

Registration of Generic Drugs in Central America and Mexico

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ABSTRACT

The purpose of this study is to give the idea on the regulatory requirements for the registration of generic drugs and regulatory process for the registration of generic drugs in Central America and Mexico. One of the major reasons that companies want to register them in different countries is to expand their business. India is now an emerging country in which most of the research and development is going on and it is the important step to survive in the competition, so that in semi regulated countries they not having standard guidelines for registration of generic drug. But Brazil and Mexico have standard country guidelines. These two countries had different regulations to maintain the quality of medical devices marketing in their countries.

Keywords: CAFTA-DR, MOH, CCSS, TRIPS, WTO, COFEPRIS.

1. INTRODUCTION

1.1 Global generic drug outlook¹

To get approval for a generic drug, a manufacturer should demonstrate that the generic drug was bioequivalent to the brand name version. Bioequivalence means that a generic drug must be absorbed and used by the body the same way that a brand name is absorbed and used. Besides being bioequivalent, a generic drug must also be pharmaceutically equivalent to the brand name drug. This means that a generic drug must have the same active ingredients, the same dosage form, and the same strength.

Buoyed, in part, by generally positive health care spending trends, the pharmaceuticals segment is expected to generate all-time-high total revenues of \$1.23 trillion in 2014, up from \$1.15 trillion in 2013 and \$1.13 trillion in 2012.17 Oncology was the top contributor among all therapeutic areas in 201318 and is expected to remain so.

