Research Article

Current Scenario of Generic Drug Regulation and Registration Process in Latin America Countries

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ABSTRACT

The study highlighted the "CURRENT SCENARIO OF GENERIC DRUG REGULATION AND REGISTRATION PROCESS IN LATAM (Latin America) COUNTRIES" and also a brief description about the License Applications and its requirements to fill and submit to the Regulatory Authorities. The requirements to submit to market a Generic drug registration in LATAM are country specific. It was observed that the LATAM region does not have an integrated or consistent procedure for drug registration. 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 bioequivalency. There are critical differences between countries in the region. 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. In order to help alleviate some of those difficulties and promote trade between Latin American countries, several regulatory bodies have entered into interchange agreements. 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 US.

Keywords: Generic, LATAM, US, CTD, EU.

1. INTRODUCTION: Generic medicines play an essential role in treating disease by increasing the accessibility and affordability of modern day pharmaceuticals in global healthcare systems. The sustainability of the generic medicines sector is vital to ensure that these benefits accrue into the future and essential medicines continue to be made available to as many patients as possible without deference to cost. The benefits of a healthy and dynamic generic medicines industry – historically and in the future - are evident. Currently over half of the volume of medicines are supplied as generics medicines but this represents just 18% in value terms.[1]

1.1 Global Pharmaceutical Market by Region[2]

In 2012, the global pharmaceuticals market generated revenues of $959.0 billion, growing at a rate of 2.4%. The Whole market is shared by North America, Europe, Asia, Japan and Latin America. North American pharmaceuticals market size was of $349.0 billion with growing rate of -1.0%, European pharmaceuticals market covered amount of $224.3billion with growing rate of -0.8%, Asia Registered Highest growth of 12.8% with market size of $168.1 Followed by Japan market size of $110.5 with 0.0% growth and Latin America market size of $68.6 with 10.9% growth.The global pharmaceutical market is expected to grow to $1.2 trillion by 2017, a compound annual growth of 6-8% from 2012.

Table 1: Total Unaudited and Audited Global Pharmaceutical Market by Region /2012 – 2017

	2012	2012
	Mkt Size **Const. US $	% Growth
Total unaudited and audited global market		
	959.0	2.4%
Total unaudited and audited global market by region		
North America	349.0	-1.0%
Europe (EU + non EU)	224.3	-0.8%
Asia (including Indian Sub-continent) /Africa/ Australia	168.1	12.8%
Japan	110.5	0.0%
Latin America	68.6	10.9%

Source:-IMSHealthhttp://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/Press%20R oom/Total_World_Pharma_Market_Topline_metrics_2012-17_regions.pdf

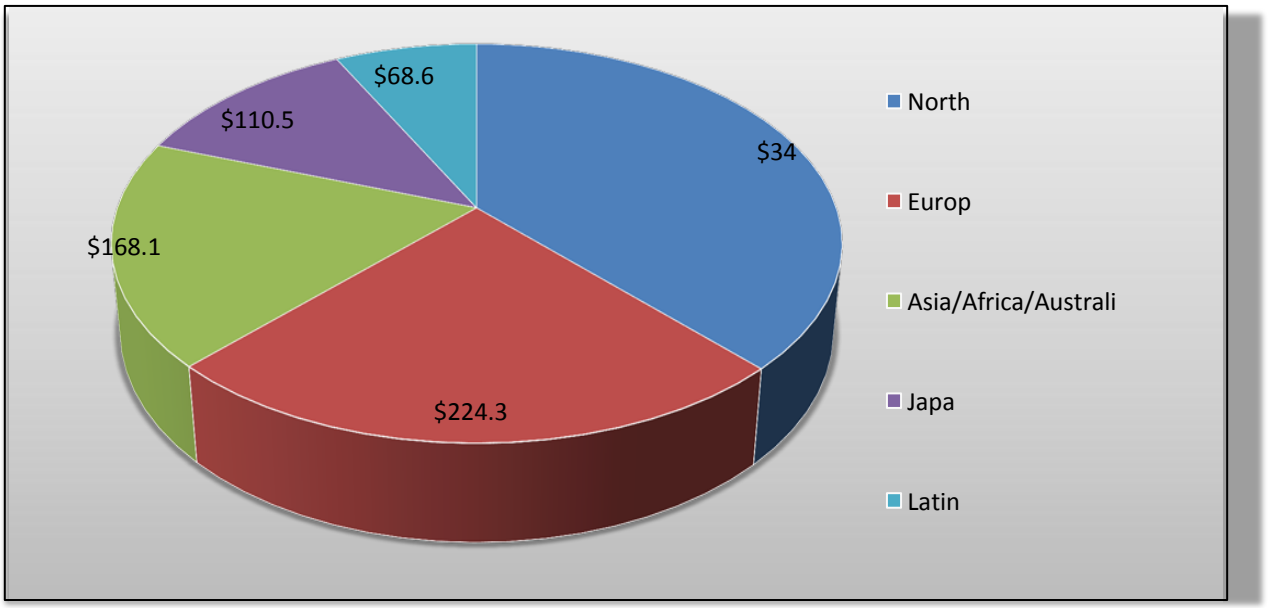
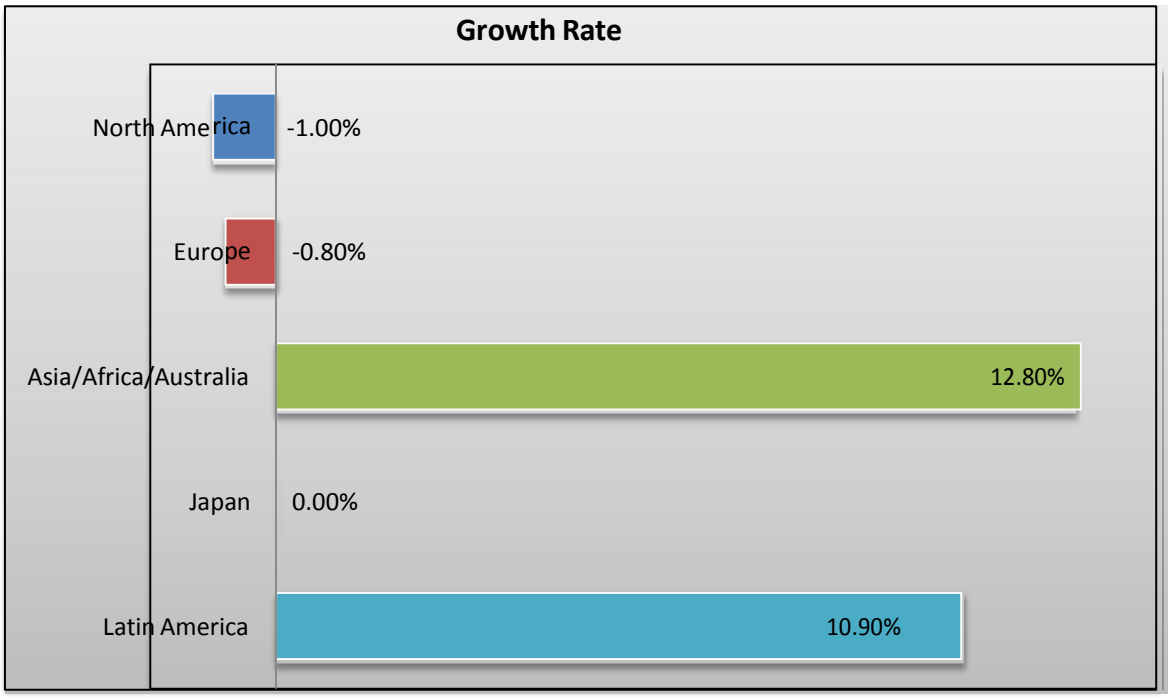


