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Review Article

Strategic planning for regulatory submission of injectables/parenterals

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ABSTRACT

The pharmaceutical industry is one of the highly regulated industries, with many rules and regulations enforced by the government to protect the health and well-being of the public. Therefore, the aim of the pharmaceutical industry is to identify and develop a drug product which can be tailor made to meet the diverse market requirements. The regulatory process to obtain marketing authorizations (MAs) for drugs in Latin American (LATAM) countries and EU counties, despite regional harmonization efforts, is highly country-specific. Complex and evolving ad-hoc requests from reviewers must be proactively addressed to avoid costly delays or show-stoppers to local product launches. Overall mission is to protect and promote public health by helping to ensure that human drugs are safe and effective for their intended use, that they meet established quality standards, and that they are available to patients. The range and complexity of the human drug supply and development pipeline, and the global nature of regulated industry operations present unprecedented challenges to effective regulatory oversight. the complete pathway of drug from R&D to the developing the product with the goal of obtaining regulatory market approval in desired markets , specific country reference , supporting data and labeling requirements, drug registration procedures and dossier filing of modules 1, 2, 3 respectively.

Key words: *Regulatory submission; Injectable; Parenteral; Dossiers*

INTRODUCTION

The Indian pharmaceuticals market is the third largest in terms of volume and thirteenth largest in terms of value. Branded generics dominate the pharmaceuticals market, constituting nearly 70 to 80 percent of the market. India is the largest provider of generic drugs globally with the Indian generics accounting for 20 percent of global exports in terms of volume. Of late, consolidation has become an important characteristic of the Indian pharmaceutical market as the industry is highly fragmented. India enjoys a prominent position in the global pharmaceuticals sector. The country also has a large pool of scientists and engineers who have the potential to steer the industry ahead to an even higher level. Presently over 80 percent of the anti-retroviral drugs used globally to combat AIDS (Acquired Immuno Deficiency Syndrome) are supplied by Indian pharmaceutical firms.[1]

The Indian Pharma industry, which is expected to grow over 15 percent per annum between 2015 and 2020, will outperform the global Pharma industry, which is set to grow at an annual rate of 5 per cent between the same periods. The market is expected to grow to US$ 55 billion by 2020, thereby emerging as the sixth largest pharmaceutical market globally by absolute size. India has also maintained its lead over China in pharmaceutical exports with a year-on-year growth of 7.55 per cent to US$ 12.54 billion in 2015, according to data from the Ministry of Commerce and Industry. The Injectable Drug Delivery market is expected to reach $574.8 Billion by 2020 from $326.1 Billion in 2015, growing at a CAGR of 12.0% from 2015 to 2020. Injectable drug delivery offers a promising alternative for the delivery of drugs that are ineffective when administered orally. Injectable drug delivery is aimed to maximize patient compliance and reduce the frequency of dosage administration without compromising the effectiveness of the treatment.[2]

EUROPEAN MARKET AN OVERVIEW

Since the last ten years, the European pharmaceutical industry has undertaken major changes to respond to global challenges, namely, the competition from emerging countries, the escalating

cost of drug development and the expiry of the patents on blockbuster drugs. The European Union represents a major manufacturer and exporter of pharmaceutical products. According to the European Commission the EU is the second global manufacturing location for pharmaceuticals behind the US and ahead of Japan, and holds a dominant position in a number of areas, including the production of vaccines where 90% of major manufacturer's global output is produced in Europe. The EU exports of pharmaceuticals in current USA dollars have continuously increased since 2002 in spite of the global economic crisis. In 2012, the EU exports of pharmaceuticals represented 291.6 billion of dollars. The EU pharmaceutical trade surplus has also increased from 21.5 billion of dollars in 2002 to 70 billion of dollars in 2012.[3]

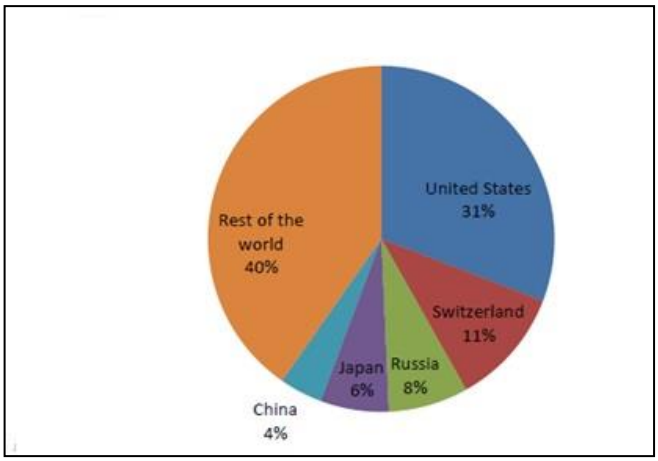

Figure 1: Export of pharmaceuticals from Europe to other countries

European Union	
Area	10,180,000 km
Population	742,452,000
Currency	Euro
Official languages	Dutch, English, French, German, Greek, and Swedish
Regulatory Authority	EMA (European Medicine Agency)