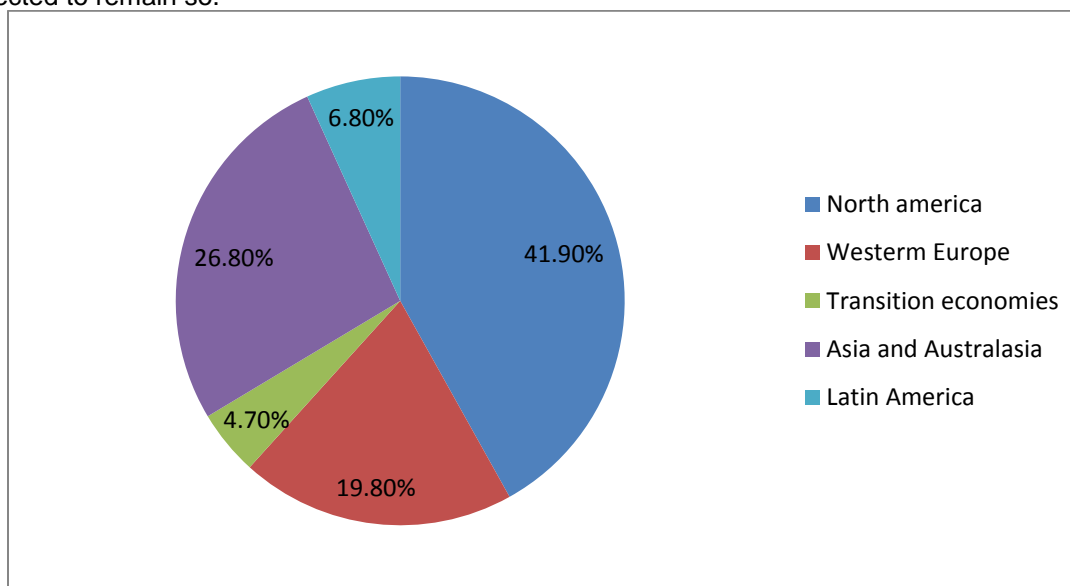


Fig. 1: Estimated 2014 pharma sales

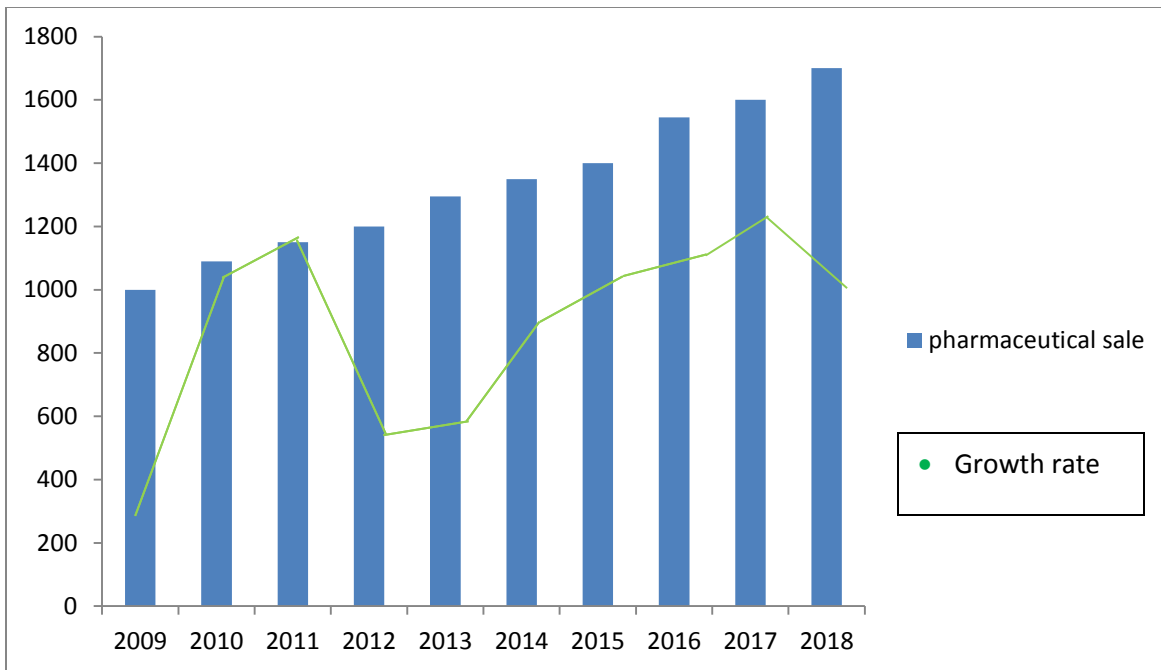


Fig. 2: Pharmaceutical sale

1.2. Global Generic drug market²

Global market can divide into 2 types regulated and semi regulated countries. US, EU, Japan Canada Australia, New Zealand and South Africa these countries are follow the regulated market. ROW Countries fallows semi regulated market. Emerging markets is important and expanding globally and are raising demand for general and lifesaving medicines. Developing countries are fallows the Emerging Market. ROW countries are, Asia, African countries, Middle East countries, Latin America and CIS (common Wealth of independent states)

Total global spending on medicines will reach about \$1.2Tn in 2017, an increase of \$205-235Bn from 2012

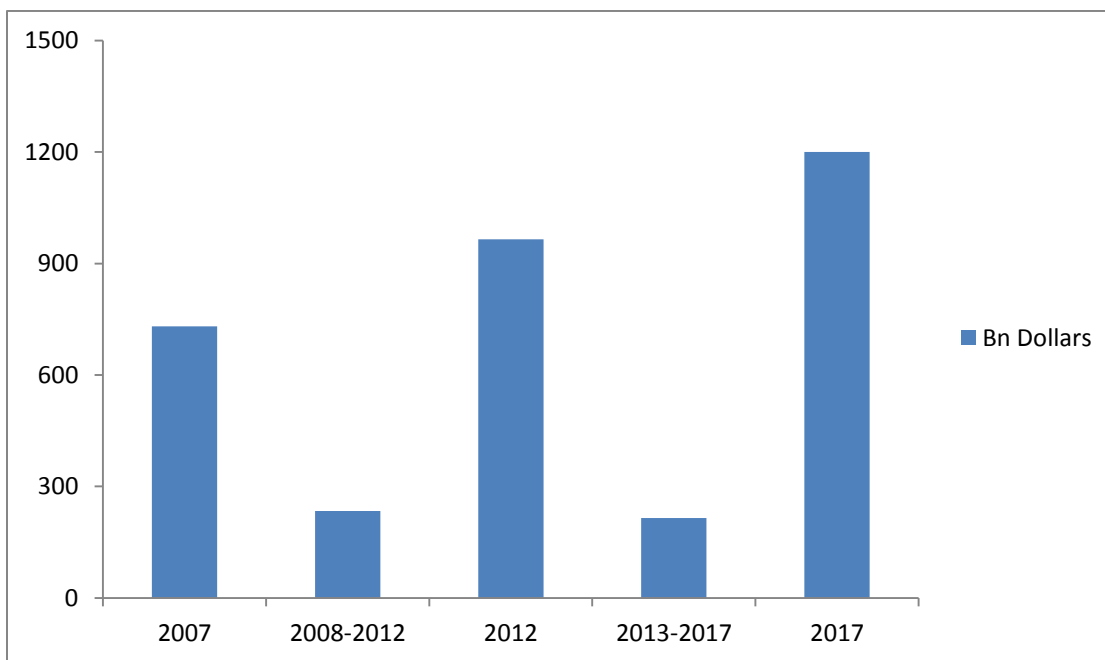


Fig. 3: Global Spending and Growth

Spending on medicines globally is expected to reach \$1Tn in 2014 and exceed \$1.17Tn by 2017. • The absolute global spend for pharmaceuticals will increase by \$230-260Bn on a constant dollar basis, compared to \$217Bn in the past five years; using variable exchange rates, absolute growth is expected to be \$205-235Bn, compared to \$234Bn in the prior five years. • Off-invoice discounts and rebates are not reflected in these forecasts but are estimated to be \$125-135Bn in 2012, rising to \$190-200Bn by 2016, resulting in net global spending growth being overstated by 0.5-1.5% per year through 2017.

1.3. Latin American Pharmaceutical Market³: -

With its population reaching 600 million people in 2011, Latin America is a fast-growing region with equally fast growing economies. The top four Latin American economies and Pharmaceutical markets account for more than 60% of the total population: Brazil (194 million), Mexico (115 million), Colombia (46 million), and Argentina (41 million). Other major players include Chile, Peru, and Venezuela.

Latin American pharmaceutical sales in 2011 were at \$62.9 billion, registering 8.9% growth in 2012. This is particularly significant when considered within the context of global sales of \$995 billion in 2011.

1.4 Generic Drug Regulation⁵: -

Generic drug regulations in LATAM are country specific. Some countries are having tough and stringent rules and regulation, that form obstacles in the path of Generic drug approval process, and some have lax regulations that make plenty of drug registration without a thorough looks over the safety and efficacy, simply bio-equivalency.

