

## International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: [www.ijrpns.com](http://www.ijrpns.com)



### LATIN AMERICAN PHARMACEUTICAL REGULATORY ENVIRONMENT - REVIEW ARTICLE

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#### ABSTRACT

The regulatory process to obtain marketing authorisations (MAs) for drugs in Latin American (LATAM) countries, despite regional harmonisation efforts, is highly country-specific. Complex and evolving ad-hoc requests from reviewers must be proactively addressed to avoid costly delays or show-stoppers to local product launches. This article offers a pharmaceutical regulatory environment in LATAM, resulting from more than a decade of experience in a biotech company, to ensure successful global regulatory strategy. The quality, safety and efficacy data has its own importance in the registration dossier. The commercial significance of markets is increasing globally. It is vital for pharmaceutical industry to cope with the regulatory requirements for betterment of public and to ensure their place in the market. Although the International Conference on Harmonisation (ICH) Common Technical Document (CTD) can serve as a resource for most local MA applications, it is not necessarily required in its full length. Additionally, a significant amount of mandatory and highly country-specific documentation (related to infrastructure, legal documents, stability studies, labelling, etc) require strategic planning and allocation for successful and timely local approvals. Exhaustive identification of actual requirements can present challenges due to frequent changes in regulations, unclear expectations, etc. Having as much early visibility and command of the LATAM country-specific requirements and health authorities' (HAs) expectations will help the pharmaceutical industry to improve planning for global MA applications, optimally manage internal expectations, and most importantly give patients in the region faster access to therapies and better quality of life.

#### KEY WORDS

Legislation, Latin America, Marketing authorization and Latin America manufacturing practice.

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#### INTRODUCTION

The LATAM pharmaceuticals market has grown steadily in the past 15 years. It has also been dominated by multinational companies based in Europe and the US<sup>1</sup> that have spread to these emerging economies mainly to expand their businesses or to find untreated patients for clinical trials.

This trend has also influenced the evolving growth of the local drug regulations in the LATAM region: with the rapid introduction of high-technology medicines into import, export and distribution networks, it has become critical for each HA to guarantee that the medicines allowed to reach local patients are in compliance with specific standards of quality, safety and efficacy<sup>2</sup>.

With varying levels of sophistication, resources and overall expertise, each LATAM HA has strengthened its health legislation. The region offers a wealth of opportunity for both the pharmaceutical industry and local patients but the variation in the drug registration processes causes time-consuming and costly obstacles for companies.

Based on more than ten years of experience registering drug products in LATAM, this article provides a practical overview of drug registration requirements in the region, with specifics on issues critical to consider for efficient regional regulatory strategies.

The main focus here relates to MAs for prescription drugs (including biologics/biotech). It does not cover the registration processes for devices, biosimilars/generics or clinical trials.

Countries in Latin America need to harmonize their basic vocabulary on pharmaceutical products and agree the technical procedures needed to ensure the quality of multisource products. Drug regulatory agencies need to be strengthened so that the population can have confidence in the quality of the drug supply. Agreeing on basic principles would also facilitate the exchange of information, the ability to build on one another's experience and the study of how different pharmaceutical policies affect the affordability of and access to pharmaceuticals.

#### **Latin America's Growing Pharma Industry**

Latin America has been a long sought after, though difficult to penetrate pharmaceutical market. With the market size of Latin America at \$66 billion as of May 2012, many companies have developed strategies to enable access to a portion of this growing market. Part of these strategic discussions center around how to address different regulations between countries in the region and the various

components required to register a product from country to country.

Adaptation and Growth - For years, pharmaceutical companies have turned to emerging markets as low cost manufacturing destinations, utilizing lower wages and, frequently, less stringent environmental, health and safety regulations.

As emerging markets capture a greater share of the global pharmaceutical market, these countries are altering and adapting their regulations to compete with the quality expectations of highly regulated markets like the EU and U.S., while addressing their own sourcing needs.