Fig. 1: Global Pharmaceutical Market by Region (2012)

Source: - IMS Health http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/Press%20R oom/Total_World_Pharma_Market_Topline_metrics_2012-17_regions.pdf



Source: - IMS Health http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/Press%20R oom/Total_World_Pharma_Market_Topline_metrics_2012-17_regions.pdf

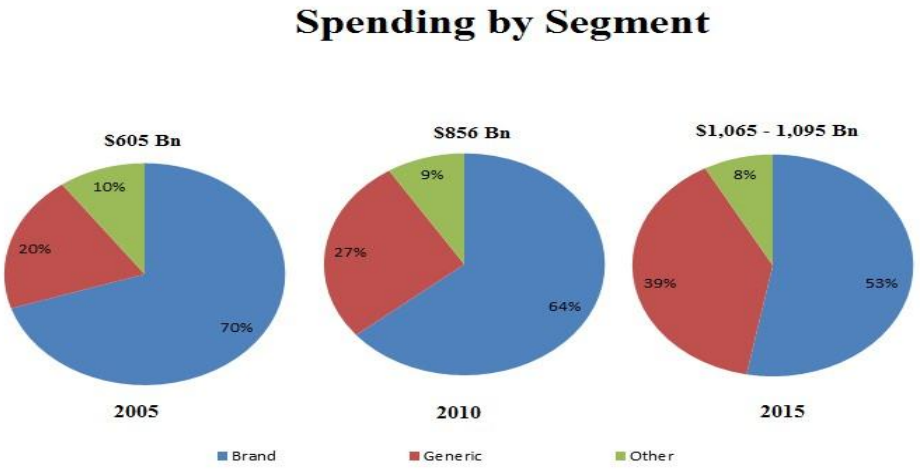
[3]

1.2 Global Generic Drug Market

A generic is defined as a pharmaceutical product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference product, and whose bioequivalence with the reference product has been demonstrated.

Generic drugs are marketed under a non-proprietary called as International Nonproprietary name (INN) or approved name rather than a proprietary or brand name. These are cheaper than, brand- name (Innovator drugs). Because of their low price, generic drugs are often the only medicines that the poorest can access.

All of the increase in spending on brands – both new and existing – will be offset by patent expiries which will reduce brand spending by $120Bn through 2015. Only spending on generics will increase in developed markets over the next five years. In high growth emerging markets, spending will increase by $150Bn, as improved access and strengthening economies drive higher demand, primarily for generic drugs.



Source: http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20fo r%20Healthcare%20Informatics/Global_Use_of_Medicines_Report.pdf

Fig. 3: % Sale and expected sale of Brand, generic and other Product

1.3 LATAM (Latin American) Pharmaceutical Market[4]

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.

The regulatory regime in Latin America (LATAM) countries can be divided into three categories:

1. Countries which have established regulations (Brazil, Chile, Mexico, and Venezuela) to demonstrate the efficacy, safety through clinical trials and therapeutic equivalence studies with the proper drug approval systems.

2. The countries (Argentina, Columbia, Ecuador, Paraguay) which have the regulations to register a new drug or generics but not as stringent as the first category.

3. The countries (Guatemala, Barbados, Bolivia, Nicaragua, and Peru) which have imperfectly formed drug regulations for the approval of drugs.

Key Players of LATAM Pharmaceutical market, are: -

1. Brazil
2. Mexico
3. Argentina
4. Venezuela
5. Chile
6. Colombia
7. Peru

1.4 Generic Drug Regulation[5]

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.

(a) Types of drug available in LATAM market.

1. Manufactured by the originator:
    a. Branded original drugs on patent
    b. Branded original drugs off patent
    c. Generic original drug (off patent, identified by the international non-proprietary name [INN])
2. Secondary source Drugs:
    a. Bioequivalent:
        i. Branded generic drugs
        ii. INN (Proper) Generic drug
    b. Non-bioequivalent:
        i. Branded similar drug
        ii. INN (Proper) Similar Drug

- **Originator** refers to the company that holds the patent and the brand name of the drug.
- **Branded original** drug refers to a product sold by the originator or by a company licensed or authorized by the originator.
- **Generic original drug** refers to an original drug sold under INN (international nonproprietary name). It is assumed that it is off patent.
- **Similar drug (copy)**: Pharmaceutical product that is off patent but there is no proof of

bioequivalence. It can be sold under brand name (Branded Similar) or under INN.

- **Branded Generics**: - products that are either novel dosage forms of off-patent products produced by a manufacturer that is not the originator of the molecule, or a molecule copy of an off-patent product with a trade name.[6]

Objective:

The **objectives of dissertation work include**:

1. Compilation of all regulatory changes related to the generic drugs in Latin America.
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.

4. METHODOLOGY: Data Collection

The study is the result of exclusive research over the topic to expedite the results. At most a large amount of secondary data collection was done by means of following sources

Literature Review

Typically covered the regulatory directives published officially by government/regulatory authorities including the on-line journals, newspaper articles, market research reports available from on-line library and other resources.

Internet using the web page content

The literature was collected using numerous search engines e.g. official government websites:

1. Argentina: ANMAT
   Website: http://www.anmat.gov.ar/principal.asp
2. Brazil: ANVISA
   Website: http://portal.anvisa.gov.br/wps/portal/anvisa-ingles
3. Chile: ISP
   Website: http://www.ispch.cl/
4. Colombia: INVIMA
   Website: https://www.invima.gov.co/

5. DISCUSSION

5.1 GENERIC DRUG REGULATION & REGISTRATION PROCESS IN ARGENTINA

Agency:

Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT) National Administration of Drugs, Food and Medical Technology (In English)

ANMAT is a decentralized agency of the Ministry of Health that deals with pharmaceutical regulation, established by Decree 1490/92. 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.

