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PHARMACEUTICAL MARKET AND DRUG REGISTRATION PROCESS IN MAJOR LATAM COUNTRIES

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ABSTRACT

The regulatory process to obtain marketing authorisations (MAs) for drugs in Latin American (LATAM) countries, despite regional harmonization 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 Harmonization (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, labeling, 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:- Marketing authorization, Latin America (LATAM), Emerging markets, Pan American Network for Drug Regulatory Harmonization (PANDRH), Certificate of Pharmaceutical Product (CPP), Chemistry, Manufacturing and controls (CMC).

INTRODUCTION

An increasing number of pharmaceuticals are available in the world market and yet many people in developing countries do not have access to medicines that can save lives and/or reduce suffering. To make certain that countries have admission to needed medicines at an affordable price, WHO recommends the use of Essential Drug Lists and implementation of Generic Drug Policies. In recent years many countries in Latin America (LA) have taken steps to increase access to cheaper drugs (Anonymous 1,2).

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Global Market is divided into (Anonymous 3)

1. **Regulated Market:** US, EU (UK, Germany, France, Ireland, and Sweden etc.), Japan, Australia, New Zealand, Canada, and South Africa.
2. **Semi Regulated Market: (ROW Countries):**

a.) **Asia (**Sri Lanka, India, Bangladesh,; ASEAN: 10 Countries group – Philippines, Vietnam, Singapore, Malaysia, Thailand, Indonesia, Laos, Cambodia, Brunei Darussalam, Myanmar**)**
b.) **African countries** (Algeria, Zambia, Ethiopia, Ghana, Kenya, Malawi, Mozambique, Namibia, Nigeria, Sierra Leone, Tanzania, Zimbabwe etc)
c.) **Middle East countries** (gulf cooperation council countries i.e. Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE)
d.) **Latin America** (Mexico, Brazil, Peru, Colombia, Chile, Argentina, Venezuela, Cuba, Panama)
e.) **CIS** (common wealth of independent states): Russia, Ukraine, OFSUs (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kirgizstan, Moldova, Tajikistan, Turkmenistan, Uzbekistan etc.)

Difference from regulated market:

- Degrees of implementation are different.
- Intensity of audits/ inspection is different and similarly penalties for GMP violations are different.
- Regulated market guidelines are very clear and are to be adhered to 100%.

Pharmaceuticals in Latin America

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.

Pharmaceutical market

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.

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 centre around how to address different regulations between countries in the region and the various components required registering a product from country to country (Anonymous 1).

Objective

- To understand the pharmaceutical market in Latin America.
- To study about generic drugs and biosimilar drugs market in Latin America.
- To understand regulatory approval process for Latin American Countries.
- To List out the administrative requirements of documents for registration of drug products in Latin American countries.
- To list out the quality requirements of documents to the countries of Argentina, Brazil, Cuba, Chile, Colombia, Mexico, Peru and Venezuela.
- Comparative study of dossier requirements between Latin American countries (Argentina, Brazil, Cuba, Chile, Colombia, Mexico, Peru and Venezuela).

Methodology

The methodology is as follows

Literature search

- Understanding the different regulatory aspects in Latam countries.
- Searching regulatory websites of Latam countries with special emphasis on the regulatory requirements, review process, documents, timelines, fee requirements that are required throughout the lifecycle of the product and their pharmaceutical market.
- Various published articles related to regulatory strategies, the most critical regulatory concerns that drive the regulatory submission in those countries.

Regulatory submissions

- Types of Registrations and application forms required for the countries.
- Timelines involved in the approval.
- Fee Requirements.
- The various documents need to be submitted along with the application forms for Latam country specific manufacturing and import.

- Annexure's for Regulatory approval process involved in the approval of these drug products for both manufacturing and import

Comparison of the main regulatory concerns

1. Preparation of comparison tables for Latam countries and mainly emphasizing on the following parts namely

a. Comparison of administrative requirements of dossier.

b. Comparison of quality requirements of dossier.

General consideration of drug registration process

- Unlike the EU or the Association of Southeast Asian Nations (ASEAN) countries, LATAM drug registration processes are not harmonized. Substantial harmonization 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 harmonization.

To date, there are five national reference authorities in the region, as recognized by PAHO, those from Argentina, Brazil, Colombia, Cuba, and Mexico (Anonymous 2).