Led in large part by substantial growth in Brazil and Mexico, countries in Latin America are firmly establishing their place in the market<sup>3</sup>.

#### **Indication of the region**

With the exception of Mexico, located in North America, all LATAM countries are situated in either Central America (Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama), South America (Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Peru, Suriname, Uruguay, and Venezuela), or the Caribbean (more than 20 countries and territories including Aruba, the Bahamas, Cuba, the Dominican Republic, Haiti, Jamaica, and Trinidad and Tobago).<sup>4</sup> This region has a population of 582.5 million,<sup>5</sup> compared with approximately 734 million in Europe,<sup>6</sup> with 80-85% of the population concentrated in metropolitan areas. LATAM is ethnically and geographically diverse. From a practical perspective, the first language of most Latin Americans is Spanish except for Brazilians, who speak Portuguese. Other languages are spoken (for example, English in Trinidad and Tobago, French in French Guiana, and Dutch in Suriname) but only by a minor fraction of the population. The Spanish language varies markedly between countries, especially the more vernacular or spoken language.

Socioeconomic and demographic factors, like literacy and quality of healthcare, also present with strong variations between countries, and, within countries, between urban and suburban areas.

Culturally, the panoply of countries of this region is as varied as their geography, which runs from impressive mountains to coastal lowlands, from tropical rainforest, arid deserts and vast grasslands to cold, windswept Patagonia. This diversity influences the politics and to a certain extent contributes to the HAs' idiosyncrasies.

#### **Key trends**

The main key pharmaceutical trends that have been detected for the region in the short to medium term are several, and one of the most important is likely to be the fast growing domain of the generics market in the region. By 2015, branded and unbranded generics are expected to be growing faster than patent protected and non-protected branded drugs. In the region, pharmaceutical sales are growing fast and especially in the areas of vaccines, oncology, high cost medicines, biologicals and rare diseases. In terms of demand, there is an increasing demand for drugs as more people move into middle class, urging the region to increase drug access in spite of intensifying cost containment measures taking place in most countries. Additionally, attractive opportunities have arisen for biopharmaceutical producers in Latin America, also due to the first biotech drugs having gone off patent recently, allowing for the emergence of a new Biosimilars market that still represents a consistent regulatory challenge in many Latin American markets.<sup>7</sup>

#### **Latin America health and pharmaceutical market overview**

With its population reaching 6 million people in 2011 (WHO 2012)—Argentina Brazil and Mexico accounting for 60% of the population—Latin America is a fast growing region with equally fast growing economies. Brazil, Mexico, Argentina and Colombia are considered as the “top 4” Latin American economies and pharmaceutical powers. As a pharmaceutical market overview, Latin American sales in 2011 were at USD 62.9 billion, registering a 8.9% growth in 2012, which is particularly significant if considered within the wider picture of a global market value of USD 995 billion dollars in 2011 (source: WHO 2012).

In 2009, the national expenditure average in Latin America represented 85 of the region's GDP, equivalent to a per capital annual expenditure of USD 671 USD divided partly into public expenditure and partly into private out-of-pocket expenditure and payments made through insurance schemes. Latin America is also experiencing a transition in major health risk trends, going from infectious diseases to more traditionally westernized health risk trends such as hypertension, obesity, cancer, ischemic heart diseases and diabetes. This significant change in demographics, disease patterns, economics and market size are creating new challenges for domestic and international pharmaceutical companies operating in the country. Companies are facing other considerations such as emerging science, new products and services, shifting demographics, evolving regulations and transformed business models which consequently trigger increased stakeholder expectations in the region.<sup>7</sup>

#### **Specific considerations of the drug registration process**

Unlike the EU or the Association of Southeast Asian Nations (ASEAN) countries, LATAM drug registration processes are not harmonised. Substantial harmonisation efforts have been ongoing for the past fifteen years, mainly through the initiative of the Pan American Health Organization (PAHO) via the Pan American Network for Drug Regulatory Harmonization (PANDRH). PANDRH has periodically generated recommendations for a number of key topics (including pharmacovigilance and pharmacopoeias) to strengthen local HAs and regional regulatory harmonisation.<sup>8</sup> However, in practical terms, every country has its own regulatory requirements. There is no regional “CTD”-like application and each MA application needs to be planned and executed as per the requirements of each country's HA, thus bringing country-specific challenges to pharmaceutical companies seeking marketing penetration in the region.