Availability of registration applications in large number also produces burden over the competent authorities. Sometime application fee or time taken for review of the application also makes hurdles for the authority. For example, previously there were only 7 days' time period for review of the application in Peru, if authority didn't answer within this period product will be automatically registered without any question. This made more than 12,000 products registration by 2002.

1.5. A Trade Agreement's Impact on Access to Generic Drugs⁶

Millions of people lack access to affordable medicines. The intellectual property rules in the Central America Free Trade Agreement (CAFTA) provide pharmaceutical companies with monopoly protections that allow them to market some drugs without competition by less costly generics. We examined availability of certain drugs in Guatemala and found that CAFTA intellectual property rules reduced access to some generic drugs already on the market and delayed new entry of other generics. Some drugs protected from competition in Guatemala will become open for generic competition in the United States before generic versions will be legally available in Guatemala.

The Central America Free Trade Agreement has kept some generic drugs from Guatemala even though they're available in the United States.

THE CENTRAL AMERICA FREE TRADE Agreement (CAFTA) covers the United States, five Central American countries (Costa Rica, El Salvador, Guatemala, Honduras, and Nicaragua), and the Dominican Republic. Its rules protect the products and processes of brand-name pharmaceutical companies—intellectual property—from competition by generic companies. Generic competition can lower drug prices. CAFTA's rules on intellectual property provide stronger monopoly protections than in existing U.S. law or the World Trade Organization's multilateral Agreement on Trade-Related Aspects of Intellectual Property (TRIPS). The World Health Organization and others have expressed concerns that these "TRIPS-Plus" rules will further delay competition from generic companies and will have the most serious consequences in lower-income countries, where price is an important factor in access.

We examined intellectual property provisions of CAFTA and their effects on access to lower-price medicines, including generics, in Guatemala—a low-income country that also has a domestic generic drug industry. This paper focuses on one key TRIPS-Plus rule, known as data exclusivity, which provides relatively quick access to monopoly protection, and related higher prices⁷.

In 2007 the U.S. Congress took steps to reduce the extent of some TRIPS-Plus rules, including data exclusivity, in an agreement with Peru. Nevertheless, the rules remain in place in CAFTA and other agreements, some are included in ongoing negotiations, and all may resurface in the future. This review therefore provides a useful case example of issues that other countries may confront in implementing CAFTA and similar agreements, and it offers policy recommendations.

2. Scope and objective

Scope

Main aims to provide the strategic regulatory framework for the submission, to advise on procedures and formats, to collect, evaluates and compile the scientific data and information on the product in Central American countries and Mexico for market approval in those countries.

The **objectives** of the project include:

1. Compilation of all regulatory changes related to the generic drugs.
2. Make a comparative summary of deep-rooted and new-fangled regulations.
3. Highlight the modifications and alteration in pharmaceutical industries policies over these regulatory changes.
4. Determine the effectiveness and shortcomings of changes.
5. Catch on the details of procedure and requirements for generic drug registration.
6. Speculation of future aspects.

3. METHODS AND DISCUSSION

CENTRAL AMERICAN COUNTRIES

5.1. Costa Rica

Costa Rica is located in Central America and borders Nicaragua to the north, Panama to the south, the Pacific Ocean to the west, and the Caribbean Sea to the east. It has a total area of 51,100 square kilometres and a population of 4,509,290 (2009). The population is mostly of Spanish ancestry and has a literacy rate of 96%⁸.

According to **Multilateral Evaluation Mechanism** [MEM] these are Following Costa Rican national institutions which provided information for dealing with the drug problem¹⁴.

- Costa Rican Institute on Drugs:
 - National Information and Statistics Unit on Drugs
 - Unit for Control and Oversight of Chemical Precursors
 - Prevention Projects Unit
 - Financial Intelligence Unit
 - Unit for Seized and Forfeited Goods
 - Legal Consultancy

Costa Rica's Regulatory framework on IP for pharmaceutical has been shaped by the Trade-Related aspects of TRIPS and CA

FTA-DR. since 1996, Costa Rica as a signature to the World Trade Organization [WTO] Agreement of TRIPS. This provided the baseline for IP protection for all WTO member countries. Costa Rica also adopted, along with all other WTO members, the 2001 Doha Declaration on TRIPS and public health, which clarified several TRIPS-Provisions on exemptions and exception contained in the agreement. For instance, it states that each member has the right to grant compulsory licenses and the freedom to determine the ground upon which such licenses are granted. It also clarifies that each member country is free to establish its own regime of exhaustion of IP rights without challenge. When CAFTA-DR come into force in January 2009. It introduced additional regulation that affected IP provisions applicable to the Pharmaceuticals market¹⁵.

5.1.1. HOW HAVE CAFTA-DR'S IP RULES AFFECTED THE CCSS? ¹⁶

As the primary provider of Costa Rica's health care services. The CCSS has developed policy jointly with health ministry to provide universal medicine coverage under health rights regulations (CCSS and COMEX 2013). One of these policies is to define the essential medicine policy and the official medicine list, which includes those medicines deemed necessary to solve the majority of the population's health requirement. This list ensure that Cost Rica has access to the medication needed [CCSS and COMEX 2013]. The purchase and supply of medicines for the national population one of the most important activities of the CCSS, and it requires careful definition and management.

5.1.2. Generic drug registration process

MOH is the regulatory author in Costa Rica. For the registration of generic drug submit the dossier to the MOH and marketing of that drug get the approval from the CCSS. This is the one of the country to get the approval for marketing. 5 years is the license time for marketing.

