IJBPAS, April, 2024, 13(4): 1545-1554

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

A REVIEW ON POST COVID REGULATORY REQUIREMENTS FOR GENERIC DRUG PRODUCT REGISTRATION IN LATIN AMERICAN COUNTRIES ARE COMPARED (BRAZIL, CHILE, BOLIVIA AND HONDURAS)

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Received 17th April 2023; Revised 15th May 2023; Accepted 3rd July 2023; Available online 1st April 2024

https://doi.org/10.31032/IJBPAS/2024/13.4.7809

ABSTRACT

The drug registration process to acquire marketing authorizations for medicines in Latin American countries is highly country specific despite of various regional harmonization activities. Organizations must short out an effective worldwide strategy to get into the environment of pharmaceutical industry in Latin America so that complex and vivid requests from reviewer's can be solved without delaying local product launches. In this study four LATAM countries (Brazil, Chile, Bolivia and Honduras) were selected based on the increasing number of populations, prevalence of disease, increasing pharmaceutical imports and rise in economic growth. Study the Post Covid generic drug product registration guidelines and identify the change between Before Covid and Post Covid. There is regional "CTD-like" application for Brazil and Chile. For Bolivia and Honduras countries has its own requirements regarding to drug registration. The one major post covid change in the ANVISA (Brazil regulatory authority) the change is in GMP. ANVISA provides TEMPORARY GMP for the company after covid for the Medicine or health product used

in cases of serious health risk intended for the control, diagnosis, prevention or treatment to meet the health needs caused by the new Corona Virus

Keywords: Generic Drug, Latin American regions, Regulatory requirements, Product Registration, Regulatory Body, Common Technical Document (CTD), Corona Virus

INTRODUCTION:

- The pharmaceutical industry in LATAM has expanded. It has recently experienced remarkable growth. They consider the product when developing policies and processes. LATAM has been the pharmaceutical industry's fastest-growing area since 2008 **[10]**. Each nation in this region has its own set of regulations and laws guiding the approval of medications. Industries from other nations who want to register their products must abide by these rules and submit the required paperwork.
- Brazil, Chile, Bolivia, and Honduras are the nations that make up the LATAM area. Regulatory agencies have authority over the pharmaceuticals' value, protection, and quality. The generic medication business in Latin America is currently expanding quickly.
- In terms of dosage, dangers, potency, side effects, and intended usage, generic medications are bioequivalent to brand-name medications. These medications can have size, color, shape, and packaging variations from their branded counterparts **[12]**.
- List of countries under Latin America **[11]**:

  Brazil, Mexico, Colombia, Argentina, Peru, Venezuela, **Chile,** Ecuador, El Salvador, Costa Rica, Guatemala, Cuba, Haiti, **Bolivia,** Dominican republic, **Honduras**, Paraguay, Nicaragua, Panama, etc.

➢ **MARKET OF GENERIC DRUG IN LATIN AMERICA [12]:**

- It was predicted that by 2026, the market for generic drugs in Latin America will be worth over 51 billion dollars, up from an expected 37 billion dollars in 2021.
- Among Latin American nations, Brazil had the largest market for pharmaceutical products in 2020. The demand for generic medications in the countries of Latin America is growing every year, according to data. In recent years, the LATAM pharmaceuticals market has experienced tremendous expansion.
- Development in this area is driven by the developing pharmaceutical industry in Latin American nations, for example, Brazil, Mexico, and Argentina; expanding

focal point of MCs on putting resources into the pharmaceutical and medicinal services parts in Latin America; quick development in maturing populace and the ensuing increment in the commonness of related infections; and the accessibility of nearby and government subsidizing for R & D exercises.