Key issues in the registration of pharmaceuticals

- 50% of respondent pharmaceutical companies conduct pivotal clinical trials in Latin America, thus involving the region in their global development plans.
- Few companies are currently achieving their goal of simultaneous submission to major Latin American markets; the climate is not conducive to simultaneous submission and it is clear that harmonization within the region has yet to be achieved.
- Approval rates have remained relatively fast; despite this, the length of regulatory review times is commonly perceived by industry as a barrier to registration in Latin America.
- A Certificate of Pharmaceutical Product (CPP) is required in most markets at submission and is usually legalized; the timing and legalization of CPPs are two important barriers to registration for the pharmaceutical industry (Thomas KE *et al*., 1999).

Perspective

- Continued economic growth has ensured that Latin America remains attractive to the pharmaceutical industry. But for companies, there are hurdles that must be overcome before a new medicine achieves marketing approval. A CMR International survey in 1998 investigated the factors inhibiting successful and timely registration of new medicines in the region, and explored company strategies for development and registration.
- The survey has been repeated in order to provide an update of the key issues currently affecting the registration of new active substances (NASs) in Latin America. The regulatory environment in this region has changed in recent years, and such change has the potential to affect the industry's ability to bring medicines to market in a timely manner.
- Five of the major Latin American markets were investigated in the present survey - Argentina, Brazil, Chile, Colombia and Mexico. This R&D briefing contains aggregated results from 22 of the 46 international pharmaceutical companies invited to participate.

Barriers to registration

The main barrier to registration in Latin American markets is the requirement for a Certificate of Pharmaceutical Product (CPP) from the source country prior to submission of a Marketing Authorization Application (MAA). This barrier was identified by between 41% and 55% of companies for each market. Other identified barriers are similar to those of the previous survey, however the necessity to legalise CPPs and the length of regulatory review times have been identified as additional issues of concern in the present study.

CPP (Certificate of Pharmaceutical Product) requirement

- The practice of requiring a CPP is often a necessary prerequisite to the approval of medicines in certain markets as it guarantees that the product has undergone a thorough review in one of the more experienced agencies. In fact, almost all companies will have already submitted MAAs to the EU, and approximately two-thirds to the US, prior to submitting to Latin American markets.
- CPPs are generally supplied by companies at the time of MAA submission, although in some cases CPP provision was delayed until just prior to product marketing approval. Some companies indicated that CPPs were not required in some countries, but these cases were rare. Such a situation could arise if the product was manufactured locally.
- Companies, agencies and patients must therefore usually await approval of the medicine in the source country before the approval process can begin in

Latin America. Encouragingly, the regulations in Brazil have recently changed allowing companies to delay the provision of CPPs until prior to approval. This measure should speed up patient access to new medicines in Brazil, and may encourage companies to submit to Brazil alongside ICH regions.

CPP (Certificate of Pharmaceutical Product) legalization

- An additional step in the production of a CPP is its legalization, a process deemed unnecessary by the World Health Organization. CPP legalization causes additional delays to marketing approval, and hence to patient access to new medicines.
- At least 80% of companies generally had their CPPs legalized prior to presenting them to Latin American agencies, an action which emerged as the second major barrier to registration in Latin America. Recent regulatory changes in Mexico should enable CPPs to be provided without legalization. However, this has not affected the results of the present survey since 18 of 22 companies (82%) have generally ensured that their CPPs are legalized for submissions to Mexico.

Regulatory approval times

- The third most common barrier is the length of regulatory approval times in Latin American markets. The regulatory review is perceived to be particularly slow in Brazil and Chile, this being the principal barrier to registration in both countries.
- Approval times for individual compounds were not collected in the present survey, however the approval rates in all markets have remained reasonably high. More than 70% of NASs submitted to Latin American markets since 1998 have been approved, with Chile having the lowest and Argentina the highest rates of approval (74% and 88%, respectively). These rates are comparable to those of the previous survey.

Submission strategies

- Despite these barriers to registration, results suggest that companies are putting more effort into achieving approval of their NASs in Latin America. In recent years, an average of 34% of NASs has been submitted to Latin American markets within 12 months of the first submission to an ICH market.
- The number of these submissions, although small, is greater than that in the previous survey and may signal intent by the pharmaceutical industry to synchronies regulatory submissions. Consistent with the move towards higher rates of simultaneous global submissions, most respondents indicated that their ideal submission strategy is simultaneous submission to all major Latin American market.
- Disappointingly, fewer companies are actually achieving this ideal than in the previous survey. Instead, the number of companies submitting on a case-by-case basis or on a country-by-country basis has increased. These results indicate that despite the widespread industry support for simultaneous submissions and harmonization within the region, the harmonization process still has hurdles to overcome.

