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RESEARCH ARTICLE

An Evaluation and Comparative Study of Regulatory of Regulatory Requirements for Registration of Generic injectables in USA, European Union and Canada

D.S. Naveen Kumar[*1], J. Praveen Kumar[2]

[*1]*Krishna Teja Pharmacy college, Tirupati*
[2]*Associate professor, Krishna Teja Pharmacy College, Tirupati*

ABSTRACT
Regulatory affairs professionals are key players in drug development to approve and through life cycle management of a drug. They are the primary communications link between the company and agencies such as FDA, MHRA, TGA etc., and they are responsible for keeping up the increasing scope and complexity of regulations both domestic and international. In the pharmaceutical industry, regulatory affairs professionals have expertise in the legal and regulatory environments, as well as in clinical research protocols. The present investigation helped to understanding the regulatory requirements relating to approval of applications for marketing the generic injectables in US, EU and Canada. In US and Canada, there is only one procedure however in Europe, there are four procedures viz Centralized Procedure, Decentralized Procedure, Mutual Recognition Procedure and National Procedure. And also explain the comparison of regulatory requirements between US, Europe and Canada with respect to Module 1, 2, 3, 4 and 5.
Keywords: Regulatory affairs, Pharmaceutical industry, Marketing, Generic injectable, Clinical research

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Corresponding Author
D.S. Naveen Kumar
Krishna Teja Pharmacy College,
Tirupati, A.P., India

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CONTENTS

1. Introduction

The pharmaceutical industry is one of the most regulated industries. No drug would be available without the teams of medical researchers and other specialists who worked to make sure it received Regulatory Authorities approval. Regulatory affairs professionals are key players in drug development to approve and through life cycle management of a drug. They are the primary communications link between the company and agencies such as FDA, MHRA, TGA etc., and they are responsible for keeping up the

increasing scope and complexity of regulations both domestic and international.[1] In the pharmaceutical industry, regulatory affairs professionals have expertise in the legal and regulatory environments, as well as in clinical research protocols. They are the primary interpreters of the laws and regulations for other members of the R&D, manufacturing, and compliance staff. Regulatory affairs professionals must have a thorough understanding of the complex set of regulations within which Regulatory Authorities' operate.

Regulated Markets: These are the markets which have stringent regulation and processes for drug approval.

FDA (Food and Drug Administration):

- **FDA** is an agency of US department of Health and Human Services which is one of Unites States' federal executive departments.
- It is responsible for promoting and protecting public health through regulation and supervision of food safety, tobacco products, dietary supplements, prescription, OTC, vaccines, biopharmaceuticals, blood transfusions, medical devices, EMR emitting devices, cosmetics.[2]
- FDA led by commissioner of F&D, appointed by president with the advice and consent of the senate. The commissioner reports to secretary of Health and Human Services.
- The current commissioner is Dr. Margaret A. Hamburg.
- The FDA has its headquarters at Silver Spring, Maryland. It has 223 field offices and 13 laboratories located throughout the 50 states, the US Virgin Islands, Puerto Rico.
- In recent years, the agency began undertaking a large-scale effort to consolidate its operations its operations in the Washington Metropolitan Area from its main headquarters in Rockville and several fragmented office buildings in the vicinity to the former site of the Naval Ordnance laboratory in the White Oak area of Silver Spring, Maryland.
- While most of the centers are located around Washington, D.C., area as part of the headquarters divisions, two offices – the office of regulatory affairs (ORA) and the office of criminal investigations (OCI) are wide spread throughout US.
- ORA are considered eyes and ears of the agency, conducting the vast majority of FDA's work in the field. ORA is divided into five regions, further divided into 13 districts. Each district comprises a main district office, and a number of resident posts.

ICH:

"International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals For Human Use". ICH is an agreement between European Union (EU), Japan and the United States(US) joint initiative between government regulators and industry manufacturers in scientific and technical discussions of testing procedures required to asses and ensure safety, quality, efficacy of medicines[3].

Need for Harmonisation:

- Rapid increase in laws, regulations and guidelines for testing safety, quality and efficacy of new products,
- Different technical requirements by regulatory agencies, although fundamental guiding principles same,
- Industry becoming global,
- Duplication of time consuming and expensive testing.