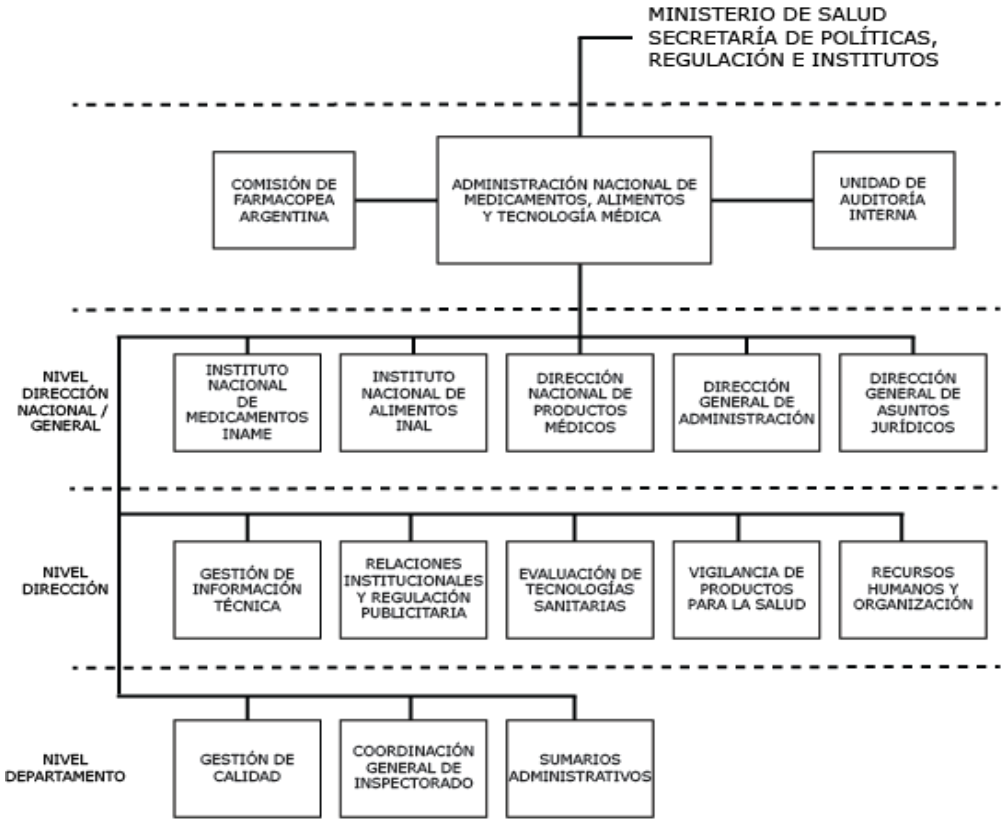


Fig. 4: - Organization structure for Argentina[12]

5.1.1 Legislation applies for generic drug[13, 14]

S. No.	Decree Number	Year of publication	Topics Covered
1.	Decree 150/1992.	1992	This establishes the procedure that must be followed to register medicinal products with the Medicines, Food and Medical Technology National Administration (ANMAT) and the requirements that must be met to manufacture, fraction, prescribe, issue, commercialize, import and export medicinal products.
2.	Decree 1299/199	1997	This regulates all stages of the marketing chain of medicinal products and determines how manufacturers or importers can
3.	Provision No. 3185/99	1999	Requirement of Bioequivalence Studies
4.	National Law 25,649	2002	This establishes that medical practitioners must prescribe all medicines using the generic name of the medicine
5.	Regulation No. 3554/02	2002	Requirements for Registration of Pharmaceuticals recorded and processed in a State of the Mercosur (State Party Producer) related to products registered in the country (State Party Receiver). Deadline for completion of the process. Deadline to begin marketing products.
6.	Provision No. 758/09	2009	MEDICAL PRODUCTS criteria bio-waiver Bioequivalence Studies for oral solid medicines immediate release
7.	Disposition 2819/2004	2004	This establishes good manufacturing practices (GMPs) that must be followed by manufacturers, importers and exporters of medicinal products.
8.	Regulation No. 7066/13	2013	Provides that the companies authorized by ANMAT to develop and / or importing and / or exporting medicinal and / or pharmaceutical active ingredients, must present the SITE MASTER FILE annually according to the specifications provided for in this provision
9.	Regulation No. 2574/2013	2013	Gluten Free Drugs.

Types of Assessment[15]

Data Assessment Type 1 ('Verification' Assessment)

This type of approach avoids duplicating the assessment of a new product that is identical to one which has been approved in other country. The elements are:

- Recognition of an authorization by one or more 'reference' or 'benchmark' agencies
- A 'verification' process to validate the status of the product and ensure that the product for local marketing conforms to the authorized product.

Data Assessment Type 2 ('Abridged' Assessment)

This approach also preserves resources by not re-assessing the complete scientific supporting data but focuses on aspects that must be evaluated specifically for the local environment.

- It is a pre-requisite that the product has been registered by a 'reference' or 'benchmark' agency
- An 'abridged assessment' is carried out in relation to the use of the product under local conditions (e.g. concentrating on aspects of quality such as stability and on a benefit-risk assessment for the local medical practice/culture and forms of disease)

Data Assessment Type 3 (Full assessment)

In this approach the agency has appropriate resources, including access to suitable internal and external experts, to carry out a 'complete' review and evaluation of the supporting scientific data.

- A full, independent review of quality, pre-clinical (safety) and clinical (efficacy) data is carried out;
- Information on registrations in other country (if any) is taken into consideration but is not a pre-requisite to filing or for authorization.
- In practice, prior authorization was a legal requirement in some countries, before local authorization could be finalized, but filing the application and the review was not delayed.

Argentina uses "Data Assessment Type 1" so there will be some recognized agencies or countries that use to be followed by Argentina.

Reference Countries[16, 17]

Argentina is a country that relies profoundly on decisions made by countries that it reflects of 'high sanitary surveillance'. Thus, the registration process will depend on in what countries a drug product is already being marketed in, irrespective of the country of origin or countries where the pharmaceutical is registered but not marketed. For this purpose ANMAT made two lists of countries, based on the level of sanitary surveillance, called Annex I and Annex II. The lists have been created in 1992 under the scope of Decree 150/1992.

Annex I countries:

USA	France
Japan	United Kingdom
Sweden	Netherlands
Switzerland	Belgium
Israel	Denmark
Canada	Spain
Austria	Italy
Germany	

Annex II countries:

Australia	China
Mexico	Luxembourg
Brazil	Norway
Cuba	New Zealand
Chile	Hungary
Finland	Ireland

Category of product[16, 17]

The different registration cases are described in the 150/1992 Decree, which classifies products into three categories based on the countries in which they are manufactured and/or commercialized. Each category is described in a separate article of this Decree.

1. 'Article 3' Product
2. 'Article 4' Product
3. 'Article 5' Product

1. 'Article 3' Product (Generic Product)

Timeline for approval: about 12 months

- Drug products manufactured in Argentina or in an Annex II country, when there is a similar drug product already registered in Argentina.
- Drug products manufactured in Argentina, with marketing authorization in any Annex I country, even if there are no similar products registered in Argentina.

Summary of documents required for submission:

1. Product information: name, formula, pharmaceutical form, pharmacologic classification, marketing condition.
2. Technical information: testing standard, specifications, shelf life, manufacturing method, pharmaceutical equivalence evidence.
3. Labeling texts (packaging and leaflets)
4. If manufactured in an Annex II country: CPP of origin
5. GMP certificate from Annex I country or Argentina

2. 'Article 4' Product

Timeline for approval: about 10 months

Drug products with marketing authorization in at least one Annex I country.

Summary of documents required for submission:

1. CPP from Annex I country – Marketed status
2. Labeling texts (packaging and leaflets)
3. Technical information: to be submitted only upon authority request

3. 'Article 5' Product (New Product)

Timeline for approval: not less than 3 years

- Drug products manufactured in Argentina, when there are no similar products already registered in Argentina.
- Drug products manufactured in an Annex II country and not marketed in any Annex I country, when there are no similar products already registered in Argentina.
- Drug products manufactured in a non-Annex I, non-Annex II country, and not marketed in any Annex I country.