Following data will submit to the MOH for getting the marketing of the generic drug.

Requirements

- 1 COPP
- 2 Generic Letter
- 3 Qualitative-Quantitative Formula
- 4 Method of Analysis (Finished Product)
- 5 Validation of Method of Analysis (Finished Product)
- 6 Specifications of Finished Product
- 7 Stability Studies
- 8 Monograph/ Leaflet
- 9 Samples
- 10 Working Standard
- 11 CoA Of Finished Product
- 12 CoA Of Working Standard/Raw Material
- 13 Safety Data
- 14 Artworks
- 15 Power of Attorney

After submission of the dossier within 6 months get the notification with related to that generic drug approval.

Another point is along with the dossier we submit the 250 samples to that country, he assesses that samples for their country standards. All we are satisfied get the approval.

Our fees: By each product sanitary registration are US\$ 520.00, plus the official registration fees and filling the dossier examination tests ordered by the Ministry of Health, which will depend of the pharmaceutical specialty.

Timeframe: The sanitary registration process of pharmaceutical products can take about **12 or 15 months**.

5.2. EL Salvador

Control of Pharmaceutical Products El Salvador reports that the following laws and regulations are in force for the control of pharmaceutical products¹⁷:

- Health Code (May 1988);
- Pharmacies Law (July 1927);
- Law Regulating Drug-related Activities (March 1991 and amended in 2003);
- Law on the Control and Commercialization of Substances and Products Containing Liquid Solvents and Inhalants for Industrial and Non-Industrial Use (September 1990);

- Regulation on Pharmaceutical Specialty Products (November 1959);
- Regulation of Narcotic Drugs, Psychotropic Drugs, and Additives (June 1988).

5.2.1. Procedure for registration of generic drug¹⁶

The process of generic drug registration is same as that of Costa Rica. One of the special features in this country is batch cord interaction and Monograph of API. Batch cord interaction means in case of sampling process batch no's giving to that sample batch those ones are may be numbers r or latter's or both no's and latter's, why given that number to that batch must be explained in that dossier.

Another important point is for registration process, if the generic drug will be having any other country registration will having that copies also submit along with that dossier, it can help for easy to get the approval.

Remaining documents which is to submit are same that of the Costa Rica.

Our fees: By each product sanitary registration are US\$ 529.42, plus the official registration fees and external and internal examination, which will be asked by the Superior Council of Public Health during the registration process, which besides will give us the analysis type and its cost when we filed the Quality – quantitative Formula and the Free Sale Certificate.

Timeframe: The sanitary registration process of pharmaceutical products can take about **10 or 12 months**.

5.3. Guatemala

5.3.1 Guatemalan intellectual property laws¹⁶

Intellectual property rules have been a contentious legislative issue in Guatemala since the late 1990s. Key provisions of the initial 1999 Law on Industrial Property, Accord 712.99, have been amended almost every year since it was adopted. The rules on data exclusivity were changed on every occasion. Legislators alternatively enacted data exclusivity in 2000 to run for a fifteen-year term on each covered drug, repealed it entirely in 2002, re-enacted it to provide a five-year term in 2003, and repealed it again in 2004, before codifying it with a five-year term after the approval of CAFTA in 2005.¹⁶ The United States threatened that Congress would not approve CAFTA unless Guatemala adopted laws that were harmonious with CAFTA on data exclusivity and other matters, prompting a letter of protest from some members of Congress. The United States is Guatemala's most important trading partner, acting as the market for 36 percent of Guatemalan exports and the source of 40 percent of its imports.

CAFTA passed in Guatemala's Congress in March 2005 and in the U.S. Congress—by two votes—in July 2005. It specifically states that trade agreements will prevail over the relevant domestic laws in the event of conflicts.

5.3.2. Requirements for Generic drug registration

1. Basic Information
2. Composition Ratio/ Q&Q Formula (original document with the company's letterhead, signed by quality control person).
3. Original Validated Method of Analysis (original document with the company's letterhead signed by person responsible for method analysis).
4. Certificate of Analysis (original document with the company's letterhead signed by person responsible for method analysis).
5. Validation of Analytical Methodology
6. Stability Tests (original document with the company's letterhead, signed by quality control person. All pages must be signed).
7. Working Standard (WS)
8. Two (2) samples.
9. Product literature.
10. Ingredient functions (Declare active ingredients and excipients)
11. Usage, storage conditions and warnings.

12. Monograph
13. Original and copy of packaging artwork (copy can be colour scan as long as it is 100% legible).
14. Certificate of Free Sale with GMP (Good Manufacturing Practices) statement issued by the appropriate Health Authority (Notarized and Consularized)

Documents mentioned to be Legalized

1. Certificates of Free Sale should be notarized and consularized for high risk foods, cosmetics and pharmacy products only
2. All documents should be originals & should be properly signed / sealed.
3. All %'s should be precise, no ranges.
4. Documents what are required to be legalized at the CR Consulate in New Delhi are;
 - Quality-Quantitative Formula
 - Free Sale Certificate (free sale certificate must include the product name)
 - GMP Certificate
 - Stability studies

Our fees: By each product sanitary registration are US\$ 620.00, plus the official registration fees and filling the dossier examination tests ordered by the Ministry of Health, which will depends on the pharmaceutical specialty.