Clinical development

- Clinical development is commonly conducted in Latin American markets and, for 50% of respondents; trials in Latin America provided pivotal evidence in support of global clinical development plans. This reflects the quality of clinical research conducted in the region. Pivotal trials were particularly common in what are considered to be the major markets of Latin America - Argentina, Brazil and Mexico.
- Other reasons for conducting trials in these markets are to provide local experience of the compound and because of local expertise in the clinical area.
- Clinical trials are not a prerequisite for registration in any of the five markets studied. At the time of the previous survey, however, completion of a local trial was a regulatory requirement in Mexico (Anonymous 4).

LATAM Market

- 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.
- 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.

Latin Americas booming pharma industry is a local affair

Getting older and wealthier by the day, Latin Americans increasingly visit their pharmacy. Since 2008, the region is by far the fastest growing pharmaceutical market in the world. By 2017, Brazil will become the fourth largest Pharma market, behind the U.S., China and Japan. But, this impressive growth story is not a victory for multinationals. The real winners are Latin American generic drug makers and locally owned retailers.

Strength

Former Brazilian health minister, Jose Serra famously stood up to the international pharmaceutical industry in the 1990s by criticizing the lengthy patent protections of expensive HIV drugs. After winning their showdown with global Pharma, Brazil began opening the regulatory door to more generics. Though considered more respectful of intellectual property rights than Argentina, Brazil nonetheless supports one of the world's largest generic industries. EMS, Brazil's largest drug laboratory, began producing generics in 2000, and today employs over 5,000 Brazilians and exports generics to 40 plus countries. Even Mexico, bound by the rigors of Nafta, has developed an impressive homegrown generics industry.

Latin American Pharmaceutical sector

The Latin American pharmaceutical market is among the fastest growing in the world and is expected to be $51.3 billion in 2014, for average growth of 10% per year (Eyzaguirre Nicolas, 2011). The region is better prepared to face global instability than in the past due to improved government finances, reduced external debt and higher international reserves, more flexible exchange rates, and strengthened financial regulation and oversight. Growing populations, improved infrastructure and increased government spending on healthcare are helping create a thriving pharmaceutical market in Latin America. The region's dedication to reducing timelines for drug registration and R&D requirements should make market access easier. The largest markets in Latin America, by both population and value, are Brazil, Mexico and Argentina (Anonymous 5).

Drug registration requirements in LATAM countries

It is reasonable to say the bulk of the information needed to build an MA submission in any LATAM country can be obtained working from the ICH CTD. However, most countries require an additional, substantial amount of information that can be challenging to obtain (eg, raw data from the manufacturing or testing process). Dossiers must often also include significant country-specific information (eg, labeling or legal documents). It should not be assumed that local regulations are fully aligned with ICH guidelines. This assumption could create delays or barriers to building fully compliant dossiers.

In many countries, all pharmaceutical products, whether small molecules or biologics/biotech products, are regulated via the same set of regulations or guidelines. Factors such as regional commercial treaties, access to information from reference agencies, and the evolution of countries' knowledge and expertise in the complexities of manufacturing and quality control of biologics (and especially products produced by DNA-recombinant technology) have triggered a relatively recent wave of regulations for biologics/biotech and other legislation related to more specific patient populations, eg, orphan drugs for patients with rare diseases.

Early identification of documentation or activities needed prior to filing, and optimal allocation of the time, cost and resources for these issues, are essential for the success of the global regulatory strategy.

Examples of the difficulty of local MA applications in LATAM in terms of either content or process, and the associated challenges, are detailed below.

- Approvals of reference agency (EMA/US FDA)
- Quality (chemistry, manufacturing and controls (CMC)) requirements
- Nonclinical and clinical requirements
- Legal documentation
- Local labeling
- Samples (registration testing) and/or repetition of release testing locally
- Compilation (translations) and submission
- Review process

Clinical trials in Latin America
Turn on Challenges

Over the past ten years, as clinical research activities have been mounting steadily within Latin America (LATAM), the level of interaction and alignment between Latin American regulatory agencies has been developing in parallel (Anonymous 6). A remarkable example of this collaboration is the publication of Good Clinical Practice (GCP) guidelines, which were agreed upon under the sponsorship of the Pan American Health Organisation (PAHO) in the "Documento de las Americas" and have served as a reference for local regulations since 2003. While each country has its personal specific requirements and processes, a number of common features have been evolving, albeit at a different

pace across the region. These include: the certification and/or registration of Ethics Committees (ECs) by a national or provincial Competent Authority, the accreditation of investigational sites, the implementation of parallel processes to reduce review timelines, the electronic submission of documents, and electronic tools for interacting with regulators, ensuing in faster and easier issue resolution (Anonymous 7).