To date, there are five national reference authorities in the region, as recognised by PAHO, those from Argentina, Brazil, Colombia, Cuba, and Mexico.<sup>9</sup>

Recent attempts at homologation, or allowing the approval from one regional reference authority to facilitate approval in another country, have presented challenges. For example, a homologation process was recently announced for both El Salvador and Ecuador if an approval from the Mexican Federal Commission for the Protection against Sanitary Risks (COFEPRIS) is granted.<sup>10</sup> Salvadorean and Ecuadorian experts, however, have confirmed that, from a practical point of view, this is still in the process of implementation until the local HAs issue further regulations related to this initiative. Thus, to date, registration in these countries must be pursued independent of Mexican approval, and according to local requirements.

## DISCUSSION

One of our most important findings was that the term generic means different things between and within countries. With the exception of Brazil, which has about 1033 generic pharmaceuticals, the markets in the rest of the Latin American countries studied have few drugs proven to be therapeutically equivalent or interchangeable with the proprietary product. The result is that generic drug policies relate to the use of similar drugs (or copies), and in daily speech most policy-makers, consumers, and many health professionals use the terms generic and similar interchangeably, which further confuses the issue.

Indiscriminate use of the term generic in Argentina is a good example of the confusion that can be produced. When in 2002 the Minister of Health announced his initiative to promote the use of generic drugs (resolution 326 and law 25.549) national and provincial medical associations pointed out that none of the drugs sold in the country as generic had proven bioequivalence as required by law. The Argentine pharmaceutical market did offer many similar drugs under branded and INN names, and the intent of the initiative was to stimulate competition among drug producers so that expensive branded originals could be replaced with similar drugs. The government expected that the new

initiative would promote competition and lower prices, resulting in increased accessibility.<sup>11</sup>

The ambiguity of the term generic was one of the reasons why some medical associations and consumer groups opposed the policy. For them the quality of the similar drugs was questionable. Although the term generic includes a quality component the government had limited its mandate to prescribing by generic name (that is, it used the word generic to indicate that prescriptions had to be written using nonproprietary names) and substituting similar drugs for proprietary drugs. For obvious reasons the pharmaceutical industry also opposed the policy. All those who opposed the generic initiative used this opportunity to claim that similar drugs or copies could be unsafe and of poor quality, and that the ministry did not adequately regulate the production of drugs.<sup>12</sup>

Many parties have an interest in how pharmaceutical products are classified. Some countries in the region have developed a typology that includes three types of drugs: original, similar and generic. The others use a binary classification of branded and generic products. WHO has proposed a different typology: single source and multisource pharmaceuticals. Single source pharmaceuticals correspond to the original drugs (usually on-patent), while multisource drugs can be produced by multiple pharmaceutical firms and include drugs that are pharmaceutically equivalent and may or may not be therapeutically equivalent to the original drug. Single source drugs are usually identified with a brand name, and multisource drugs can be identified by the INN or by brand names. The merging of the categories of similar drugs and generic drugs offers several advantages.

Drug regulatory agencies have to ensure that the supply of medicine is safe and that medicines are efficacious for treating the ailments for which they will be prescribed. In the case of multisource drugs, however, there is no agreement on the tests that each pharmaceutical product should undergo in order to be considered to have met acceptable efficacy and safety standards. For some products it is sufficient to document that the new product is pharmaceutically

equivalent to the original drug; in other cases therapeutic equivalence needs to be proven. Therapeutic equivalence can be proven by clinical trials, in vitro or through pharmacodynamic studies. The type of testing used has significant implications in terms of costs, technical capacity and time. Consequently, those parties interested in restraining competition advocate for lengthy testing and those interested in expediting the availability of cheaper versions of drugs argue for limited testing that is sufficient to guarantee the efficacy and safety of most drugs.