Europe is a continent that comprises the westernmost peninsula of Eurasia. It is generally divided from Asia by the watershed divides of the Ural and Caucasus Mountain, the Ural River, the Caspian and Black Seas, and the water ways connecting the black and Aegean Seas.

However, in the case of medicinal products for human use, the introduction of changes to the labeling or package leaflet that is not connected with the summary of product characteristics is not governed by the procedures of the Variations Regulation. In accordance with Article 61(3) of Directive 2001/83, these changes are to be notified to the relevant competent authorities and they may be implemented if the competent authority has not objected within 90 days.[4]

These guidelines cover the following categories of variations, defined in Article 2 of the Variations Regulation:[5]

- Minor variations of Type IA
- Minor variations of Type IB
- Major variations of Type II

Regulatory Acts & Rules[6]

The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 and Volume 5 of the publication "The rules governing medicinal products in the European Union".

Volume 1 - EU pharmaceutical legislation for medicinal products for human use

Volume 5 - EU pharmaceutical legislation for medicinal products for veterinary use

- Medicines Act 1968
- Medicines for Human Use (Marketing Authorizations Etc) Regulations 1994
- The first and basic EEC Directive to control medicines was introduced in 1965 (Directive 65/65/EEC)

The current relevant legislation is given in Directive 2001/83/EC.

Regulations of Parenteral Drugs in EU

Good Manufacturing Practice Guidelines Medicinal Products for Human and Veterinary Use, Annex 1- Manufacture of Sterile Medicinal Products (Corrected version) gives the detailed guidance on Manufacturing of Sterile medicinal products. Rest of the marketing authorization procedures are general - single application for all type of approval.

Medicines can be authorised throughout the EU by means of a single application procedure.

Centralized procedure[7]

- All human medicines derived from biotechnology and other high-tech processes must be evaluated by the Agency via the centralized procedure.
- The European Medicines Agency is responsible for the scientific evaluation of applications for centralized marketing authorizations.
- Once granted by the European Commission, the centralized marketing authorization is valid in all EU and EEA-EFTA states (Iceland, Liechtenstein and Norway).
- This allows the marketing-authorization holder to market the medicine and make it available to patients and healthcare professionals throughout the EEA.

Regulatory Bodies[8]

- European regulator, the European Medicines Agency (EMEA)
- EMEA works closely with United Kingdom Medicines & Healthcare Products Regulatory Agency (UK-MHRA)
- Committee for medicinal products for human use (CHMP)
- Committee for proprietary medicinal product (CPMP)
- Heads of Medicines Agency (HMA)
- National Patient Safety Agency (NPSA)

Labeling

Outer packaging

- For the statement of active substances, the active substance(s), adjuvant/adsorbent, if present, should be expressed qualitatively, and quantitatively per dose unit, as they appear in Section 2 of the SPC.[9]
- For multi-dose preparations, the number of doses in the container(s) should be stated.
- The word "micrograms" should normally be spelled out as such in the labeling, with the exception that, in case of severe space limitations, it may be acceptable to use "µg" if justified and there are no safety concerns.
- The list of recipients should appear on the carton labeling and be expressed as in Section 6.1 of the SPC.
- A full statement of the precautions for disposal of unused product and/or waste material should appear on the carton labeling, unless space considerations prevent this.[10]

Small Immediate Packaging

- Pharmaceutical form short terms "List of Standard terms" may be used in case of space limitation.
- However in cases of severe space limitation, the pharmaceutical form may be omitted.

Package leaflet[11]

- Complete information regarding instructions for use, handling and disposal by the user should be included in the PL.
- The word "micrograms" should be used instead of the abbreviations "µg"
- Abbreviations of terms should not be used, as there are no space limitations in the leaflet.
- Where an adjuvant or adsorbent is present in a vaccine, the leaflet should include the following statement :
  - "Substance-X is included in this vaccine as an <adjuvant>, <adsorbent>
  - <Adjuvants> <Adsorbants> are substances included in certain vaccines to accelerate, improve and/or prolong the protective effects of the vaccine".

