mail must contain the following address, and no fax or copies thereof are accepted:

To the National Health Surveillance Agency
Board of Directors or General Management or Management or Unit to which the document is addressed
Care (A / C) of Document Management
Ref: Number of the Process or File or Petition, when applicable.
Address: SIA, section 5, special area 57
CEP 71.205-050
Brasilia DF

STEP 6 - FOLLOW - UP

After filing the application, the interested party can follow the progress of their request, through the system of Consultation to the Situation of Documents .

- ANVISA has established eight categories for the registration of medicines. These include new medicines, generic medicines, similar medicines, botanic medicines, biological & biotechnological medicines, parenteral medicines in bulk, homeopathic medicines and medicines that do not need registration.

Criteria for the granting and renewal of drug registration with synthetic and semi-synthetic active ingredients, classified as new, generic and Similar, and other measures published by the ANVISA vide Board Resolution - RDC No. 200, OF 26 OF 2017 DECEMBER can be identified at http://portal.anvisa.gov.br/documents/10181/3836387/RDC_200_2017_COMP.pdf/3b8c3b31-24cb-4951-a2d8-8e6e2a48702f.

Reference Product - innovative product registered at the federal agency responsible for sanitary surveillance and marketed in the country, whose efficacy, safety and quality have been scientifically proven by the competent federal agency, upon registration (Law No. 9.787 of 10/02 / 1999);

Generic Drug - drug product similar to a reference or innovative product, which is intended to be interchangeable with it, usually produced after the expiration or waiver of patent protection or other exclusivity rights, proven its effectiveness, safety and quality, and designated by DCB or, in his absence, by the DCI (Law No. 9,787, of 10/02/1999);

Similar Drug - one that contains the same or the same active ingredients, has the same concentration, dosage form, route of administration, dosage and therapeutic indication, and which is equivalent to drug product registered at the federal agency responsible for health surveillance, which may differ only features relating to size and shape of the product, shelf life, packaging, labeling, excipients and carriers must always be identified by its trade mark; (Provisional Measure No. 2190-34, 2001);

New Medicine - Medicine with Input Active Pharmaceutical API again in the country;

Innovative Drug - Drug with incremental innovation, developing improvements in relation to a drug already registered in the country, including novel salts, isomers or mixture of isomers, esters or ethers molecules previously registered;

GENERIC - Generic Drug Registration

List of Instruction Documents

1. Duly completed FP1 and FP2 petition forms.
2. Proof of payment, or exemption, of the Health Surveillance Inspection Fee (TFVS), by means of a specific Union Recruitment Guide (GRU).
3. Copy of the Operating License of the Company (Health Permit) updated Copy of the Authorization for Operation of the Company published in the DOU or, where applicable, the Special Functioning Authorization, published in the DOU
4. Statement of Simultaneous Registration of a similar and generic drug, 1315/05, if applicable
5. Copy of the updated Good Manufacturing and Control Certificate (CBPFC) issued by Anvisa for the production line in which the drug will be manufactured

6. FOR IMPORTED MEDICINES:
   a) Proof of registration in the country of origin for imported medicines i.e Copy of the Certificate of Registration of the Medication issued by the sanitary authority of the country of origin, or equivalent document, or justification for exemption from this document
   b) Sworn translation of the Certificate of Registration of the Medication, or justification for exemption from this
   c) Statement with the global regulatory situation.
   d) Certificate of Pharmaceutical Product (CPP) in accordance with the standard adopted by WHO or a copy of the letter of approval of the registration in the country of origin, pursuant to article 18 of Law 6360/76.
   e) Sworn translation of the Certificate of Pharmaceutical Product (CPP) or the letter of approval of the registration in the country of origin, pursuant to article 18 of Law 6360/76.
   f) Specify the phase of the drug to be imported as a finished product, bulk or in the primary packaging
   g) Copy of the Certificate of Good Manufacturing Practices and Control (CBPFC), issued by ANVISA, for the production line in which the drug, object of registration, will be manufactured , or a copy of the protocol for requesting inspection for the purpose of issue

of the BPFC certificate accompanied by a copy of a document certifying good manufacturing practice of pharmaceutical products by a valid production line issued by the body responsible for the Sanitary Surveillance of the manufacturer country and the respective sworn translation.

h) FOR PRODUCTS IMPORTED IN BULK OR IN PRIMARY PACKAGING: Copy of the Certificate of Good Manufacturing and Control (CBPFC), issued by ANVISA, for the production line of the company responsible for the packaging stage

7) Documentation on the Active Pharmaceutical Ingredient:
   a) Technical Documentation of the Manufacturer of the Drug (Master File of the Drug DMF) in its latest version.
   b) Document of the official sanitary organ of the country of origin proving authorization for the activity of manufacturing API
8) API Quality Control by the Manufacturer of the Drug:

   a) Comparative table of the specifications adopted by the API manufacturer with the specifications adopted by the manufacturer of the finished product for the API with justifications for any differences.
   b) Document containing API specifications adopted by the manufacturer of the finished product.
   c) Justifications and technical references used to construct the specifications adopted by the manufacturer of the finished product for the API.
   d) Document containing updated API analytical methods adopted by the manufacturer of the finished product.
   e) Protocols and Validation Reports / Adequacy of analytical methods.
   f) Certificates of analysis of the lots of API used in the manufacture of batches of medicinal products submitted for registration, issued by the manufacturer of the input and by the manufacturer of the finished product.