Timeframe: The sanitary registration process of pharmaceutical products can take about **12 or 15 months**.

5.4. Honduras

Intellectual Property Protection Regulatory Data Protection Neither country has effectively implemented its international obligations, arising from the World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and the CAFTA-DR, related to the protection of pharmaceutical test and other data. The Government of Honduras published draft regulations for consultation in 2008, but the regulations for effectively implementing regulatory data protection were not promulgated. Similarly, the health authorities in Nicaragua have yet to promulgate a clear and transparent regulatory data protection mechanism that would comply with the CAFTA-DR. Measures for the Effective Enforcement of Patents Neither country has effectively implemented its international obligations, arising from CAFTA-DR Article 15.10.2, related to the effective enforcement of patents, including those obligations which would prevent patent infringement. The Government of Honduras published draft regulations in 2008, but the regulations for implementing effective enforcement mechanisms were not promulgated. Similarly, the Government of Nicaragua has yet to implement effective mechanisms for enforcing patents prior to marketing approval decisions.

5.4.1. Honduras Generic Drug Registration¹⁸

Proposal for El Salvador Sanitary Registration of generic drugs:

The following information is an actual March, 2011 proposal requested to Gold Service, a Layer Firm located in Central America that we serious recommend.

Requirements

1. A special POA granted to our attorneys. This document must be duly authenticated by a Salvadoran Consulate or by Apostille. We'll provide the draft once our offer is accepted.
2. FREE SALE CERTIFICATE. This document must contain the manufacturing good manners. This document expires two years after its date of issuance and must be duly authenticated by a Salvadoran Consulate or by Apostille.
3. MANUFACTURING GOOD MANNERS CERTIFICATE. This one is needed just in case the before one don't include it. This document must be duly authenticated by a Salvadoran Consulate or by Apostille.
4. Original Quality – quantitative Formula. This document must be signed by the person in charge to prepare the same and must express the units in the International system. The name of scientist

- and part of the plant must be declared in case the formulation contains vegetables species. (Don't must be qualitative one) And must be identical to the one expressed in the Free Sale Certificate.
5. Terminated Product Analysis Method. This document must include the requirement of validation authenticated by a Salvadoran Consulate or by Apostille.
 6. Stability Study
 7. Terminated Product Analysis Method Original Certificate. This document must be for the lot numbers of samples to present and must be signed and sealed by the responsible people.
 8. Packaging Project (primary or scheme including details of how many units are in blister and secondary) as such will be marketed, in Spanish. The label must include: information on the product, formula per unit dose, registration number, date of manufacture and expiry date, or date by which the product should be consumed. Sales mode and route of administration among others.
 9. Samples of the products, which expiration can't be lower than six months at the filling date of the application. We recommend that the samples be issued to be valid for a year at least.
 10. Working standard or actives in an amount not less than 1 gram and its corresponding analysis certificate. This document must be issued to be valid for a year at least at the filling date.
 11. Chromatograms and absorption spectra of the batch of samples that will be registered.
 12. Drug information and literature (for prescribing information)
 13. Chemical Monograph of the active.

Our fees: By each product sanitary registration are US\$ 650.00, plus the official registration fees and filling the dossier examination tests ordered by the Ministry of Health, which will depend on the pharmaceutical specialty.

Timeframe: The sanitary registration process of pharmaceutical products can take about **12 or 15 months**.

5.5. Nicaragua

Nicaragua's standards system is not well developed due to lack of adequate laboratory equipment and funding. The Ministry of Development, Industry and Commerce (MIFIC) is responsible for the formulation and implementation of the requirements and standards that local and foreign companies must follow in order to sell their products in the local market.

5.5.1. Nicaragua Authorizes Honduran Pharmaceutical Chain¹⁶

The government claims that the delay in the adoption of the eight outlets claimed by the company is due to red tape and not obstacles to investment.

"There is no obstruction. What there is a process that must be met, and well, we have no problem with the eight more pharmacies added," said Orlando Solorzano, the Minister of Development, Industry and Trade (Mific) to Elnuevodiario.com.

The United Association of Pharmacies in Nicaragua (Afun) recorded 2600 pharmacies across the country of which 500 belong to the macro sector and the rest are small and medium sized enterprises that could be at risk from the opening of Kielsa establishments in the country.

Solorzano said that currently there is no risk but if that were to happen the laws to prevent unfair competition would apply. "The same laws establish that when dealing with business mechanisms that tend to suppress competition taking advantage of their dominance, our own competition and consumer protection laws also establish that this is not possible," he added.

5.5.2. Requirements for registration of generic drug¹⁸

Requirements:

1. A special POA granted to our attorneys. This document must be duly authenticated by a Nicaraguan Consulate. We'll provide the draft once our offer is accepted.
2. FREE SALE CERTIFICATE. This document must be duly authenticated by a Nicaraguan Consulate.
3. Original Quality – quantitative Formula. This document must be duly authenticated by a Nicaraguan Consulate and signed by the person in charge to prepare the same and must express the units in the International system. The name of scientist and part of the plant must be declared

in case the formulation contains vegetables species. (Don't must be qualitative one) And must be identical to the one expressed in the Free Sale Certificate.