Module 3 – quality (drug product)

3.2.P.1 Description and Composition of Drug Product
3.2.P.1.1 Description of the Dosage Form
3.2.P.1.2 Composition
3.2.P.1.3 Description of Accompanying Reconstitution Diluent(s)
3.2. P.1.4 Type of Container Closure Used for the Dosage Form
2 ml USP Type-I Fiolax dark amber ampoules. The ampoules are provided with blue snap off and blue double band ring in Ketoprofen Injection, 100 mg/2ml, 2ml ampoule,
3.2.P.2 Pharmaceutical Development
3.2.P.2.1 Components of the Drug Product
3.2.P.2.1.1 Drug Substance
3.2.P.2.1.2 Excipients – Benzyl alcohol, arginine, WFI
3.2.P.2.3 Manufacturing Process Development
Compounding, filtration, ampoule filling and sealing
3.2.P.2.4.1 Choice of Container Closure System –
2 ml USP Type-I Fiolax dark amber ampoules
3.2.P.2.5 Microbiological Attributes
Bacterial endotoxins NMT 0.8 EU/mg
3.2.P.3.1 Manufacture
3.2.P.3.2 Batch Formula- min 30 L max 200L
3.2.P.3.3 Description of Manufacturing Process and Process Controls- filteration, sealing, sterilization
3.2.P.3.4 Control of Critical steps and Intermediates
In process and finished process
3.2.P.3.5 Process Validation and/or Evaluation
3.2.P.4.1 Specification
3.2.P.4.2 Analytical Procedures
3.2.P.4.3 Validation of Analytical Procedures
3.2.P.4.4 Justification of Specifications
3.2.P.4.5 Excipients of Human or Animal Origin
3.2.P.4.6 Novel Excipients
3.2.P.5 Control of Drug Product
3.2.P.5.1 Specification- storage, label claim, pack size, PH
3.2.P.5.2 Analytical Procedures
particulate contamination, HPLC, bacterial endotoxins in USP
3.2.P.5.3 Validation of Analytical Procedures
3.2.P.5.4 Batch Analyses
3.2.P.5.5 Characterization of Impurities
list of impurity with release limits and shelf life units
3.2.P.6 Reference standards or Materials
3.2.P.7 Container Closure System
3.2.P.8.1 Summary and Conclusion
3.2.P.8.2 Post Approval Stability Protocol and Stability Commitment- ongoing batches are summarized, stability conditions& testing time points
3.2. P.8.3 Stability Data- accelerated, long term

CONTAINERS—GLASS [12]

Glass containers for pharmaceutical use are intended to come into direct contact with pharmaceutical preparations. Glass used for pharmaceutical containers is either a borosilicate (neutral) glass or a soda-lime glass. Borosilicate glass contains a significant amount of boric oxide, aluminium oxide, and alkali and/or alkaline earth oxides. Borosilicate glass has a high hydrolytic resistance due to the chemical composition of the glass itself; it is classified as Type I glass. Soda-lime glass is a silica glass containing alkali metal oxides. Soda-lime glass has a moderate hydrolytic resistance due to the chemical composition of the glass itself; it is classified as Type III glass. The inner surface of glass containers may be treated, for example, to improve hydrolytic resistance. The treatment of Type III soda-lime glass containers will raise their hydrolytic resistance from a moderate to a high level, changing the classification of the glass to Type II.

The outer surface of glass containers may be treated to reduce friction or for protection against abrasion or breakage. The treatment of the outer surface does not come into contact with the inner surface of the container. Glass may be colored to provide protection from light or may have a coating applied to the outer surface. The quality of glass containers is defined by measuring their resistance to chemical attack. In addition, Type I containers for aqueous parenteral preparations are tested for

arsenic release, and colored glass containers are tested for light transmission.[13]

Latin America is a region of the America where Roman languages (i.e., those derived from Latin) – particularly Spanish and Portuguese, and variably French are primarily spoken.