Summary of documents required for submission:

1. Product information: name, formula, pharmaceutical form, pharmacologic classification, marketing condition.
2. Technical information: testing standard, specifications, shelf life, manufacturing method, pharmaceutical equivalence evidence.
3. Labeling texts (packaging and leaflets)
4. If manufactured in an Annex II country: CPP of origin
5. GMP certificate from Annex I country or Argentina
6. Safety and efficacy evidence

First Batch Verification[16, 18]

For the first product release of new drug products, or after variations that could affect the quality of a locally manufactured or imported drug product, a procedure known as first batch verification applies. When products are manufactured locally in Argentina and when they are imported from other countries, quality check is required for local product release. The quality control duties can be performed by the manufacturing or importing company, or by an authorized third party. For the following cases:

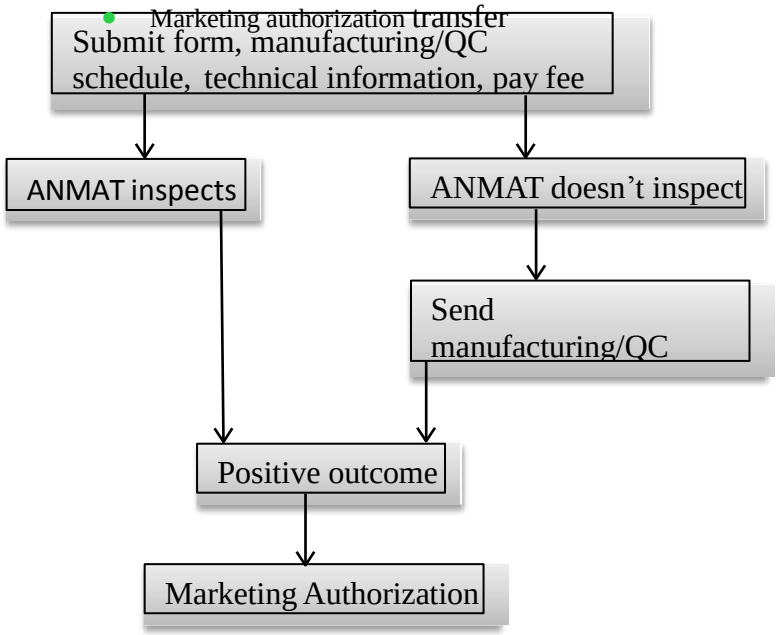
- new product registration
- new concentration of biologic or small-therapeutic-window APIs
- new pharmaceutical form
- marketing authorization transfer

Before the release of the first batch for commercial purposes, the manufacturing or importing company has to make request the first batch verification, by submitting the corresponding form, the manufacturing and/or quality control schedule, the relevant technical information and by paying a fee. ANMAT will then physically inspect the manufacturing and/or control processes in the dates provided in the schedule, OR review the manufacturing and/or control records afterwards as a 'documental verification'. Upon a positive outcome, a marketing authorization will be granted.

Process Flow:

- Local manufacturing Importation of drugs → Local QC

- New product registration
- New concentration of biologic or small-therapeutic-window APIs
- New pharmaceutical form
- Marketing authorization transfer



GENERIC DRUG REGISTRATION[14, 16, 17]

As per ANMAT rule any product registration will be valid for 5 (five) years only. After that, applicant will have to make a new application for re-registration purpose.

New registration[17, 19]

Application for a fresh new registration for generic drug can be made according to the rules and requirements given in Regulation No. 3554/02.

Renewal or registration

In Argentina, once granted the registration by ANMAT, product certificates expire in 5 years. The registration renewal procedure is relatively very simple, almost an entirely administrative procedure. The request for renewal has to be submitted within 30 days prior to the certificate expiration date, and should include the following documents:

1. Written request
2. Sworn statement – marketed/non marketed status
3. Evidence of marketing
4. Certified copy of original certificate
5. Copy of last approved labeling texts

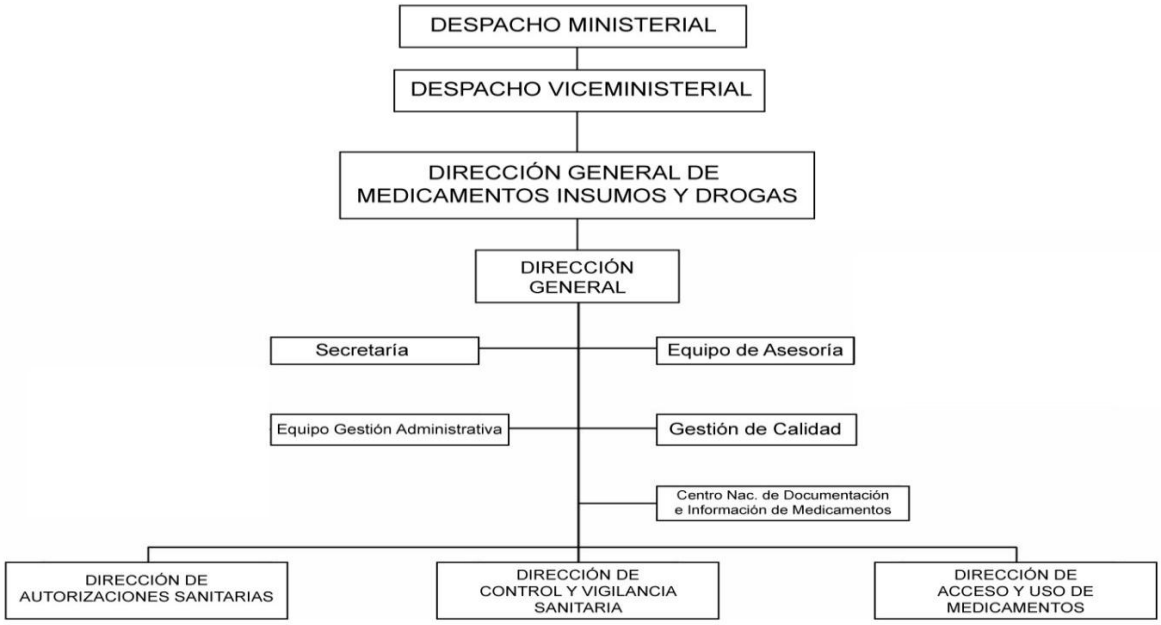
GENERIC DRUG REGULATION & REGISTRATION PROCESS IN PERU

Agency: Dirección General de Medicamentos, Insumos y Drogas (DIGEMID)
Directorate-General of Medical supplies and Drugs (In English)

The Directorate-General of Medical supplies and Drugs (DIGEMID) is an agency of the Ministry of Health, created with the Legislative Decree No. 584 of 18 April 1990. The DIGEMID is technical institution legislation's main purpose, to make people have access to safe, effective and quality medicines and these are used rationally and therefore have established a policy to develop activities seeking to provide better service to customers, Apply continuous improvement in each of its processes[20]

It establishes and maintains a system of quality management based on compliance with ISO 9001:2001 and legislation. Also provides workers with training and resources necessary to achieve the objectives

ORGANIZATION CHART[21]



RULES GOVERNED THE GENERIC DRUGS[22]

S. No.	Law No.	Date of Publication	Topic Covered
1.	Law No. 29459	November 26, 2009	Act Pharmaceuticals, Medical Devices and Health Products.
2.	Law No. 27444	April 11, 2001	Approves Law on General Administrative Procedure.
3.	Law No. 26842	July 20, 1997	General Health Law.
4.	Supreme Decree No. 016-2013-SA	December 24, 2013	Amending articles of the Regulation for Registration, Control and Health Surveillance of Pharmaceutical Products, Medical Devices and Health Products
5.	Ministerial Resolution No. 461-2013-MINSA	July 26, 2013	Approved Technical document entitled "Administrative Simplification Plan procedures of the General Directorate of Environmental Health and the General Directorate of Medicines, Supplies and Drugs"
6.	Supreme Decree No. 001-2012/SA	January 22, 2012	Amending articles for the Regulation for Registration, Control and Health Surveillance of Pharmaceutical Products, Medical Devices and Health Products.
7.	Supreme Decree No. 016-2011/SA	July 27, 2011	Approves Regulations for the Registration, Control and Health Surveillance of Pharmaceutical Products, Medical Devices and Health Products.