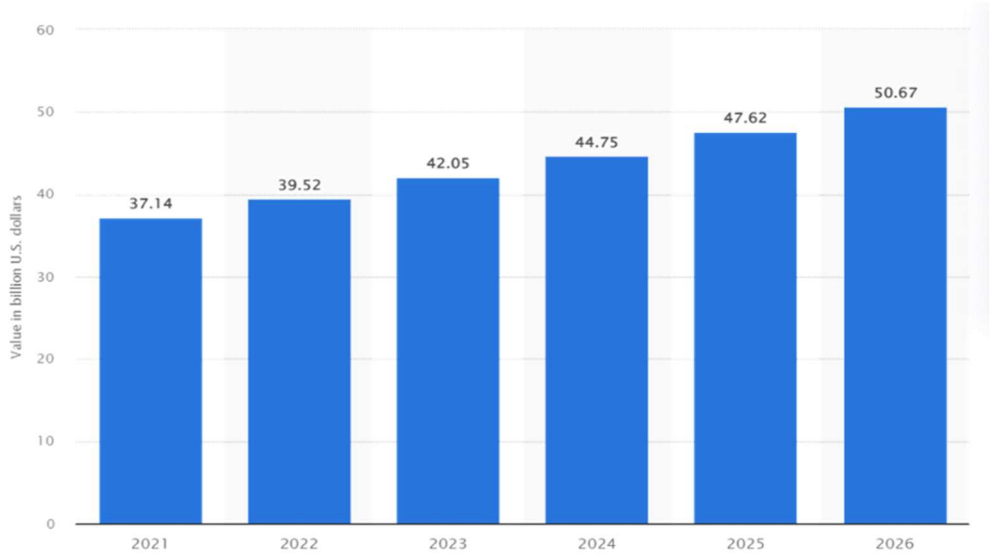

Figure 1

- **INTRODUCTION OF SELECTED COUNTRIES**:
- **BRAZIL:**

- Regulatory body: National Health Surveillance Agency (ANVISA) was established by law 9.782 of January 26,2004. The agency is an independently administered, financially autonomous regulatory agency, with security of tenure for its directors during the periods of their mandates. The agency is managed by a collegiate board of directors, comprised of 5 members.
- Product registration in Brazil is a time-consuming process that must be sought by the local manufacturer Brazilian based office of the foreign company or its distributor in Brazil. The registration is valid for 5 years can be renewed continuously for the same period. Law must complete the registration within 90 days after the registration is required, or denied.
- From 2015 to 2022, the generic medication market in Brazil was predicted to rise significantly **[13]**. The generic medication market is currently

worth USD 16.6 billion. Over the next five years, it is anticipated that the patent on some branded medications worth about USD 2 billion would expire **[14]**.

- The country's regulatory agency is now a model for other Latin American countries. ANVISA regulates all registration, import, export of medicines in Brazil
- At the end of the 1980s, when senators and representatives were debating drug prices, forgery, smuggling, and concerns pertaining to controls and inspections, the history of generic medications in Brazil began.

➢ **CHILE:**

- Regulatory body: Ministry of health. Current market size for generic drug is USD 3.7 Billion **[1]**. In the past ten years, Chile has created a number of pharmaceutical policies with the goal of enhancing patients' access to medications.
- The generic substitution policy, which was intended to improve market competition by regulating the substitution of generic products for original pharmaceuticals, was one of the most significant measures introduced in 2014 **[1]**.
- The use of generic drug is mandatory and a large number of generic drugs are marketed
- The Bacteriologic Institute (Instituto Bacteriológico) was established in 1929 as a part of the Ministry of Social Welfare (Ministerio de Bienestar Social), and it was responsible for general health and sterility until 1980. The current Institute of Public Health of Chile was developed at the time the Supreme Decree No. 79 was recently granted on April 1st, 1980. The Department of Public Health's Regional Health Department (Secretarias Regionales Ministeriales de Salud, SEREMI) is in charge of certifying the validation of pharmaceutical products.

➢ **BOLIVIA:**

- Regulatory body: Medicines and Laboratory Accreditation Unit (UNIMED) under Ministry of Health. Current market size for generic drug is USD 1.3 Billion
- The ministry o health is governing body of the sector that promotes and guarantees the rights and duties to the health of Bolivians. Through the regulations and execution of policies inclusion and access to

comprehensive, intercultural health of individuals, families and communities without exclusion or discrimination, implementing the Community Family Health Intercultural Policy, the Unified Health System with social participation.

- India is 3rd largest exporter of pharmaceuticals to Bolivia. Bolivian pharmaceutical production is limited & there is virtually no local production **[15]**. Bolivia relies heavily on imported medical products
- That is why it is potential market

➢ **HONDURAS [16]:**

- Regulatory body: Sanitary Regulation Agency (ARSA)
- Current market for generic drug is USD 621 Million. Honduras public spending on health is approximately 4 percent of its GDP
- 4th largest pharma market in Central America. Country heavily depends upon imports of pharma goods. No legal production or small-scale production
- Market is dominated by low-cost generic medicines high demand for cost effective. Low-cost generic medicines will continue to dominate market as the government look to improve healthcare coverage within a limited budget.
- The has underdeveloped health care system, weak regulatory environment low level of affordability will hold back innovative medicines sales
- Honduras has a legitimate and institutional structure for approach advancement and reinforcing of institutional limit with regards to general wellbeing guideline and control. The legitimate system doles out guideline and control capacities to the Ministry of Health through the Bureau of Regulation. Guideline is characterized as "the arrangement of activities through which the State, by means of the approved open organizations, endorses, issues, refreshes, deciphers, applies and implements consistence with the compulsory lawful, specialized, and regulatory gauges to be trailed by all people and lawful substances that give or get merchandise and ventures of clean intrigue."