The basic geographical sub-regions in Latin America are North America, Central America, the Caribbean, and South America;[14]

Latin America Overview

- Legislation and review process varies from country to country in Latin America.
- Presentation and evaluation of a dossier is as per local country regulation and requirements.
- Product approval in one of the reference countries or in a country of high development (Japan, Canada, EMEA, USA) presentation of a CPP per WHO (World Health Organization) guideline is followed all Latin American countries.[15]
- The approval time varies between 2 to 24 months.[16]
    - There are many groups working on harmonization initiatives:
        - **NAFTA** – The North American Free Trade Agreement, limited to the exchange of information as an instrument for promoting harmonization. (Canada, Mexico and USA)
        - **MERCOSUR** - Southern cone Common Market (Brazil, Argentina, Paraguay and Uruguay, Chile and Bolivia participate as observers)
        - **CAIS** – Central American Integration System (Costa Rica, El Salvador, Honduras, Guatemala and Nicaragua), recently approved mutual recognition of drug registration among Guatemala, El Salvador and Honduras for product manufactured locally.
        - **CAN** – Andean Community of National (Bolivia, Colombia, Ecuador, Peru and Venezuela)
        - **CARICOM** – Caribbean Community
        - **PAHO/WHO** – Pan American Health Organization/ World Health Organization

1.1 Technical documents for pharmaceutical evaluation

a) Pharmaceutical form and commercial presentation
- Include all the commercial presentations that you want to market in Colombia.

b) Product composition or quantitative formula
- With generic and chemical names of all substances according to IUPAC nomenclature, indicating in separate way the active substances and other ingredients.

c) Structural and condensed formula of active substances.

d) Formula of the standardized manufacturing batch

e) Detailed description of manufacturing process.

f) Method of Analysis

This methodology corresponds to one of the pharmacopoeias accepted in Colombia, the manufacturer must indicate the Pharmacopoeia, its edition and page number.

The method should be validated in the following aspects: specificity, sensitivity, precision and accuracy.

g) Summary of pharmacological information
- Way of administration
- Dosage and frequency
- Pharmacological indications and therapeutically use
- Contraindications, secondary effects and warnings

h) Stability studies and shelf life of the product

Should include Protocol, methodology and following parameters: type of stability (accelerated or long term), lots number, samples for lot, primary packaging material, storage conditions.

i) Dosage forms

j) Drug groups

Antiepileptics and lithium, immunosuppressants, digitalis, theophylline and their salts, antiarrhythmics, anticoagulants, antineoplastic

k) Quality Specifications for raw materials

Active Ingredients, Excipients and Specifications of container primary packaging material.

l) Quality specifications in-process controls

Physical, chemical and microbiological

m) Quality Specifications of the finished product

Physical, chemical and microbiological

1.2 Legal documents of Columbia

a) Power of attorney to importer[17]

A **power of attorney** is a legal document giving one person (called an "agent" or "attorney-in-fact") the **power** to act for another person (the principal). The agent can have broad legal authority or limited authority to make legal decisions about the principal's property and finance.

b) Trademark certification[18]

A trademark, or trade-mark is a recognizable sign, design, or expression which identifies products or services of a particular source from those of others, although trademarks used to identify services are usually called service marks. The trademark owner can be an individual, business organization, or any legal entity. A trademark may be

located on a package, a label, a voucher, or on the product itself. For the sake of corporate identity, trademarks are often displayed on company buildings.

c) **Certificate of Free Sale (CFS) or (Certificate of Pharmaceutical Product (CoPP)[19]**

A document required in certain countries or for certain commodities (such as pharmaceuticals), certifying that the specified imported goods are normally and freely sold in the exporting country's open markets and are approved for export. The COPP is the legal document that declares a certain manufacturing company is legally allowed to sell their pharmaceutical product in the country they are producing. When registering a pharmaceutical product overseas, the government body in charge of approving the application will usually require a COPP to ensure that the product is being sold as a commercial finished product in the country that is producing it.

d) Certificate of Compliance with Good Manufacturing Practices (GMP Certificate)

The drug product manufacturer Caplin Point Laboratories Limited has been awarded with GMP certification from international authorities including European GMP from Poland authority and GMP accreditation from ANVISA, Brazil. It also received WHO-GMP certificate as issued by Indian Drug control authority.

e) Import authorization letter[20]

A letter of authorization may aid a person who requires help to perform critical duties in a formal setting. Legally, a letter of authority is sufficient to delegate sensitive legal, health or financial obligation to another person or entity.

Typically, the letter of authorization is typed following an acceptable professional business format and applies correct grammar. The letter must expressly specify full particulars of the concerned parties and provide precise, in-depth details for clarity and communication purposes. If the letter regards medical information, be sure to include all relevant medical and insurance account number.