4. MANUFACTURING GOOD MANNERS CERTIFICATE. This document must be duly authenticated by a Nicaraguan Consulate.
5. Terminated Product Analysis Method Original Certificate. This document must be for the lot numbers of samples to present and must be signed and sealed by the responsible people.
6. Trademark certificate just in case the owner of the product market the product in different way than generic.
7. Terminated Product specifications, tests and methods.
8. Stability Protocol Studies.
9. Flow Diagram Product Manufacturing
10. Product secondary packaging
11. Commercial substantiation of the product;
12. Samples of the products, which expiration can't be lower than six months at the filling date of the application. We recommend that the samples be issued to be valid for a year at least.
13. Working standard or actives in an amount not less than 1 gram and its corresponding analysis certificate. This document must be issued to be valid for a year at least at the filling date.
14. Product labels;
15. Drug information and literature (for prescribing information)
16. Chemical Monograph of the active.

Our fees: By each product sanitary registration are US\$ 632.00, plus the official registration fees and external and internal examination, which will be asked by the Ministry of Health pending to the kind of the product to be registered, and the analysis costs depends of the product pharmaceutical specialty. The fee payment receipt will be provided by the authority before to file the application

Timeframe: The sanitary registration process of pharmaceutical products can take **about 12 months**.

5.6. Panama

According to Decree 93 of February 16, 1972, the Regulation on Registration of Pharmaceutical Specialties, almost all pharmaceuticals must be registered in Panama, The Ministry of Health controls the registration process and works in conjunction with the National University of Panama and specialized laboratories to review applications. In evaluating an application, the Ministry compares the safety and therapeutic advantages of the drug with similar products, and bases its decision on these comparisons¹⁸.

The following information must be included in a registration application:

1. Trade mark or generic name of product;
2. Name and address of manufacturer and distributor;
3. Dosage form and route of administration;
4. Name of the responsible pharmacist;
5. Details of therapeutic class;
6. A sample of the container
7. Complete formula of finished dosage;
8. Draft of proposed packaging copy and package insert;
9. Active ingredients;
10. Indications;
11. Contraindications;
12. Warnings, precautions;
13. Recommended route of administration;
14. Draft outline of proposed information to the medical profession;
15. Recommended dosage: usual dose, frequency, range;
16. Summary of pharmacological data and data relevant to proposed use;
17. Summary of all clinical trials; and
18. Data on adverse reactions and drug interactions.

Panama also requires that any "physician-oriented" information be included with the registration application. It takes an average of 2 years for a full registration application to be approved. Drugs that are

not new chemical entities and that already are listed in locally approved pharmacopoeias are subject to lesser requirements, which include provision of a Free Sale Certificate, a Certificate of Analysis, the product formula, and samples of the product.

Printed packaging copy and package inserts also must be reviewed at the time of registration. The following information, in Spanish, is required on the package label:

1. Qualitative and quantitative formula;
2. Strength and pack size (contents);
3. Registration number;
4. Trademark;
5. Manufacturer's name and address;
6. Statement that dose must be as prescribed by physician, and that sale is subject to prescription; and
7. Expiration date and batch number.

Package inserts are not required for all products. The decision to include a package insert is left to the discretion of the manufacturer, but there are legal requirements for their content if an insert is included. Inserts usually are physician oriented. Companies are not required to notify the government of changes in labelling for registered products.

5.6.1. Registration procedure for Generic Drugs

This is also same like Costa Rica but main difference in panama country registration BE report of that drug must submit in panama regulatory authority, accelerate and long term stability date submit compulsory, these reports are submitted in dossier of drug and Inter changeable certificate of BE study is submit. Batch code interpretation submit in dossier to regulatory authority

Three different justification latter are submitted in dossier, in that latter having following information

1. The Identification, Average Weight, Friability and Uniformity of dosage Units are not included at stability studies. These tests are not proving evidence of chemical stability of the product nor the performance of the pharmaceutical form, instead of that, those are QA tests and for that reason they aren't included at study of stability.
2. Accommodate the changes over a period of shelf life there is a difference in specification for release and stability specification
3. Submit long term stability study for the product.

MEXICO

Mexico has access to the most well-established and emerging pharmaceutical markets in North and Latin America. The strength of the Indian pharmaceutical industry is in utilising the country's skills in organic synthesis and process engineering, which is facilitating the rapid development of cost-effective technologies without compromising on quality²⁰.

In addition to this, India holds the largest number of US Food and Drugs Administration licenses for their manufacturing facilities. It also holds the largest Drug Master Files, which are used to penetrate the generic drugs market.

India has invested millions of pounds in Mexico, with Indian giant pharmaceutical companies such as Ranbaxy Laboratories and Wockhardt Limited leading the way in the expansion of generic drugs in Mexico. Today, India holds the largest portion of generic drug manufacturing in Mexico along with the export of Ayurveda medicines.

1. The changing Mexican healthcare system²¹

The expanding production and distribution of generic medicines within the public health sector has been greatly influenced by Mexico's changing healthcare system. The Mexican healthcare system was developed under the presidency of Vicente Fox in 2000 with a simplified system designed to provide millions of families with healthcare. As a result, generic drugs generate \$2bn (£1.31bn) in annual sales, which has translated into a domino effect whereby increasing numbers of people are accessing medical services, including purchasing over-the-counter (OTC) and prescription medications.