Our study documented high levels of confusion among our respondents (all of whom were working in regulatory agencies or were pharmaceutical experts). Therefore, it is not useful to maintain the classification of pharmaceutical products commonly used in Latin America. The classification of products that we used in our survey was inappropriate but because there is a lack of consensus on classifying these products, we would have encountered the same problem if we had selected a different typology. Interestingly, our respondents also had different interpretations of the word bioequivalence. For some the term implied that clinical trials had to be conducted to ensure that the generic product was pharmaceutically equivalent and its bioavailability was the same or similar enough to have essentially the same effects as the proprietary drug. Others used the terms bioequivalence and interchangeability indiscriminately and asserted that for a drug to be classified as a generic it had to be interchangeable with the reference product. Documents from Chile<sup>13</sup> specify that the test of bioavailability can be done in vitro.

Our findings suggest that countries are trying to reach agreement on the type of testing that needs to be done before the commercialization of multisource drugs can be approved. Argentina, Brazil, Chile and Costa Rica have developed lists of the pharmaceutical products that need to be tested for therapeutic equivalence, and these countries have often identified the corresponding tests needed. This is a first step. Ideally such a list would include all

products and the types of tests needed, if any, before a drug can enter the market. The tests for many products will be simple and inexpensive.

The case of Brazil highlights some of the difficulties encountered in making these types of determinations. Brazil passed resolution number 391 in September 1999; it stated that for a product to be registered as generic there was a need to prove bioequivalence. Subsequently, the requirement for proving bioequivalence was modified (in February 2002 by resolution 10 and in March 2002 by resolution 84). Resolution 10 included a list of medicines that for safety reasons could not be registered as generic drugs. (Uruguay has a similar list and Colombia is considering adopting one.) Resolution 10 also mandated the creation of a guide to substitute bioequivalence testing with other tests to demonstrate the interchangeability of the new product with the reference drug. In addition, resolution 84 modified the list of products identified in resolution 10. Other issues under discussion in Brazil include the determination of the minimum number of volunteers needed to demonstrate bioavailability and bioequivalence in clinical trials.

It is impossible to carry out comparative cross-national studies of generic policies as a result of the lack of consensus on the meaning of the term generic. For example, in our study we found that it was impossible to make cross-national comparisons of the share of generic sales as a proportion of each country's pharmaceutical market or even to compare the number of registered generic and similar products.

#### **Drug Registration**

The regulatory regime in LATAM countries can be divided into three categories i.e. Countries which have established regulations (Brazil, Mexico, and Venezuela) to demonstrate the efficacy, safety through clinical trials or Bioequivalence studies with the innovator's product in the drug approval process. The countries as Argentina, Chile, Columbia, Ecuador, and Paraguay also have the regulations for registration of new or generic drug but are less stringent from first category. The last category of countries (Guatemala, Barbados, Bolivia, Nicaragua

and Peru) has imperfectly formed drug regulations for the approval of drugs.

In many of the LA countries the amount of time that the regulatory agency has to register a product is very short. Peru requires the least amount of time for registration: only 7 days. If the regulatory agency fails to prove that a particular product may be harmful during this period of time, the product is automatically registered. Except for Brazil and Chile, which have between 8 and 14 months, the rest of the countries for which we obtained information have less than 6 months to register a product. The 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 ranges between 50 dollars in Bolivia (for 5 years) and \$27,000 in Brazil. Argentina, Brazil and Chile offer significantly lower fees for the registration of generics and similars than for the registration of a new product. Chile and Colombia charge a different fee for registration than for re-validation. Ecuador offers a cheaper registration price to national companies (US \$535) and for essential drugs (US \$344) than to foreign companies (US \$1,339). Nicaragua also favours local producers (US \$485 for a foreign product and US \$166 for a nationally produced drug).<sup>14</sup>

#### **Key Challenges**

1. Lack of harmonization in regulatory requirements
2. Lacking new or changing regulations
3. Lack of quality manufacturing capacity and differences in Labeling
4. Emerging market health authorities have limited resources
5. They necessitate local patients in clinical trials/ B.E study to take part.
6. Lack of sufficient human resources and funding for drug regulatory activities.