1.3 Overall drug registration requirements

Dossiers must often also include significant country-specific information (eg, labelling or legal documents). It should not be assumed that local regulations are fully aligned with ICH guidelines. This assumption could create delays or barriers to building fully compliant dossiers.

a) **Local infrastructure needed for filing[21]**

Even before planning a product registration in LATAM, companies need to research the country-specific mandates related to the entity legally allowed to file an MA application. In many countries, the applicant must hold an authorisation or certification in order to eventually become a marketing authorisation holder (MAH), as granted by a relevant local authority or agency. Local dossiers usually require proof of the required local infrastructure to register and eventually market a product: local authorisation(s), power of attorney, letter of authorisation, contracts, business and/or quality agreements, etc.

b) **Approvals of reference agency (EMA/US FDA)[22]**

To a certain extent, and regardless of the evolution of local registration requirements, in many cases each local registration process can still be perceived as a "validation" of those from reference agencies. The European Medicines Agency (EMA) and the US FDA are still "the" main reference authorities not only for local approval but also for issues like labeling. Most countries rely on the Certificate of Medicinal Product (CMP), issued by the EMA, or a Certificate of Pharmaceutical Product (CPP) from the US FDA or country of origin, as applicable. Brazil accepts a dossier without a CMP/CPP for submission but it is needed before local approval (recently, however, the lack of CMP/CPP has been used as a reason for rejection). Mexico accepts dossiers without a CMP/CPP under certain conditions and as long as clinical data in Mexican patients is available.

c) Non-clinical and clinical requirements[23]

Some countries, for example Argentina, do not need the submission of nonclinical or clinical data if the product is approved by a reference agency. Most other countries, such as Brazil, require safety and efficacy information. Some has accept summaries and some, like that of Venezuela, require the full set of clinical data (full study reports), and some require that it be fully translated. More recently, countries such as Argentina and Mexico request risk management plans (RMPs) and pharmacovigilance plans to further ensure proper follow-up of patients once the product is approved locally.

d) Local labeling[24]

Usually, the MA application requires the inclusion of the proposed local labelling (inserts, patient information, vial label, etc, as applicable). In many cases, a "mock-up" of the proposed labelling must be included. As much as a company would prefer to harmonise labelling for the region, this intention is often challenged by the diversity of local regulations and also by independent reviews from each HA. Thus it is extremely difficult to implement harmonised labelling. Some countries, for example Peru, only accept indications which are aligned with those from another reference agency (for example, the FDA and EMA).

Agencies often require the labeling to include local information (registration number, manufacturer, licensed pharmacist, distributor, packer, etc). Once approved, countries may also require implementation of specifics such as local barcodes, traceability devices (Argentina and Brazil), and braille (Brazil).

CONCLUSION

LATAM include North America (Mexico), South America, Central America and Caribbean Islands which constitute a total of 39 countries, constitute about 12% of world population. LATAM countries don't follow CTD format for filing dossier.

Most of the countries do not have well framed regulations or no regulation at all regarding BE studies except in the cases of Brazil, Mexico and Chile. In LATAM: Brazil, Mexico, Argentina, Colombia, Venezuela, Chile, Peru are the leading markets in this region. Brazil dominates the sales approximately and is the only stringent market in this region. Columbia has variation guidelines which give the brief information about the variations, and other countries have no specific guidelines.

Important Observations from this study on the filing generics in **LATAM region** are listed below:

- No country accept CTD format.
- Each country has different timelines for approval. (Brazil - 24 months and Mexico- 16 months.)
- All countries have terms of license for 3 years.
- Only Brazil and Mexico requires API technical packaging information.

The **European Union (EU)** is a political and economic union of 28 member states that are located primarily in Europe. eCTD format is strongly recommended for all referral submissions and is mandatory for referrals related to Centrally Authorized Products (CAPs), Nationally Authorized Products (NAPs), submitted in any format, are not available via the Common repository.

Important Observations from this study on the filing generics in **EU region** are:

- All countries accept CTD format.
- All submission for Centrally Authorized products by eCTD format only
- All Centralized Procedure submissions should be made via EMA submission Gateway/Web Client only.

This explains about the drug registration procedure and timelines in EU and LATAM countries (Columbia). However, it should be kept in mind that any amendment to documentation, any deletion and/or any change to the content will lead to a variation procedure. eCTD format is strongly recommended for all referral submissions in EU but not in LATAM.

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