9) Quality control of excipients by the manufacturer of the Finished Product:
   a) Document containing the specifications adopted.
   b) Document containing updated analytical methods.
   c) Copy of the reference pharmacopoeia used, where applicable.
   d) Declaration of the accomplishment of all the tests listed in the official monograph.
   e) Certificates of analysis of the excipients.
10) Quality Control of Primary, Secondary, Packaging and Wrapping Material:
   a) Description of the materials used in the primary, functional secondary packaging, wrap and accessories, except diluents.
   b) Document containing the specifications and methodologies adopted and adequacy to the general chapters of pharmacopoeias recognized by the agency.
   c) Declaration regarding the performance of all the tests listed in the specifications.

d) Certificates of analysis issued by the manufacturers of the materials and the finished product.

11) Technical Report on the development of the formulation:

a) History of batches produced during development with the detailing of the qualitative and quantitative composition and its relation with the studies of equivalence, bioequivalence, stability and other applicable tests.
b) Critical evaluation of the formulation of the product subject to submission with appropriate justification of the components used in the formulation in qualitative, quantitative and functional aspects.
c) Characterization of the API with respect to particle size and solubility or technical justifications regarding the need of this characterization.
d) Characterization of the API for the polymorphism with the evaluation of possible conversions between the polymorphic forms during the manufacturing and throughout the stability study of the finished product. Justify the impact of polymorphs on efficacy, safety of the product and controls in the desired way.
e) Characterization of the API as to its enantiomeric forms and their respective impact on the efficacy, safety of the product and the controls in the desired way.
f) Safety data of the innovative use of excipients in the formulation, including use in a new route of administration.
g) Technical justification of the choice of the specification (physical-chemical characteristics) of the excipients that may impact the final performance of the product or manufacturing process.
h) Demonstration of the effectiveness of the preservative system.
i) Technical justification for the use of additional quantities of the API in order to compensate for losses in the production process.
j) Dissolution method development report.
k) Assessment of the compatibility of the API (s) with the excipients.
l) Assessment of the compatibility of the primary packaging with the product, including extractable and leachable for parenteral and inhalation products.
m) Documentation proving the functionality (effectiveness) of the grooves in case of grooved tablets and justification / rationale for the presence of groove.
n) Study of the degradation profile for all concentrations, according to RDC 53/15.
o) Identification data of degradation products that exceed the limits described in Art. 9, § 4 of DRC 53/15.

12) Manufacture and Packaging Instruction:

a) Flowchart of the manufacturing and packaging process, containing all unit operations, inputs and outputs of materials, process controls, identification and operational parameters of the equipment used and description of the generated intermediates that are stored.

b) Copy of the Instruction of Manufacture and Packaging of a lot of each concentration, with due record of execution of all steps related to production and packaging.
c) Annex I of RDC 200/2017 filled with data from the other batches, including copying of the reports of analysis of the quality control of the medicament, the weighing sheets, the performance calculation sheets of the handling, packaging and final stages.
d) Certificates of analysis for the three lots of each concentration.

13) Summary report of the process validation

14) Quality Control of the Finished Product carried out by the Manufacturer.
a) Document containing the specifications adopted by the manufacturer of the finished product.
b) Justifications and technical references used to construct the specifications adopted by the manufacturer of the finished product.
c) Description of the General Chapters applicable to the product according to the pharmacopoeias recognized by the agency with due technical justification if any tests are not covered.
d) Rationale for non-performance of the residual solvent test in cases where it is not specified in the specification.
e) Document containing updated analytical methods.
f) Declaration if the methods and specifications cited in the previous item are also used for stability purposes and, if not, technical justifications for the difference.
g) Protocols and Validation Reports / Adequacy of analytical methods for all companies involved in the flow of development or transfer of analytical method.
h) Graphical representation of the dissolution profile of 1 batch submitted for registration.

15) Product Quality Control performed by the Importer:
a) Comparative table of the specifications adopted by the manufacturer of the finished product with the specifications adopted by the importer with the justification of the differences.
b) Document containing the specifications adopted by the importer of the finished product.
c) Document containing updated analytical methods.
d) Protocols and Validation Reports / Adequacy of analytical methods performed by the importer.