In the primary LATAM clinical research markets, the following regulatory changes are worth noting:

Argentina

Because several provinces add their own clinical trial regulations to the national ones (Disposición 6677/10 and Resolución 1480/11), the location of a site has an impact on how quickly enrollment can begin. The "ANMAT Federal" program launched by the national regulatory agency provides a framework for collaboration and harmonisation between national and provincial requirements, with the goal of improving the efficiency of the process. The Ministry of Health (MoH) has also opened a public register of clinical trials, including ECs and Investigators, giving the public visibility into clinical research activities.

Brazil

The National EC (CONEP) review continues to log the slowest turnaround time, however, ANVISA (MoH) introduced an important change in June 2012 through RDC 36. This resolution allows for a simplified review of protocols that have already been approved by the FDA (USA), EMA (Europe), PDMA (Japan), TGA (Australia) or Health Canada, or in cases when conscription has already begun in another participating country. However, this process does not apply to studies for vaccines or antiretroviral.

Colombia

The current clinical trial regulation (issued in 2008) requires registered investigational sites to be certified by INVIMA (MoH) through a site inspection. However, the rapid growth of clinical research activity in this country over the past few years has exceeded the agency's ability to certify new sites, often creating a bottleneck. Therefore, site selection should take into consideration a site's certification status.

Mexico

Due to the increase in the number of clinical trial applications, COFEPRIS (MoH) has recently extended the review and approval process from three months to a maximum of four months. This minimises the use of "negative ficta," a condition that implies a tacit rejection when the competent authority has not issued an opinion within the set timeframe (Anonymous 8).

Many physicians now view participating in clinical trials as an attractive opportunity, and they can offer sponsors several advantages:

- Many of them are both well trained and very motivated to participate in research protocols.
- They have access to large patient populations, making recruitment easier and retention strong. Most investigators work at sites and institutions with adequate infrastructure and so are capable of producing good quality data.

LATAM's relatively long regulatory timelines habitually decrease the time allotted for patient recruitment. Sites compensate for this by increasing recruitment rates, and they usually not only complete their assigned quota, but they often surpass it. This fast pace creates workload peaks that require more common and longer on-site visits to monitor progress. Monitoring Reports need to be written in English, a task that usually takes more time than expected, even for CRAs who have an intermediate or advanced knowledge of English.

The context within which LATAM CRAs work is thus very challenging and demands more of their time and dedication. CRAs who strive to ensure that research sites recruit to the best of their ability and produce good quality data are a vital part of making Latin America an attractive market for clinical research (Anonymous 9).

Project Delivery

The basic requirements for delivering a successful clinical development project in Latin America are probably not different than elsewhere in the world. There are, however, number subtleties within the Latin American cultural framework that are worth considering, as they can sometimes make the difference between success and failure. These include:

Investigator selection

It is, of course, necessary to interact with investigators at the start of a study to explain the requirements of the protocol and how they relate to the local epidemiology, healthcare practice, and regulatory environment. However, in Latin America, developing closer, long-standing relationships with investigators through frequent contact and having an on-site presence is equally important for the CRO and the sponsor. Through an open discussion with investigators, you can:

- Provide solutions to their practical needs.
- Gain a better understanding of the competitive scenario surrounding a study.

- Pick up clues as to the root cause of poor recruiting performance at individual sites (in many cases this can relate to matters other than the inclusion and exclusion criteria, ranging from an internal political conflict at the institution, to a change in the coverage of a comparative treatment by the health system).

Challenges to Conducting Clinical Trials in Latin America

The rapid growth in Latin American clinical trials has created increasing competition for patients and investigators. Although there is a large patient population in each city, there are a limited number of sites. Therefore, it is important to continue developing more sites with good clinical researchers.

Here are other challenges to consider

- ❖ Investigators' support staffs are key to success. Because Latin Amer0ican physicians who run clinical trials also see regular patients at their clinics, sponsors should seek the best investigators who have staff capable of helping run the study.
- ❖ Rigid regulatory environment can cause delays.
- ❖ Regulations vary among the countries and different country-specific procedures are needed to authorize a clinical trial. The two main requirements are regulatory authorization and ethics committee approval. In some countries, sponsors can pursue both simultaneously; in others, there is a sequential approval process.

The regulatory approval process takes approximately three to six months. Sponsors who do not know how to navigate each country's system may experience longer timelines. Also, in many countries, it is difficult to obtain approvals for studies that include placebos. Establishing good relationships with regulatory authorities is key to shortening clinical development and approval times.