REGULATORY CHANNGES IN PERU[22]

S. No.	Changes	Before (2011)	After
1.	Classification of Drugs	No	Three categories
2.	Approval time	7 days	Depends on category Category one – 2 months Category two – 3 months Category three – 12 months
3.	Fee	US $ 89	Category one - 59.74% of tax unit Category two - 99.95% of tax unit Category three - 99.65% of tax unit Tax Unit - US $1284.80
4.	BA / BE requirement	No	Yes
5.	GMP requirement	No	Yes

GENERIC DRUG REGISTRATION:

The Peruvian pharmaceutical market is the second smallest in the region. The market is expected to increase by a moderate CAGR in dollar terms between 2011 and 2016. Pharmaceutical expenditure per capita is the lowest in the region. The market increased five times between 1995 and 2010.[23]

To be marketed, medicines require an authorization by the Ministry of Health called the "Sanitary Registration (RS)" or marketing approval. According to previous laws, the process involved in obtaining the Sanitary Registration must not exceed seven days. If it takes longer, the RS is automatically granted. This flexibility in the law had considerably increased the number of pharmaceutical products entering the country, with more than 12,000 products registered by 2002. A revised law on obtaining Sanitary Registration has been implemented, with the support of the Ministry of Health and civil society.[10]
In Peru, marketing approval for Generic drugs is given by competent authority named Directorate-General of Medical supplies and Drugs (DIGEMID), whereas National Institute of Health is there for any assistance over approval of drugs.

CATEGORY OF PRODUCTS:

According to the new law "Law 29316, enacted in 2009" there are three categories for registration purposes: [24]

Category 1: - active ingredients found on the national essential drug list.
Category 2: - active ingredients not found on the national essential drug list but found in the records of a drug regulatory body from one of the twelve countries with high health monitoring standards.

Category 3: - active ingredients that do not fall within either category 1 or 2 descriptions.

REGISTRATION REQUIREMENT:-

1. **Registration Fee**
   New Registration: - $ 1284.1576
   Re-registration: - $ 1284.1576
2. **Dossier**

   The Dossier must be translated in Local Language i.e. Spanish, and should contain all required information.
   Dossier can be consisted in to three parts,

   1. Index
   2. Technical Documents
   3. Legal Documents

INDEX: -

1. Qualitative and Quantitative Formula
2. Certificate of Analysis of API
3. Certificate of Analysis of Excipients
4. Analytical Technique of API
5. Analytical Technique of Excipients
6. Specification for Packing Material
7. Certificate of analysis of finished product
8. Manufacturing Process Validation Report -FP
9. Analytical Technique of Finished Product
10. Stability Documents (3 Pilot Batches- Accelerated Stability condition - 40ºC ± 2/ 75% RH ± 5%, and Long Term Stability condition - 30ºC ± 2/ 65% RH ± 5%
11. Primary Artwork (Packaging & Labeling)
12. Certificate of pharmaceutical product as format of WHO
13. Certificate of GMP
14. Information of efficacy and safety of Drugs
15. Validation of analysis method of FP
16. Monographs
17. Secondary Packing Material Specifications & STPs

TECHNICAL DOCUMENTS: -

1. MFR (Master Formula Record) including composition of coating agent
2. Batch Manufacturing Record
3. Batch Packaging Record
4. Raw Material Specification, STP & CoA's (Both Active and In actives)
5. In-Process, Finished Spec. & STPs along with COAs

LEGAL DOCUMENTS: -

1. Manufacturing License
2. Free Sale Certificate
3. WHO GMP and COPP to be provided with apostil or embassy attestation as per the country requirement.

Specific Requirements required to be fulfilled for Peru,

1. Allotment of Batch numbering system SOP
2. Pharmacopoeia Monographs for API, Excipients and Finished dosages, if any.
3. Spec. & STPs for the ingredients of coating agent
4. Spec.& STPs for Secondary Packing Materials
5. FP Spec. must include the parameters, Description, Average weight, UOD & Micro test.
6. Legal documents attestation must be done in Peru Embassy.

5.3 GENERIC DRUG REGULATION & REGISTRATION PROCESS IN VENEZUELA[25]

Agency: Instituto Nacional de Higiene Rafael Rangel (INHRR)
Rafael Rangel National Institute of Hygiene (In English)

The National Institute of Health, was created by Decree of the National Executive as of October 17, 1938 and published in the Official Gazette of the United States of Venezuela No. 19,700 dated October 18, 1938 " , by Decree No. 2104 dated March 29, 1977, is designated by the name of "Rafael Rangel". National Institute of Hygiene "Rafael Rangel" is a Health Reference Center for prevention, surveillance and control of the health of Venezuelans, to produce goods and provide quality services to meet the national demands of immunizing agents and diagnostics of infectious diseases.

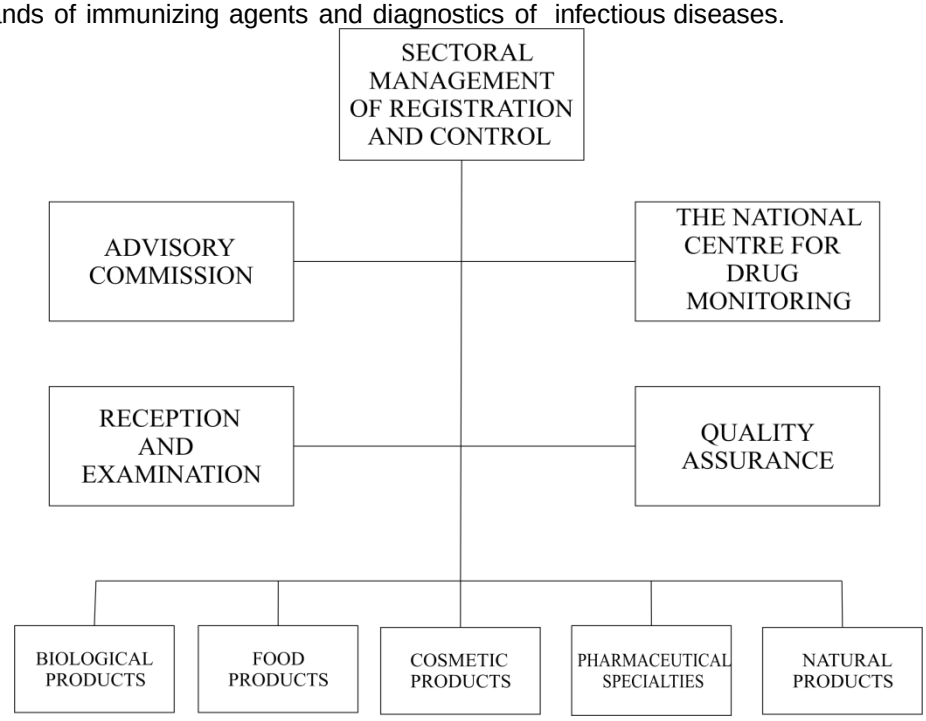


Fig. 7: Organization Structure for Venezuela:

5.3.1 Rules governed the Generic Drugs

Rules	Publication Date	Gazette no.
Standard Drug Service	2011-09-21	-
Bioavailability And Bioequivalence Rules of Pharmaceuticals	2006-08-14	No. 38,499
Standard Advertising	2004-06-23	No. 37,966
Drug Law	2000-08-03	-
Standard Register For Health Pharmaceutical Combination	Undated	-
Standards of Practice of Distribution	Undated	No. 37966-23.0

5.3.2 Product Category:

A. Known Product (Generic Drug)

It is the one that presents the same active ingredients, dosage form, dosage and indications of other product already approved in the country. The analysis time for products identified as known shall be 60 days.