➢ **COMPARISON OF REQUIRE-MENTS FOR REGISTRATION OF THE GENERIC PRODUCT [2-4, 8, 18-26]:**

Table 1

	Brazil	Chile	Bolivia	Honduras
Regulatory Authority	**National Health Surveillance Agency (ANVISA)**	**Ministry of Health**	**Medicines and Laboratory Accreditation Unit (UNIMED)**	**Sanitary Regulation Agency (ARSA)**
Administration documents comparison				
Application Form	**Required (FP1&FP2)**	✖	✖	✖
Cover letter	✓	✓	✓	✓
Proof of Payment	✓	✖	✖	✖
Approval timeline	**1.5 to 2 Years**	**6 to 8 months**	**6 to 8 months**	**4 to 6 months**
Certificate of pharmaceutical product (COPP)	✓	✓	✓	✓
Free sale certificate	**Not required if COPP is submitted**	**Not required if COPP is submitted**	**Not required if COPP is submitted**	**Not required if COPP is submitted**
GMP certificate	✓, **Issued by ANVISA**	✓, **WHO-GMP format**	✓, **WHO-GMP format**	✓, **WHO-GMP format**
License for pharmaceutical manufacturing	✓	✖	✓	✖
Site master file	✖	✓	✓	✖
Permission for manufacturing & Marketing in country of origin	✓	✓	✓	✓
Letter of Authorization	✓	✖	✖	✖
TSE/BSE Free Certificate	✓	✓	✖	✖
Pharmacovigilance Data	✖	✖	✖	✖
Labelling documents	✓, **In Portuguese as per local regulations**	✓, **In Spanish as per local regulations**	✓ **(Only 1 label)**	✓ **(Only 1 label)**
Summary of product characteristics	✓	✖	✖	✖
Patient information leaflet	✓	✓	✓	✓
Package insert	✓	✓	✓	✓
Dossier language	**Portuguese**	**Spanish**	**Spanish**	**Spanish**
Technical documents comparison				
Drug substance				
General information	✓	✓	✓	✓
Quality and quantitative formula	**Required as dose/unit**	**Required as dose/unit**	**Required as dose/unit**	**Required as dose/unit**
Reference standard	✓ **(When applicable)**	✓ **(When applicable)**	✓ **(When applicable)**	✓ **(When applicable)**
Container closure system	**Required for primary and secondary packaging**	**Required for primary and secondary packaging**	**Required for primary and secondary packaging**	**Required for primary and secondary packaging**
Drug master file	✓	✓	✖	✖
Batch manufacturing record	✓	✓	✖	✖
Raw material specification	✓	✓	✓	✓
Material safety data sheet	✓	✖	✖	✖

Raw material Method of Analysis (MOA)	✓	✓	✖	✖
Spectrum or chromatogram	**Required for identity of the API**	**Required for identity of the API**	✖	✖
Certificate of analysis (COA)	✓	✓	✓	✓
Stability	✓	✓	✓	✓
Drug product				
Description & composition	✓	✓	✓	✓
Manufacturing process	✓	✓	✓	✓
In process quality control	✓	✓	✓	✓
Quality control of excipients	✓	✓	✓	✓
Process validation	✓	✓	✓	✓
Site master file	✖	✖	✖	✖
Finished product specification	✓	✓	✓	✓
Product monograph	✓	✖	✓ **(Summary)**	✓ **(Summary)**
Product permission	✓	✓	✖	✖
Analytical method validation	✓	✓	✓	✓
Finished product analytical process	✓	✓	✓	✓
Justification of specification	✓	✖	✖	✖
Batch analysis	✓ **(At least 3 commercial batches)**	✓ **(At least 3 commercial batches)**	✓ **(At least 3 commercial batches)**	✓ **(At least 3 commercial batches)**
Batch coding system	✓	✖	✖	✖
Container closure system	**Required for primary and secondary packaging**	**Required for primary and secondary packaging**	**Required for primary and secondary packaging**	**Required for primary and secondary packaging**
Stability protocol	✓	✓	✓	✓
Finish product stability	**Required, 30°C ± 2°C & 75% ±5% RH for long term stability study, 40°C ± 2°C & 75% ±5% RH for accelerated stability study for 3 batches**	**Required, 25°C ± 2°C & 60% ±5% RH for long term stability study, 40°C ± 2°C & 75% ±5% RH for accelerated stability study for 3 batches**	**Required, 30°C ± 2°C & 70% ±5% RH for long term stability study, 40°C ± 2°C & 70% ±5% RH for accelerated stability study for 3 batches**	**Required, 30°C ± 2°C & 65% ±5% RH for long term stability study, 40°C ± 2°C & 75% ±5% RH for accelerated stability study for 3 batches**
Certificate of Analysis (COA)	✓	✓	✓	✓
Periodic Safety Update Report	✓	✖	✖	✖
Non-clinical data				
Non-clinical data	✖	✖	✖	✖
Clinical data				
Clinical data	**BA/BE study required as per applicability**	**Bioequivalence study required as per applicability**	**BA/BE study required as per applicability**	✖

CONCLUSION:

- Regions in Latin America fall under the category of "Emerging Markets" for pharmaceutical export. The LATAM region's drug product policies are promoting the import of high-quality generic medicines from other nations. For the purpose of registering a medicinal product in a reference nation, the LATAM area adheres to regional submission formats. The generic medication product registration in Latin American nations is essentially the same as it was in the four countries that were chosen.
- One major Post Covid change in Brazil guidelines that is in GMP (Good Manufacturing practice) ANVISA provides the TEMPORARY certification for GMP.

➢ Only in cases,

- Medicine or health product used in cases of serious health risk intended for the control, diagnosis, prevention or treatment to meet the health needs caused by the new Coronavirus
- Essential product for the maintenance of life whose availability is threatened by shortage

Acknowledgements: NA

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