- ❖ Requirements for informed consent forms (ICFs) can be stringent. Sponsors who do not understand local requirements often run into trouble with ICFs. The forms must be customized to meet regulations in each country. ICFs for trials that involve complex medical procedures are especially demanding; regulators expect them to be understandable to patients of all education levels. Therefore, forms should be prepared in uncomplicated language.

Advantages of Conducting Clinical Trials in Latin America

- ♦ Time and Cost Efficiencies
- ♦ Accessible and Compliant Patients
- ♦ Population
- ♦ Competent and Enthusiastic Investigators

Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and the recommended storage conditions.

As different countries have different climatic conditions, each health authority requires stability studies to be conducted in the conditions corresponding to their 'climatic zone'. There is also ICH guidelines for stability testing that are to be followed in order to ensure broad acceptance of the studies.

Below, a summary of the stability conditions per zone and here a list of countries with their respective climatic zones. As stability testing is a long process, (you need to produce real time-scale data for as long as the intended shelf life of the product you intend to register) it is recommended to run tests for all the climatic zones in parallel as early as possible after definition of the final formulation (Anonymous 10).

Drug registration process in major Latam Countries
ARGENTINA
The Argentinean Health Authority

The ANMAT, National Administration of Drugs, Food and Medical Technology is the decentralized organism of the Ministry of Health that deals with pharmaceutical regulation. Apart from drug products, ANMAT is responsible for the regulation of food, medical devices, and reactants for diagnose, cosmetics, dietary supplements and cleaning and other household products.

It was created in 1992 and it has jurisdiction over the whole national territory.

In 2011, the Pan American Health Organization awarded ANMAT the status of Regulatory Authority of Regional Reference for a period of three years. The recognition follows an evaluation of the agency's performance of basic functions, recommended by WHO, for ensuring the quality, safety and efficacy of medicines in the country.

Drug registration in Argentina

Drug registration in Argentina is regulated by Decree 150/1992 and posterior modifications. Argentina is a country that relies heavily on decisions made by countries that it considers of 'high sanitary surveillance'. Thus, the registration process will depend on in what

countries a drug product is already being marketed in, regardless of the country of origin or countries where the pharmaceutical is registered but not marketed.

ANMAT made for this purpose two lists of countries, based on the level of sanitary surveillance, called Annex I and Annex II. (These lists are annexes to the drug registration decree) The lists have been created in 1992 and have not been updated ever since. Maybe for this reason, the EU is not considered as a block and some individual EU countries are listed in the two lists, while some others are just left out.

Argentina Pharmaceutical market value

- As the graphs below show, the value of the Argentine pharmaceutical market has been growing in recent years. Although generally, on some pharma stock exchanges, we try to use USD as the standard measurement of value, because of the decline in the Argentine peso over the years covered on this page, we have kept the figures in their original ARS amount.
- In the charts, 'total domestic production' refers to the total value of 'domestic market sales' of domestically produced pharmaceuticals, plus 'export sales' of the same. 'Total turnover' is this figure added to 'imported products.
- Domestically produced pharmaceutical products being sold internally have been driving value in the sector some years now, showing a much steeper growth curve than either the export segment or sales of imported products.
- While the above graph shows the market until 2012, the graph below looks at 2013 as well. However, because data was only available until the end of the third quarter, this graph shows the results from the first nine months of each year, in an attempt to best show the market's evolution (Anonymous 11).

BRAZIL

Drug Registration 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/similar 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 (Anonymous 12).

❖ **Time & Fees**

The cost of registering a product is low in Latin America. While Chile offer higher fees for the registration of generics and similar than for the registration of a new product; Brazil offer incentives for the registration of generics/copies/similar and discount the registration application fee for generic drugs.

Types of Product Registration

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

- Medicine products (Drugs): For human use, their active substances and other inputs.
- Pharmaceutical raw materials: Drugs or raw materials to be used in medicines.
- Health product: Medical-hospital, Odontological, and Hemotherapic equipment and materials and those intended for laboratory and image diagnosis.

Intellectual Property Rights (IPR) Protection

Brazil's industrial property law (Law 9,279/1996) became effective in May 1997. Concerns continue about a provision in Brazil's industrial property law that disallows importation as a means of satisfying the requirement that a patent be "worked" in Brazil. Law 10,196 (2001) includes some problematic provisions, including a requirement that Health Ministry approval be obtained prior to the issuance of a pharmaceutical patent. This raises concerns with respect to Article 27 of the TRIPS Agreement.