B. New product

There are two categories available for new product.

“New Product category A” to the one whose active ingredient is not approved in the country. "New Product Category B" one in which the active principle is approved in the country that presents a modified-release formulation, a new route of administration, new dosage form, new salt of an active principle approved new concentration that does not fit the approved dosage range or new combination of active principle adopted. The time of analysis for the new products will be of 180 days.

5.3.3 GENERIC DRUG REGISTRATION

As per INHRR rule any product registration will be valid for 7 (seven) years only. After that, applicant will have to make a new application for re-registration purpose.

5.3.3.1 New Registration

Under the Medicines Act and the Regulations of the Law Practice of Pharmacy, for authorization of sale throughout the country in a Specialty Pharmacy, applicant must meet the requirements of Form F-023-RCDM Application for National Registration of Pharmaceuticals.

Steps

1. For each specialty pharmaceutical to register, applicant must complete Form F-RCDM-023 Application for National Register of Pharmaceutical and submit an additional copy of the same to be stamped and signed by the Receiving Unit Drug Samples.
2. Documents have to be prepared and separated as legal annexes, chemical - pharmaceutical, preclinical - clinical, depending on the category of the proprietary medicinal product. A sample of the product, the original of the certificate of pharmaceutical product and an empty copy of the Form F-RCDM-017 report for the admission of applications for registration of proprietary medicinal is required. Some original attachments must be legalized or in certified copies.
3. Pay the registration fee of pharmaceutical product, depending on the product category. Payment should be made on the current account of the National Institute of hygiene 'Rafael Rangel', no. 0102 - 0132-28000869-9691, Banco de Venezuela. The amount to pay depends on the category of specialty pharmaceuticals to register, according to

the Official Gazette of the Bolivarian Republic of Venezuela No. 39.819 from 13/12/2011. Rules for the payment of services of the INH "RR", present on Circular Nº P-178/2012 of date 10/02/2012.

4. After compilation of all required documents there is a requirement to make an appointment for delivery of the Registration Request.
   At the day of appointment, company representative must present at the head office of INHRR and deliver the signed form, attachments, sample of Medicinal Products, deposit the payment of the respective rate with copy and the record of the request for an event where it indicates the date of the same.
5. INHRR will verify the request, and give instructions to the Sponsor for the issuance of invoice by the payment. Subsequently, the Sponsor is directed back to the Receiving Unit, with original and copy of the invoice and the official who attends, will deliver the form F-019-RCDM, the Evidence of Receiving Applications for Licensing of Proprietary sealed and signed .
6. In a period of 20 working days the review of the application form will be conducted by applying the F-RCDM-017 report to the Admission Health Record Applications for Proprietary Medicinal Products , and if that has all required information according to the product category, the application will be accepted and relayed to Sponsor by delivering a copy of Form F-RCDM-023 Application for Registration of Pharmaceuticals with National seal, signature and date of the respective Admission.
7. If the application is not accepted, it will be notified via email and then all files must be removed for correction within a period not exceeding ten (10) business days, Monday through Friday, between the hours of 12 m 1pm . The INH "RR" keep a copy of the digital information received (CD's). If the application is not withdrawn by the respective Sponsor after the set time, the Registration Request will be canceled and the file will be deleted.
8. There will be maximum two readmissions for corrected application. Upon acceptance of the application is distributed to the departments responsible for assessing the quality, safety and efficacy; they may request additional information, if required.

Request for Additional Information

If during the process of evaluation of the application, it detects information required to complete the process, it will be requested by the respective unit, in a letter to the sponsor of the product. The evaluation process will stop until receipt of the required documents. You must restart the entire process of application for registration health described above if the reasons or justifications to support an application are not satisfactory. In case of Comprehensive Evaluation is in compliance:

After the comprehensive evaluation of the product by the respective technical units, new products are further evaluated by the Pharmaceutical Review Board. If satisfactory the opinion, agency will proceed to issue of the respective Health Registry Office, as well as the conditions for the Commercialization authorized medicinal product registered. Applicant is requested to submit product sample for further evaluation.

In case of Comprehensive Assessment is Nonconforming

When the conclusion of the assessment of quality, safety and / or efficacy of the medicinal product subject to medical registration is not correct, proceed to the rejection of the application for licensing, indicating the reasons that led to this opinion. The Sponsor shall remove the application from respective Receiving Unit, the Office of Health Registration Rejection and technical documentation.

Reconsideration of Opinion

The Sponsor shall have 15 working days from the date of receipt of the corresponding notice, to request reconsideration of the marketing conditions granted or rejecting an application for licensing, by letter addressed to the Marketing Management and Control Register, with brackets substantiating the requested reconsideration. Presenting collections of quality, safety and efficacy will be accepted, evaluated unscheduled application, in which case should proceed to make a further application for licensing or post-registration respective change, as appropriate.

Number of Sanitary Registration and Record Holder

In the case of pharmaceutical products, medical record number consists of the initials EF,

identifying the type of drug, followed by a sequential number and the last two digits of the year in which the sanitary registration is granted. Example: EF. 32.390/11

First Batch Control of Marketing

Once registration is awarded to medicinal product, the Representative of the product in the country (health record holder) must notify the National Hygiene Institute "Rafael Rangel", through its Pharmaceutical Sponsor, the beginning of the marketing, request sample collection of the first batch and payment of the corresponding fee. Consider that the failure to start notification marketing or not marketing the product in the time stated in the regulations, leading to the cancellation of the respective authorization.

5.3.3.2 Renewal of registration or re-registration

The duration of the health registration of pharmaceutical products is seven (7) years, in accordance with the standards of the Review Board of Pharmaceutical Products. Representative of the company will have to present before the National Institute of Hygiene “Rafael Rangel“, the document that credits it as such, granted by the Holder of the Sanitary Record of the respective Medicine. At least 6 months before the expiration of the registration, the product through the pharmaceutical sponsor representative, shall request the renewal of the registration, using the F-RCMD-007 application form for renewal of the sanitary registration of pharmaceutical specialties attaching the required documents. The application for renewal of the registration shall be unacceptable, in cases of loss of therapeutic effect, non-compliance with marketing conditions or problems of quality, safety or efficacy of the product.