7. Lack of sufficient regulatory science capacity to assess generic products that potentially meet the need for crucial drugs.
8. Lack of formal pre-submission meetings or scientific advice.
9. Long review timelines for registration hence more uncertainty.
10. More detailed documentation, SOPs, validation requests

#### **Spotlight on Research and Development**

With the growing emphasis on the timely introduction of life saving drugs for diseases in Latam countries, there has also been an increase in discovery research for diseases that are more prevalent in the region than in the other countries.

#### **Dossier requirements for submission to Regulatory bodies**

- CPP / WHO GMP / Manufacturing license
- Free Sale Certificate
- Letter of Authorization / Power of Attorney
- Dossiers to be submitted in local language
- 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 definitions.

#### **Recommendations for important requirements**

##### **Brazil**

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.

##### **Mexico**

Requirement: BE Study to be done in Mexico

Recommendations: COFEPRIS to accept the BE - study performed in India against Mexico reference

product. The USFDA / ANVISA / UK MHRA approved lab.

Benefits: Time.

**Chile**

Requirement: Process validation completion before BE Batch.

Recommendation: Acceptance of process validation / evaluation report on exhibit batches.

Other General recommendations:

1. In case the manufacturing plant is approved by USFDA / UK MHRA / ANVISA, Latam countries to accept the dossiers along with and FSC. (Eg. Colombia and Chile).

**Table No.1: Comparative Study with Key Requirements for Drug Registration in LATAM Countries**

Requirements/ consideration	Argentina (ANMAT)	Brazil (ANVISA)	Chile (ISP)	Colombia (INVIMA)	Mexico (COFEPRIS)	Peru (DIGEMID)	Venezuela (INHRR)
<b>Dossier language</b>	Specific sections should be in Spanish	Portuguese	Spanish	Spanish	Specific sections should be in Spanish	Spanish	Spanish
<b>Stability condition</b>	30/75	30/75	30/75	30/75	25/60	30/75	30/75
<b>Registration fees</b>	2,300 Rias	5100 Rias	USD 2,231	USD 150	60,100 Mexican pesos 160,000 pesos (Fast Track)	USD 125	USD 175
<b>COPP</b>	Country specific (Legalized)	Country specific (Legalized)	Country specific (Legalized)	Country specific (Legalized)	Country specific (Legalized)	Country specific (Legalized)	Country specific (Legalized)
<b>Are biologics / biotech products regulated as drugs?</b>	No, recent biologics/ biotech regulation was implemented and requires a more complex dossier.	No, recent biologics/ biotech regulation was implemented	No, drugs and biologics/biotech have separate requirements.	Yes, but proposal for the regulation of biologics/biotech is under consideration.	No, recent biologics/ biotech regulation was implemented	Yes, but proposal for the regulation of biologics/biotech is under consideration	No, there are separate requirements for drugs and biologics/biotech.
<b>Orphan drug legislation in place?</b>	Recent regulations (August 2012): complex dossier, pharmacovigilance (PV) plans, monitoring of efficacy, effectiveness and safety plans, labeling requirements, not clear advantages yet.	Decreases 2577/2006, 768/2006, RDC 28/2007, RDC16/2008: in theory allows for priority review – ongoing efforts to issue further new legislation on orphan drugs registration process.	No regulations exist for orphan drugs to date (recent legislation was revoked and to date there is no indication if it will be re-issued).	Law 1392 of 2010 and Law 1438 of 2011; orphan designation application process is not yet defined.	Legal definition for orphan drugs was published in the Official Gazette in January 2012 incorporating article 224 Bis into the General Health Law – further regulations with details on dossier requirements, etc, currently in draft form.	No	No
<b>Requirements / consideration</b>	<b>Argentina (ANMAT)</b>	<b>Brazil (ANVISA)</b>	<b>Chile (ISP)</b>	<b>Colombia (INVIMA)</b>	<b>Mexico (COFEPRIS)</b>	<b>Peru (DIGEMID)</b>	<b>Venezuela (INHRR)</b>
<b>Local Testing</b>	Repetition of release testing during commercialisation	Repetition of release testing during commercialisation	Repetition of release testing during commercialisation	Not required	Repetition of release testing during commercialisation	Not required	Performed by certified laboratory as part of registration.