16) Certificate of analysis issued by the importer for each concentration.
Stability studies of the finished product:
a) Protocols for accelerated and long-term stability studies conducted with 3 (three) lots for each concentration.
b) Reports on the results of accelerated and long-term stability studies, including evaluation and discussion of the results obtained and analyzes of statistical trend, where applicable, and conclusions on conservation care and shelf-life
c) Protocols for stability studies conducted with 3 batches for each concentration of the medicinal product which, after being opened or prepared, may be subject to change in its original shelf-life or original preservation care.

d) Reports of stability studies after reconstitution / dilution and stability in use, including discussion of the results obtained and conclusions regarding the conservation care and shelf life.
e) Protocols of photo stability studies conducted with 1 (one) batch for each concentration in the industrial condition.
f) Reports of photo stability studies, including discussion of the results obtained and conclusions regarding conservation care and shelf life.

17) Documentation and evidence regarding the inclusion of more than one place of manufacture of the drug or more than one place of manufacture of the active pharmaceutical substance (IFA), according to the specific legislation in force of post-registration alterations

18) Diluent / reconstituent solutions:
a) For diluent / reconstituent solution registered with Anvisa: state the registration number or process number filed with Anvisa.
b) For diluent / reconstituent solution not registered with Anvisa: documentation according to specific legislation in force.

19) Statement signed by the legal guardian that the company will submit the following additions within 10 days after submission of the registration:
- 10471 - GENERIC - Addition to the application for registration with the Registration Document Information Form (FIDR), exclusively by electronic means
- 11212 - GENERIC / SIMILAR - Addition of package leaflet, labeling and trade name, exclusively by electronic means
- 10416 - GENERIC - Addition of a relative bioavailability study or Bioisemption, for CETER, in cases of bioequivalence or bio-registration study registration based on the biopharmaceutical classification system (SCB)
- 11314 - GENERIC / SIMILAR MEDICINAL PRODUCT - Addition of impurities qualification study and degradation products

20) Pharmaceutical Equivalence:
a) Certificates of pharmaceutical equivalence for each concentration.
b) Partial validation of analytical methods by the center.

21) Pre-bioequivalence dissolution profile:
a) Certificate of comparative dissolution profile (biolote versus reference drug).

22) Partial validation of the analytical method by the center. Biosemption - pharmaceutical form: Rationale for bio-recognition depending on the pharmaceutical form.

23) Bioisention for other dosages:
a) Rationale of proportionality between the formulation of the biolote and the formulation of each concentration subject to bio-recognition.
b) Comparative dissolution profile between the biolote and one batch of each concentration subject to bioisation.

24) Final bioequivalence or bio-survey report based on the biopharmaceutical classification system (SCB).
    a) Technical report with the results and evaluation of the Pharmaceutical Equivalence Study conducted by REBLAS Laboratory with the drug reference in the country, following the criteria of the Guide for Study Execution and Elaboration of the Pharmaceutical Equivalence Report and dissolution profile. FOR THE CENTER WHICH CARRIED OUT THE BIOEQUIVALENCE STUDY: a copy of the Certificate of Good Practices in Bioavailability and Bioequivalence of Medications, issued by ANVISA, or in the absence thereof, a copy of the protocol of the inspection request for certification purposes, or justification for exemption of these documents
    b) Technical report with the results and evaluation of the Bioequivalence Study, carried out with the reference medicine marketed in the country, following the criteria of the Guide for Tests of Relative Bioavailability / Bioequivalence of Medicines, or justification of the exemption of this document
25) In cases where the company has selected the drug that is the subject of the present case as a priority in the petition system and this prioritization is justified under Article 3-V of RDC 204/2017, in addition to the justification due to Article 3-V , it should be reported jointly in this item if the reference drug is protected by patent and, if so, inform the numbers of related patent applications, as required by §3, art. 3 of DRC 204/2017

RENEWAL OF REGISTRATION

To refresh effect of the drug registration at Anvisa, all companies in the first half of last year's record valid for five years already granted, shall present:

I - application forms, FP1 and FP2, duly completed and signed;

II - Proof of payment of SanitáriaTFVS Surveillance Inspection Fee and its Union GRU Gathering Guide, or exemption, if applicable;

III - Executive summary in Portuguese for the period of five years from the Periodical Pharmacovigilance Report for the same period; and

IV - Document of sale last five years of the term of registration, containing the numbers of invoices issued in Brazil and buyers establishments ratio at a minimum of one (1) invoice issued in Brazil by pharmaceutical form and concentration.

Fee Structure:

- For Originator Drug: 2700 USD – 27000 USD depending on the size of manufacturer
- For generic drug: 2000 USD
- For Similar product: 7000 USD.

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Details of importing country embassy in India: **http://novadelhi.itamaraty.gov.br/en-us/**

Contact details of Indian Embassy abroad**: http://www.eoibrasilia.gov.in/**

List of Local Pharma Associations:

➢ India Brazil Chamber of Commerce Rua Paraíba, 523, Belo Horizonte, Brazil Employees	Phones: +55 31 3264-5444 / +55 31 3055-3836 india@indiabrazilchamber.org www.indiabrazilchamber.org
➢ Brazilian Association of Distributors and Importers of Pharmaceuticals Raw Materials.	www.abrif ar.org.br
➢ Brazilian Research-based Pharmaceutical manufacturers Association	https://www.interfarma.org.br/