In addition, the Mexican Government has also changed its mindset regarding innovative medicine, with the Business Monitor International (BMI) forecasting a Growth Domestic Product (GDP) growth from 2.7 to three percent in 2013. This is due to the Mexican Government's approval of the production of innovative drugs by giant pharmaceutical companies, as well as increasing patient access to anti-cancer drugs.

This projection in GDP was made at the beginning of 2011, when Mexico's Ministry of Health and the Mexican Association of Industrial and Pharmaceutical Research gave a joint press conference to officially introduce 31 types of innovative drugs for cancer, hepatitis C and rare genetic syndromes, among others. In addition, in February 2012, the Mexican Federal Commission for Protection against Health Risks (COFEPRIS) agreed to the introduction of three active drug substances that are present in medicines used in treating cancer, osteoporosis and degenerative disease.

"Today, India holds the largest portion of generic drug manufacturing in Mexico along with the export of Ayurveda medicines." In 1991, the Mexican Government established laws protecting intellectual property rights. This gave pharmaceutical companies an incentive to produce high-quality and affordable medications in Mexico. The protections also gave well-established companies exclusive rights to manufacture products in and out of Mexico.

To date, the pharmaceutical industry is the second largest manufacturing sector in the Mexican economy, second only to the automobile industry. There are 400 pharmaceutical companies that dominate the Mexican industry, most of which are multinational companies manufacturing 80% of the nation's pharmaceuticals.

Among the big names are Pfizer Corp., Novartis AG, Merck & Co. and Sanofi. Japanese companies such as Taisho Pharmaceutical Holdings Co. Ltd. have also been positioning themselves as major players in the Mexican pharmaceutical industry. Taisho, which popularised the energy drink Lipovitan, acquired four Mexican pharmaceutical companies in 2012. This illustrates just how fast the industry is evolving as new players enter the scene.

2. Regulatory framework in Mexico

The main regulatory framework in relation to medical products is set out in the following federal laws:

1. General Health Law (Ley General de Salud) (LGS) (Latest Update 19-03-2014)
2. Health Law Regulations (Reglamento de Insumos para la Salud) (RIS)

3. GENERIC DRUG REGISTRATION²²

In Mexico, the drug registration procedure will depend on the type of product that it is intended to get registered. The formal application process starts when a pharmaceutical company takes the compilation of documents known as the *application dossier* to the COFEPRIS office. After document submission, 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 *prevention* in Mexico. The official timeline for an answer is 6 months.

Until last year, the norm was between 1 and 2 years. Last, year, a new option was introduced which contemplates the possibility of having third parties (consultants) previously evaluated and approved by COFEPRIS, do a pre-evaluation of the dossiers, which expedites the posterior revision by COFEPRIS, and at the same times lightens the burden for the evaluators at the health authority, allowing a quickest revision of all submissions.

4. AUTHORIZED THIRD PARTIES²³

Authorized third parties are persons authorized by the Federal Commission for the protection against sanitary risks (COFEPRIS) to support the authority in monitoring and surveillance health through various analytical testing, sampling or verification acts or to perform bioequivalence or bioavailability studies.

The pharmaceutical company that want to register a drug product, contacts an authorized third party, which is an independent professional or company authorized by the health authority by having a separate and well defined procedure. License of an authorized third party will be valid for 2 years after that there is a requirement to re-register it.

Table 1: TYPES OF REGISTRATION AND DATA REQUIREMENTS

New Molecules	Orphan drugs
Module I. Legal/Administrative information	Module I. Legal/Administrative information
Module II. Quality information	Module II. Quality information
Module III. Preclinical studies	Module III. Justification of 'orphan drug' status
Module IV. Clinical studies	Module IV. Preclinical studies
	Module V. Clinical studies
Vaccines	Generic drugs
Module I. Legal/Administrative information	Module I. Legal/Administrative information
Module II. Quality information	Module II. Quality information
Module III. Preclinical studies	Module III. Bioavailability and/or bioequivalence
Module IV. Clinical studies	

5. Generic Market in Mexico up to 84%

The volume of generic drug products consumed by the Mexican population grew from 54% to 84% in the last three years, was announced by Mikel Arreola, Commissioner for the COFEPRIS, the Mexican regulatory agency. The announcement was made at the opening of a training session on marketing authorization of allopathic medicines of the Interchangeable Generic Drug Product Manufacturers Mexican Association (Association Mexicana de Fabricants de Medicaments Generics Interminable – AMEGI).

Dr. Arreola highlighted that Mexico is the world leader in generic drug consumption, and that the Mexican people has overcome the myth that generic products are of poorer quality, safety and efficacy profile than those offered by innovative brands. He also mentioned that, thanks to expedite approval of these products, considerable savings are possible, both of out-of-pocket medicines expenditure, and public healthcare costs. **Generic products now represent 52% of market share**, the remaining 48% corresponding to innovative.

In the last 29 months COFEPRIS has approved 261 generics of 29 APIs that lost market exclusivity of intellectual property protection.