<b>Labeling Requirements</b>	In Spanish as per local regulations. Mock-ups required for submission. Local registration number and pharmacist details. Recent implementation of traceability codes. HA recently started to request voluntary inclusion of patient leaflet.	In Portuguese as per local regulations. Mock-ups required for submission. Local registration and pharmacist information. Red stripe around box for medicines sold under medical prescription. Pursuing serialized two-dimensional codes.	In Spanish as per local regulations. Mock-ups required for submission. Local registration number and pharmacist details.	In Spanish as per local regulations. Mock-ups required for submission. Local registration number and local distributor details.	In Spanish as per Mexican norm. Local registration, pharmacist, distributor (For orphan drugs, labeling from country of origin is currently allowed).	In Spanish as per local regulations. Mock-ups required for submission. Different product manufacturing sites require different registration number. Source of content based on reference agency approval.	In Spanish as per local regulations. Mock-ups required for submission.
<b>Electronic Submission</b>	No	Yes	Yes	Paper and electronic	No	Yes	Paper and electronic

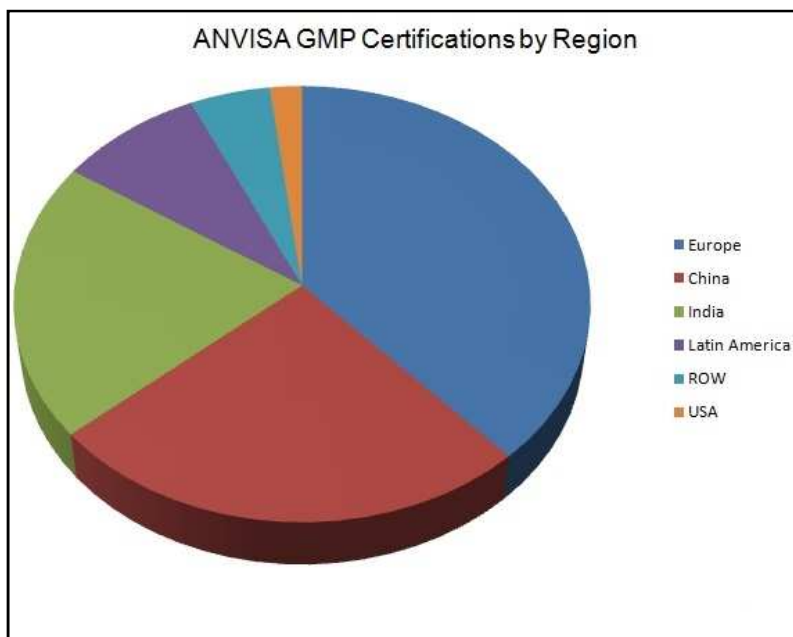


Figure No.1: ANVISA GMP Certifications by Region