5.3.4 Forms for generic drug registration

S. No.	Form No.	Purpose
1.	F-RCDM-023	New Registration
2.	F-RCDM-007	Renewal of Registration / Re-registration
3.	F-PERC-010	Post-registration Change Legal Aspects – Pharmacist
4.	F-PERC-011	Post-registration Change Legal Aspects - (Pharmacist Attached To the Sponsor)
5.	F-PERC-012	Post-registration Change Legal Aspects – Owner
6.	F-PERC-013	Post-registration Change Legal Aspects - Company Name
7.	F-PERC-014	Post-registration Change Legal Aspects – Representative
8.	F-PERC-031	Post-registration Change Legal Aspects – Store
9.	F-PERC-015	Post-registration Change Aspects-Incorporating Clinical Warnings Recommended by WHO / PAHO
10	F-PERC-016	Post-registration Change Aspects -Incorporating Clinical Warnings suggested by a Non-Governmental Organization or Recognized Independent Scientific Society
11	F-PERC-017	Change Post-Registration Clinical Aspects - Age Group
12	F-PERC-018	Change Post-Registration Clinical Aspects – Indication
13	F-PERC-019	Change Post-Registration Clinical Aspects- Introduction Previously Authorized to another Pharmaceutical Product
14	F-PERC-020	Change Post-Registration Clinical Aspects - New Presentation
15	F-PERC-021	Change Post-Registration Clinical Aspects - Dosage-range
16	F-PERC-022	Change Post-Registration Clinical Aspects - Add Restrictions on Use
17	F-PERC-023	Change Post-Registration Clinical Aspects - Remove Restrictions on Use
18	F-PERC-024	Change Post-Registration Clinical Aspects - Route of Administration
19	F-PERC-025	Post-registration Change – Texts
20	F-PERC-026	Post-registration Change - Adhesive Label Printing or Provisional
21	F-PERC-038	Modifications of the application for registration of Pharmaceutical Products Health National and imported. Legal aspects. (STORE)
22	F-PERC-039	Modifications of the application for registration of Pharmaceutical Products Health National and imported. Legal aspects. (PHARMACIST ATTACHED TO THE SPONSOR)
23	F-PERC-040	Modifications of the application for registration of Pharmaceutical Products Health National and imported. Legal aspects. (PHARMACEUTICAL SPONSOR)
24	F-PERC-041	Modifications of the application for registration of Pharmaceutical Products Health National and imported. Legal aspects. (Owner)

25	F-PERC-042	Modifications of the application for registration of Pharmaceutical Products Health National and imported. Legal aspects. (Company Name)
26	F-PERC-043	Modifications of the application for registration of Pharmaceutical Products Health National and imported. Legal aspects. (Representative)
27	PERC-F-045	Application for Certification of Specialized Centers for Studies of Bioavailability / Bioequivalence
28	PERC-F-046	Application for Certification of Clinical Studies Unit for Bioavailability / Bioequivalence
29	PERC-F-047	Application for Certification of Units where made Bioanalytical Studies Bioavailability / Bioequivalence
30	PERC-F-048	Application for Certification of Units for Statistics conducted studies where Bioavailability / Bioequivalence
31	PERC-F-049	Application for Certification of Clinical Laboratories serving the specialized centers or clinical units where studies Bioavailability / Bioequivalence perform"
32	PERC-F-050	Application for renewal of Specialized Centers for Studies of Bioavailability / Bioequivalence
33	PERC-F-051	Application for renewal of Clinical Studies Unit for Bioavailability / Bioequivalence
34	PERC-F-052	Application for renewal of Units where made Bioanalytical Studies Bioavailability / Bioequivalence
35	PERC-F-053	Application for renewal of Units for Statistics conducted studies where Bioavailability / Bioequivalence
36	PERC-F-054 PERC-F-054	Application for renewal of Clinical Laboratories serving the specialized centers or clinical units where studies Bioavailability / Bioequivalence perform"

5.4 GENERIC DRUG REGULATION & REGISTRATION PROCESS IN CHILE

Agency:

Instituto de Salud Pública de Chile (ISP) - Public Health Institute of Chile (In English)
Agencia nacional de medicamentos (ANAMED) - National Agency for Medicines (In English)

The current Public Health Institute of Chile (ISP) traces its historical roots to 1892 when, on 15 September of that year, was created by the Institute of Hygiene Law. The Institute of Public Health is in charge of regulating trough the authorization of imports, production and commercialization of drugs. The National Agency for Medicines (ANAMED) is a Department of the Public Health Institute of Chile (ISP).[26]

ANAMED is in charge of drug registration in Chile as set out in the regulation of the National System for Pharmaceutical Control, called Decreto Supremo N°3/2010. All pharmaceutical products marketed in the country must have a current health register or market authorization.

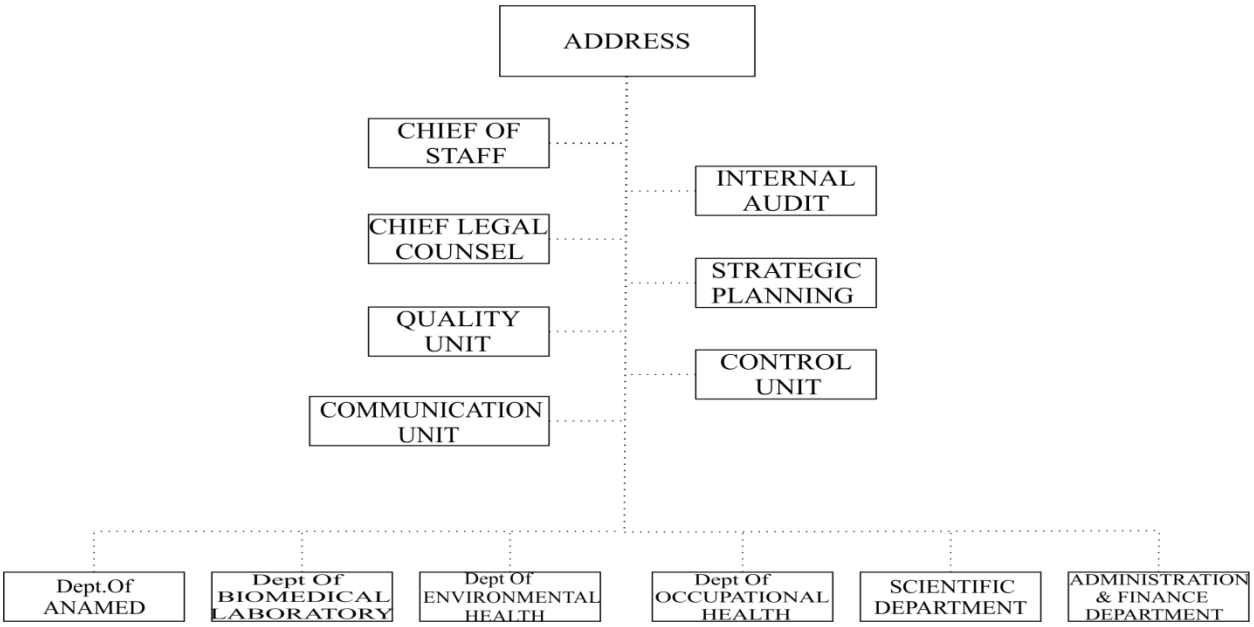


Fig 8: - Organization Structure for Chile[27]

5.4.1 RULES GOVERNED THE GENERIC DRUGS[28]

Table 11: RULES GOVERNED THE GENERIC DRUGS

S. No.	Decree Number	Year of publication	Topics Covered
1.	Ord. N ° 1026/13	2013	Requirements to be met by Health Pharmaceutical Product Registration, regarding updating your documentation.
2.	DS N ° 3/2010	2011	Regulation of the National Pharmaceutical Control Products for Human Use
3.	DS N º 239/02	2002	Regulation of the National System of Control Cosmetics.
4.	Law No. 19880	2003	Administrative Procedure Act
5.	Resolution N º 3225/08	2008	Requirements to perform BA/BE study with particular product.
6.	Resolution N º 728/09	2009	
7.	Resolution N º 2029/09	2009	

5.4.1.1 New Regulation: (New Drug Act - Enacted on 16 Jan 2014)[29]

The new Chilean pharmaceutical law, Ley de Farmacos, aims at regulating generics bioequivalence and biosimilars in the country as well as enforcing prescription by generic name as part of a joint effort between the Ministry of Health (MoH) and the Public Health Institute to regulate the pharmaceutical market in the country. The new law aims at better regulation of biosimilars and generics in the country as the "pharmaceutical environment is not regulated enough in Chile".