Figure 1. Global Market

Figure 2. Latin American Pharma Market Sector

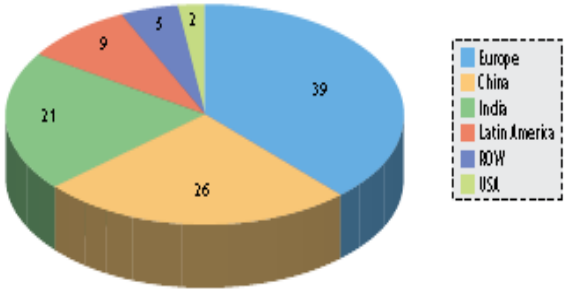


Figure 3. Certificate of Pharmaceutical Product (COPP)

CERTIFICATE OF PHARMACEUTICAL PRODUCT

No. of certificate:
Validity:
Exporting (certifying) Country:
Importing (requesting) Country:
1. Name and dosage form of the product:
1.1 Active ingredient(s)[2] and amounts per unit dose3
For complete composition including excipients see attached4:
Is this product licensed to be placed on the market for use in the exporting country? 5 Yes
Is this product actually on the market in the exporting country? If answer to 1.2 is ~ continue with the section2A and omit section 2B. If the answer to 1.2 is no, omit section 2A and continue with section 2B6
2. A.1. Number of product licence7 and date of issue:
2. A.2. Product License Holder (name and address):
2. A.3. Status of License Holders:
2. A.3.1 For categories band c the name and address of the manufacturer producing the dosage form is9:
2. AA. Is summary basis of approval appended? 10:
2. A.5. Is the attached, product information complete & Consonant with the license? II
2. A.6. Applicant for certificate, if different from the License Holder (name and address) 12:
2. B.I Applicant for Certificate (name and address):
2. B.2. Status of Applicant: 2.B.2.IFor categories band c the name and address of the manufacturer producing the dosage form is9:
Why is marketing authorization lacking? Not required not requested/Under consideration/refused
Remarks13
3. Does the certifying authority arrange for periodic inspection of Manufacturing Plant in which the Dosage form is produced?
Periodicity of routine inspections (years):
Has the manufacture of this type of dosage form been inspected?
Do the facilities and operations conform to GMP as recommended by the World Health Organization? 15
4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the Manufacture of the product? 16(Key in appropriate)

Address of Certifying Authority:
Telephone:
Fax no:
Name of the authorized person:

Signature:
Stamp & Date:

Figure 4. Pharmaceutical Sales in Latam Countries

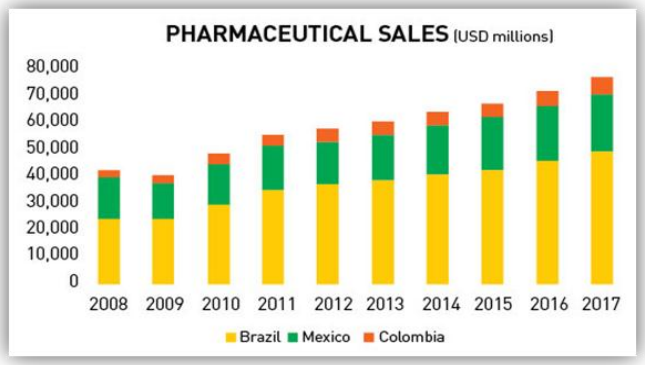


Figure 5. Clinical Trials in Latam Countries

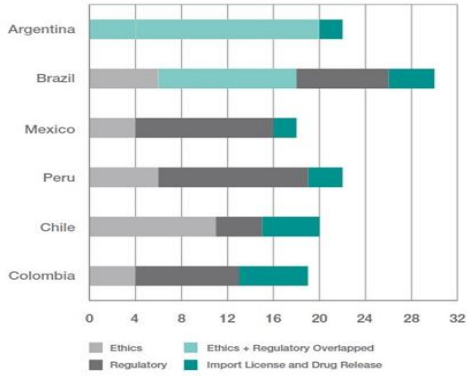
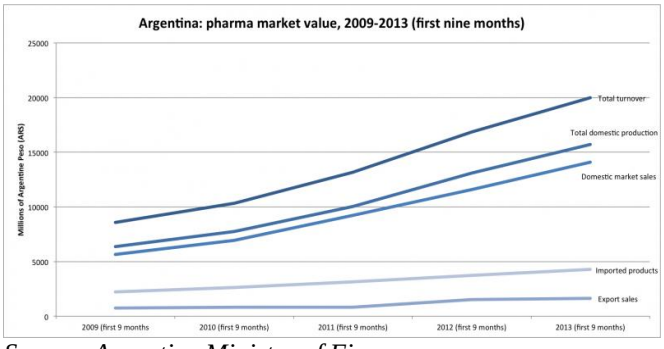
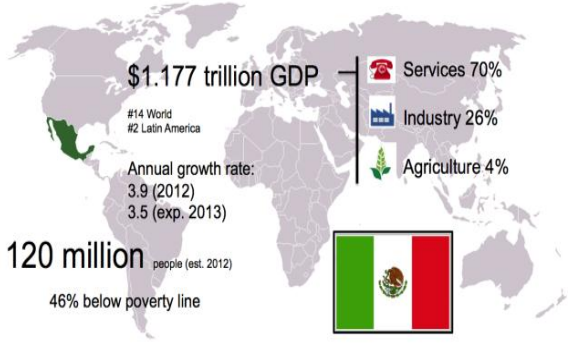