6. CHECKLIST FOR GENERIC DRUG REGISTRATION:

MODULE INFORMATION

I. LEGAL & ADMINISTRATIVE INFORMATION

Application MX

fees payment MX

Sanitary License MX

MAQUILA agreement MX

Packing information if the packaging is done in MX

Name, address, Sanitary License & Packaging type Distributor information if it applies MX

Name, address, Sanitary license & Packaging type MX

Notification of Sanitary Responsible MX

Label project MX

Insert (if applicable) MX

Prescribing Information (long and reduced version) MX

Certificate of Good Manufacturing Practice (I) of the

drug (S) manufacturer and Finished product(s) site(s) IN

For foreign-made drugs, in addition to above:

Free Sale Certificate or Certificate of Pharmaceutical Product IN

Clinical trials in Mexican Population MX

Letter describing the activities to prevent the potential risk of the product IN

Letter of representation or Power of Attorney mentioning the product IN

Brand name (commercial) MX

Patent declaration letter MX

Information about NO site requirement (in national territory, if applicable).

A document certifying the legal representative in Mexico. MX

Agreement with 3rd party authorized for quality control analysis (where the importer or legal representative is not a subsidiary) MX

Country Manufacturer License of the manufacturer IN

Conclusions of the New Molecules Committee Meeting MX

II. QUALITY INFORMATION

Drug Information

Layout of the synthesis pathway with controls IN

Validation of the manufacture process IN

Chemical name IN

Chemistry structure, formula, molecular weight IN

Characterization of the structure by an analytical test IN

Properties IN

Related Substances, Degradation products, impurities & residual solvents IN

Specifications IN

Pharmacopeia References IN

Analytical Method IN

Validation of the analytic methods not pharmacopeia's IN

COAs IN

No. Of three batches

Analytical evidence (chromatograms/spectrograms) IN

Container-Closure System Information IN

Stability Report Long term & Accelerated IN of the three batches of the COA Additives

In case of New additives IN

MSDS IN

In case of human or animal derivative additives IN

Non-adventitious agents certificate IN

Pharmacopeia references IN

Specifications IN

Analytical Methods IN

Validation of the analytic methods not pharmacopeia's IN

COAs Supplier and Manufacturer IN Finished Product

Specifications and pharmacopeia References in case IN

Analytic Methods IN

Validation of the analytic methods not pharmacopeia's IN

Analytic evidence (chromatograms/spectrograms, data sheets) IN

COAs by the manufacturer IN Mention the No. Of Batch of the batches included, it must be at least 3 for the highest and lowest strength and 1 for the middle strengths Analytic evidence (chromatograms/spectrograms, data sheets) IN

Pharmaceutical Development Report INs

Qualitative- Quantitative Formula IN

Manufacture process description IN

Layout of the manufacture process with controls in process IN

Manufacture records of the stability batches IN

Packaging record for the presentations in the stability batches IN

Leak test IN

Stability Protocol IN

Stability report with conclusions IN The stability report must be of the same batches example included in the COA and manufacture records and in the sample container-closure system you present for Mexico Market Chromatograms of the beginning and the end of the study, with data sheets IN

Container-Closure System Description of the container-closure system (primary & secondary) IN

The container-closure system must be the same described in Specification IN the stability reports.

Analytic Methods IN

COAs Supplier and Manufacturer IN

III. INTERCHANGEABILITY OR BIOEQUIVALENCE TEST

Authorized protocol of the BE studies by COFEPRIS MX

Dissolution profile made in Mexico by 3rd party MX

Report of the BE studies by the 3rd party MX

Registration Fee: (2014)

Generic drug products 62270 MXN

Innovative drug products 111341 MXN

Homeopathic herbal and vitamin products 14807 MXN

4. CONCLUSION

Medicine regulation is a legislated function of any regulatory authority in a country. As such, the authority is accountable to the citizens of the country regarding the availability, efficacy, quality, and safety of medicines.

In Central American regions are not having the certain registration procedure. There are small differences in between regions. Most countries required some additional documents that is not part of Modules 2–5 of the CTD, some of which might also be challenging to obtain.

Several similar reciprocity agreements have been reached including one between Mexico and Chile, and a recent one involving Mexico, Chile, Colombia, and Peru. The Mexican regulatory agency, the Federal Commission for the Protection from Sanitary Risks (COFEPRIS) has also been in talks with the European Medicines Agency (EMA) regarding mutual recognition of GMP information as well, indicating a strong interest in pursuing more regulated markets. On the 28th September 2012, the Chilean Public Health Institute and the Mexican federal Commission for sanitary Risk (COFEPRIS) subscribed to a cooperation agreement that will allow for the harmonization of requirements and regulatory aspects of drug production, including vaccines within the Americas region, breaking the barrier present in many countries. The agreement, which is still at the “memorandum of understanding” (MOU) stage, is a bilateral mechanism that is eventually expected to allow the mutual recognition of marketing authorizations, inspections visits and Good Manufacturing Practices (GMP) certification. COFEPRIS also holds equivalence agreements with Health Canada and the FDA for the regulation of drugs and medical device products. Mexico has also signed other equivalence MOUs with El Salvador and Ecuador, and a MOU is in the making with Colombia.

These differences are due to the different environmental conditions, races, life style and regulatory framework. Some regulatory agencies are unable to monitor whole process of drug development due to poor infrastructure and unavailability of resources. So, these countries are relying upon the developed countries and accept their data. This results in preparation of piles of document, increase in expenses and spending a lot of time to file a generic application and getting marketing authorization for generic drug. There is need for harmonization's other will be a common format for different countries for the approval or marketing authorization of generic drugs. This harmonization procedure would benefit the generic industries by saving time and money for generic authorization. There is strong need for harmonization at a global level.

As emerging markets capture a greater share of the global pharmaceutical market, LATAM 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. 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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