Public Health Institute is undergoing a process of bioequivalence testing, aimed at regulating differences between generic and bioequivalent drugs.

Another part of the new pharmaceutical law focuses on fostering prescription by generic name: doctors will have the mandatory duty to prescribe drugs by active pharmaceutical ingredient (API) or generic name. This will prevent pharmacies from pursuing their pro-branded-drug stance with patients being able to choose whatever drug suits their budget.

5.4.2 GENERIC DRUG REGISTRATION[30]

The evaluation of an application for registration of pharmaceutical product by the Institute of Public Health (ISP), is the systematic study of the pharmacological, toxicological, clinical and therapeutic pharmaceutical properties of a drug, in order to determine its quality, effective and safe for use in humans.

Requirements and procedures must follow for registration.

The application for registration shall be submitted to the Institute, in special forms approved by it, which shall be signed by the applicant or his representative legal.

Forms must include the following information:

a. Owner's name if natural person or legal representative, if legal person;
b. Name of technical director of the facility that performs the manufacture, importation or distribution, these functions registered or qualified professional for the purpose requested
c. Name and address of applicant and type of facility, if applicable;
d. Trade name generic name or other name, if applicable;
e. Dosage form, dosage unit dosage form and route of administration;
f. Therapeutic class or group;
g. Scheme of preparation:
    - Products manufactured in itself, legally and technically qualified to do labs.
    - Product manufacturing on the other production laboratory authorized on behalf of the applicant for registration.
    - Products manufactured by a laboratory authorized production. Imported finished

products, either directly or through other approved establishments.

- Finished products imported and manufactured abroad, by how much of a national pharmaceutical establishment.
- Imported in bulk to be completed in the country, products either directly or through other approved establishments.
- Semi-finished products imported to be completed in the country, either directly or through other approved establishments.

h. Full name of the foreign principal under the name that appears on the license or authority, if the procedure is done on leave or power;

i. Name and location of the manufacturer, whether manufactured in the country or abroad by the applicant;

j. Presentation of the product, or describing the contents of the various packages: for sale to the public, as for clinical and medical samples, and

k. Description of the packaging, noting their material, both in the product as their cases and other containers that are external.

The forms specified in the preceding paragraph must be accompanied by the background as follows:

a. Complete formula, attached in duplicate, both qualitatively and quantitatively expressed in units of weight or volume in metric or standard units internationally recognized, as appropriate, signed by responsible professional. For these purposes, it should be considered that:

- All the ingredients that form the dosage form are expressed by their generic or chemical names and Castilian language;
- If the product composition would have dyes, must be specified with its generic or, failing these names, by their chemical name or its equivalent in having Indices Dyes Permitted and approved in the country. The same provision shall apply when colored capsules are used;

b. Proposition efficacy period, supported by relevant stability studies in duplicate;

c. Clinical and pharmacological essay, attached in duplicate, in Castilian language and whose origin and fidelity should be responsible undersigned professional application;

d. Draft tag or label, attached in triplicate, on separate sheets and Castilian language;

e. Prospectus for information professional, in triplicate, backed by relevant scientific information and the declaration of the bioavailability and therapeutic equivalence, in the case of pharmaceutical products whose active ingredients are subject to this requirement;

f. Patient Information Leaflet in triplicate and approved by the relevant scientific information;

g. Sufficient samples of the product, corresponding exactly to the formula stated in its pharmaceutical form and are contained and labeled in similar packaging to the final;

h. Samples or standards of API and strains in specific cases, stating their origin through the corresponding analytical protocol;

i. Specification of quality and purity of the raw materials used;

j. Analytical method, in duplicate and in Castilian language, signed by the practitioner making the request and the head of quality control,

k. scientific information should refer to:

- Manufacturing and quality control;
- Selective pharmacological studies in animals;
- Toxicological studies in animals;
- Physico-chemical data;
- Properly validated pharmacokinetic studies, where appropriate, in accordance with Article 41;
- Studies to demonstrate therapeutic equivalence, duly authenticated in accordance with Article 41;
- Dissolution tests, as appropriate, conducted in the country,
- Clinical studies to support their effectiveness and safety,

l) Consisting Legal Documents, as applicable, by:

- Sanitary certificate or recommended by the World Health Organization official certification;
- License or power legalized foreign principal;
- Notarized manufacturing and distribution agreement;
- Agreement signed by domestic pharmaceutical manufacturing facility with laboratory production abroad;
- Official certificate attesting that the foreign manufacturer by convention is duly authorized in their country;
- Certificate of good manufacturing practices issued by the health authority of the country where it is situated; and
- Agreement with external quality control laboratory authorized by the Institute when procedure;

m. Any other information that the Institute, in a reasoned, deems appropriate, and

n. Proof of payment of the customs duty to what is requested.

5.4.3 New Labeling rule for generic drugs[31]

The law requires bioequivalent drugs (both generics and originators) to be readily identifiable by having a yellow seal, which must occupy 25% of the surface on at least four of the six faces of the packaging.

Fig. 9: The Figure Debiting New Labeling Changes

CONCLUSION

Despite the many harmonization efforts carried out by the major Latin American markets, the road toward total harmonization, if at all possible, seems steep and convoluted. The main reasons behind this is the size of the region and the great number of countries included in the area, each of them with different regulations and regulatory system, political background and different policy approaches to healthcare and pharmaceuticals. One proposal which is becoming quite popular in the country is that of “convergence” rather than “harmonization” in use in the Asia Pacific Economic Cooperation Area (APEC). With regulatory convergence, we mean a voluntary process where the countries in question will have their regulatory requirements similar or more aligned but it does not require a full harmonization of rules and laws, which encompasses changing the laws in each country and is therefore more difficult to achieve. Convergence of regulations can therefore be considered as the most viable solution for the Latin American region so far, an option that could also be applied for a future harmonization of drug pricing in the region. Despite recent talks of harmonization of drug pricing in the region, this is considered as highly unlikely to be achieved in the near future, as most countries in Latin American have their own pricing regulations and market mechanics that would make harmonization on front unviable. The only possible “convergence” option may be the construction of a reference pricing database where countries can draw from.

Many other changes are expected to affect the regulatory pharmaceutical sector in LATAM in the coming years. Although the environment is still challenging, the regulatory environment is becoming more open and offers greater opportunities for foreign pharmaceutical companies.

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