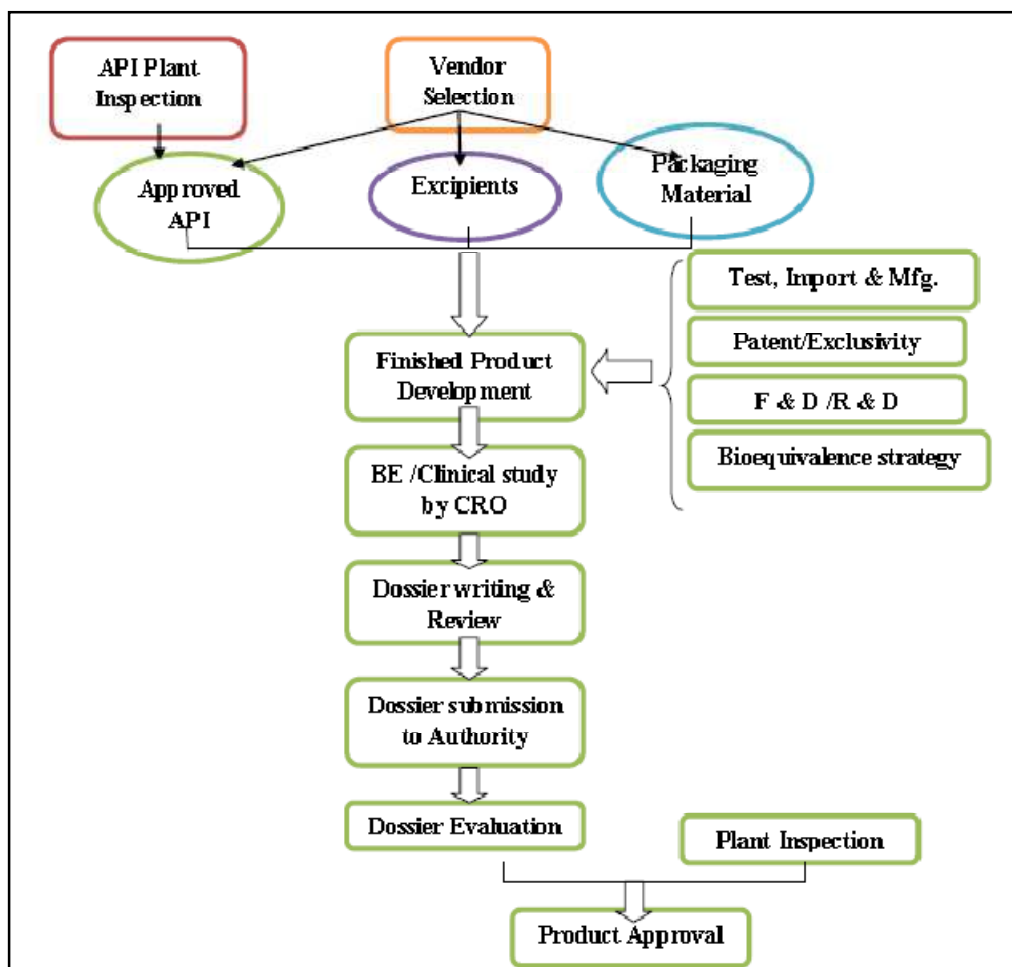


Figure No.2: Regulatory filing process

## CONCLUSION

The LATAM region does not have a centralised or harmonised procedure for drug registration. There are critical differences between countries in the region. As quality requirements and the cost of compliance continue to increase globally, Latin America and other emerging markets will continue to be in focus. Manufacturers continue to seek ways to decrease costs and capitalize on these rapidly growing markets, leading to greater partnership opportunities as governments strive to increase their local capabilities as a means of decreasing healthcare expenditures. Specialized manufacturing necessary for biologics, high potency, and cytotoxic

medications will also drive continued deal-making and regional investment in Latin America. Foreign market players looking to expand their footprint and established players in Latin America will benefit from emerging companies seeking to further develop their manufacturing and expertise in this growing region.

## ACKNOWLEDGEMENT

I would like to thank Krishna Teja Pharmacy College Chadalawada Nagar, Tirupathi-517506, Andhra Pradesh, India for continuous support and encouragement throughout this work.

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