Figure 6. Argentina Pharma Value



Source: Argentine Ministry of Finance

Figure 7. Emerging economy of Mexico



Brazilian counterparts

Due to a lack of government focus and resources, Brazil's patent office, the National Institute for Industrial Property (INPI), has total a backlog of more than 60,000 patent applications - an estimated 18,000 for pharmaceuticals -- and 500,000 trademark applications. Law 10,603 (2002) on data confidentiality covers pharmaceuticals for veterinary use, fertilizers, agrotoxins, and their components and related products; the law does not cover pharmaceuticals for human use. If the product is not commercialized within two years of the date of sanitary registration, third parties may request use of the data for registration purposes.

Pressure Rises on Drug Patents in Brazil

Brazil, leader on international intellectual property issues, has come under pressure at home and abroad over whether to lift domestic patents on foreign pharmaceuticals for AIDS to allow cheaper generic versions to be produced. Nearly 200 non-governmental organizations from around the world signed onto a letter urging the Brazilian government to issue compulsory licenses allowing domestic pharmaceutical companies to produce anti-retroviral drugs used against HIV/AIDS.

Pharmaceutical Market in Brazil

- 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 great share of the global Pharmaceutical market, these countries are altering and adapting their addressing their own sourcing needs. Among Latin countries, Brazil has the largest market share with an estimated worth of $25 billion.
- In addition to the required registration documents and fees; the Brazilian health surveillance agency (ANVISA) requires GMP certificates 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 manufacturer in recent years. Currently, ANVISA is conducting inspections of companies that are manufacturing APIs in the list of priority products established by the 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. With a substantial number of API suppliers located in Europe, maintaing existing and creating new opportunities for cooperation is vital to growth in Latin America.
- In addition to inspecting manufactures importing into Brazil, ANVISA requires inspections of 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.
- Developments of leading generics and biosimilar manufacturers in says that, The Brazilian Pharma market will reach $41.3bn in 2017 with fast expansion and by 2024 contribute strongly to world medical revenues.

Mexico

A lack of coordination between Mexico's Ministry of Health and the Mexican Institute of Industrial Property has meant pharmaceutical product registration headaches for multinational drug laboratories for years. But recently published amendments look set to provide at least a partial cure (Anonymous 13).

Mexican health authority (COFEPRIS)

- COFEPRIS stands for *Comisión Federal para la Protección contra Riesgos Sanitarios*: Federal Commission for Protection against Sanitary Risks and is the authority with competence to control and regulate drug products in Mexico.
- COFEPRIS has responsibility over all activities related to these products and services: production, distribution, commercialization, imports and exports, advertisement, sales and supply, etc.
- In July 2012, the World Health Organization, through the Pan American Health Organization, designated COFEPRIS as National Regulatory Authority of Regional Reference of medicines and biological products.
- COFEPRIS then joined other four national regulatory authorities already recognized by PAHO/WHO as National Regulatory Authorities of Regional Reference: Brazil's National Health Surveillance Agency (ANVISA), Argentina's National Administration of Drugs, Food and Medical Technology (ANMAT), the National Institute of Food and Drug Monitory of Colombia (INVIMA), and the Center for State Control of Drug Quality Cuba (CECMED).

Drug Registration in Mexico

The formal application process starts when a pharmaceutical company takes the compilation of documents known as the *application dossier* to the COFEPRIS office. The reviewers at the COFEPRIS will read everything very thoroughly and will address any question they might have about the data on the dossier in the form of a letter, commonly called deficiency letter, officially called *prevención* in Mexico. Deficiency letters are not always issued, and most of them can be avoided by following all the guidelines, submitting complete information, and avoiding common silly mistakes.

If your product falls into the category of 'new molecule', you have to request a meeting with the New Molecule Committee before submitting the application.

These are the cases in which you drug will be considered a "New Molecule"

- New drug substances (new in the world or new for Mexico)
- New combinations of drug substances (for Mexico)
- New indications
- Other special cases (e.g. similar biotherapeutic products)

- Just a year ago, an average application could take anything between 1 and 4 years to be reviewed and approved. With some key changes implemented lately, such as the pre-revision process by Third Authorized Parties, or the Agreement for Innovation, timelines are decreasing dramatically, to just some months to a year.

The marketing authorization is granted for a period of five years. Submission for registration renewal must be filed at least 6 months before expiry (Anonymous 14).

Preparing the submission dossier

The structure of the submission dossier will depend on the type of product that it is intended to be registered.

New Molecules

Module I. Legal/Administrative information
Module II. Quality information
Module III. Preclinical studies
Module IV. Clinical studies

Generic drugs

Module I. Legal/Administrative information
Module II. Quality information

Module III. Bioavailability and/or bioequivalence

Vaccines

Module I. Legal/Administrative information
Module II. Quality information
Module III. Preclinical studies
Module IV. Clinical studies

Orphan drugs

Module I. Legal/Administrative information
Module II. Quality information
Module III. Justification of 'orphan drug' status
Module IV. Preclinical studies
Module V. Clinical studies

An emerging economy of Mexico

Some interesting characteristics of the Mexican culture that influence the pharmaceutical market are a strong brand loyalty from both doctors and patients, and the presence of a black market offering low-cost medicines which compete with the legal drug products.

The Mexican balance of payments, an accounting record of all monetary transactions between a country and the rest of the world, and indicator of a country's position in the global economy, is of -1.5%, a much better figure than most developed countries.

Mexico's fiscal deficit, the difference between public expenditure and income, is only of 2.2% relative to the GDP. (Note: 2.2% if we don't consider the effect of Pemex, the state's oil company. with Pemex: 3.0) The fiscal deficit is an indicator of a government's budget and dependence on credit. For definition, the lower the better. To have an idea of how Mexico is doing, Japan, consider that the US and the UK have fiscal deficits of 10.1, 9.5 and 8.6, respectively.

The amount of direct foreign investment in Mexico year to year has been strong and consistent for the last two decades, staying at reasonable levels even after the 2008 financial crisis. With an expected GDP growth of 3.5% for 2013, Mexico establishes itself as one of the most interesting and fastest-growing economies in the world. It's GDP situates it within the 15 top markets in the world, and 2nd in Latin America.

Pharmaceutical Market in Mexico

Mexico, the second largest Pharma market in Latin America after Brazil, is one of the 10 largest drug producers in the world. According to statistics from health care market research firm IMS Health, in 2008 Mexico represented 22.5% of the Latin American region and ranked 11th in the world Pharmaceutical market.

- Mexico's Pharma market grew 0.6% in2009 to reach $10.4 billion.
- Mexico is a predominantly patented drug market, in 2009 patented drugs accounted for $7.9 billion while the value of OTC drugs $1.49 billion.
- The patent expiry of several blockbuster drugs likes to further boost the generics segment.
- The government has also embarked on revamping the regulatory regime, including a new registration renewal process, guidelines for antibiotics, a draft bill to regulate the sale and production of biologic and bio-similar drugs, and new rules for medical samples.
- The new registration process allows only patented and bio-equivalent generics in the market, this means local manufacturers face greater competition from importers.
- As part of its signing of the North American free trade agreement, Mexico has had to reform its intellectual property protection laws.
- Patent protection has helped attract investment from multinational drug companies.

CONCLUSION

The LATAM region does not have a centralized or harmonized procedure for drug registration. There are critical differences between countries in the region. Moreover, most countries require additional documentation that is not part of Modules 2–5 of the CTD, some of which might also be challenging to obtain. The primary challenges observed when working in the LATAM drug registration processes and some key recommendation for success in the region is Knowledge of the drug registration processes and submission content for each LATAM country is essential for the effective planning and execution of global regulatory strategy.

Engaging regulatory professionals with expertise regarding the region early in the development phase of a candidate product is crucial. Experts can be internal or external to the company but must be, or have strategic partnerships with, reliable regulatory professionals on the ground who are aware of the practical regulatory nuances and expectations from HAs, and who keep up-to-date with the changes to the regulatory environment in the region, to avoid delays or show-stoppers to the MA applications. Although not essential, there is an invaluable benefit if a regulatory affairs expert is fluent in the country's language and cultural nuances in addition to having robust expertise in the local regulatory framework and practices.

Local authorities in the region are eagerly learning from each other and from other international agencies. There is rapid acceptance of new technologies and paradigms but above all, there is a fundamental driver: genuine concern for access to new therapies for local patients.

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