2. Scope of Generic Injectable

Drug makers are waking up to the opportunities in the generic injectables market for several reasons,

- High-profit margins the products can deliver.
- Fast-growing therapeutic areas like oncology, anti-infectives and central nervous system (CNS) disorders.
- Areas like oncology, where key drugs are set to lose patent protection in the coming years and treatment trends in general are on rise.
- Market for generic injectables is significantly smaller than traditional oral generics. Fewer competitors compared to generic oral products.
- Price erosion varies dramatically, but experts say some injectable drug prices might erode as much as 90% with the launch of a generic, a level on par with solid generics.
- Generic Injectable products are coming into the market. Accordingly, contract manufacturing of injectables has led this sector in growth for the last two years. The market for outsourcing of injectables manufacturing is expected to grow by approximately 14% annually over the next three years, with more than 150 new sterile product approvals anticipated by 2015.
- Compared to the solid generic market, which can see as many as 10 or more versions of a product on the market after a 90-day exclusivity window, just one or two manufacturers received Abbreviated New Drug Application (ANDA) approvals for more than half of the injectable generics approved from 2003 until 2008, according to data from Espicom Business Intelligence. Over 85% of the injectable molecules had less than five generic competitors.
- USA and EU are the largest regulated markets for injectables, they together accounted for about 60% of the $856 billion in 2010 global pharmaceutical sales, but their markets are expanding by only a few percent per year.[4]
- US is the largest market for generic and non-biological injectables, accounting for about 51% of the global market, whereas emerging markets account for 20% of the global generic Injectable.

New Drug Development:

Any drug development process must proceed through several stages in order to produce a product that is safe, efficacious, and has passed all regulatory requirements.

3. Generic drug

A generic drug is a pharmaceutical product, usually intended to be interchangeable with a new drug (an innovator product) that is manufactured without a license from the innovator company and marketed after the expiry date of the patent or other exclusivity rights. A generic drug or generic is defined as a "a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use[5,6].

Generic drugs are drugs manufactured and marketed without a brand name. In practice, generics are often marketed as equivalents to branded drugs. Generic drugs are generally much cheaper than their branded counterparts for a number of reasons. First, drug development is extremely time consuming and costly. On average, brand-name drug companies spend about $800 million to discover, develop, and produce a new drug. They then have to charge fairly high prices to recoup their investment and actually make a profit. Generic manufacturers, however, don't have to spend nearly as much on drug development.

Specific Registration Procedure with Respective Authorities

US - FDA

Types of filings for FDA:

- **New Drug Application [NDA]:** Application for new chemical entity.
- **505(b)(2) Application:** Investigations relied upon by the applicant for approval, were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use[7]. Example: change in strength (to low or high), change in route of administration, change in dosage form.
- **Abbreviated New Animal Drug Application [ANADA]:** Application for approval of generic drugs for veterinary use.
- **Abbreviated New Drug Application [ANDA]:** Application for generic drugs.

Patent Certification:

An innovator drug applicant must include in its new drug application (NDA) information about any patents that claim the drug product that is the subject of the NDA, or the use of such drug product. The FDA publishes this patent information upon approval of the NDA or a supplemental NDA in Approved Drug Products with Therapeutic Equivalence Evaluations, which is generally known as the Orange Book.

An ANDA applicant must include in its ANDA a patent certification as described in section 505(j)(2)(A)(vii) of the Act. The certification must make one of the following statements shown fig. 7:

Para I: Patent information has not been submitted to FDA.

Para II: Patent is listed in the Orange Book and it is expired.

Para III: Patent is listed in the Orange Book and it is unexpired. Applicant has to specify the expiry date of the patent and commit that the product will not be launched till the expiry of the patent.

Para IV: Patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

ANDA Approved:

After all components of the application are found to be acceptable an approval or tentative approval letter is issued to the applicant. The letter details the conditions of the approval and allows with the concurrence of the local FDA district office, the applicant to market the generic drug product[8]. If the approval occurs prior to the expiration of any patents or exclusivities accorded to the reference listed drug product, a tentative approval letter is issued to the applicant which details the circumstances associated with the tentative approval of the generic drug product and delays final approval until all patent/exclusivity issues have expired. A tentative approval does not allow the applicant to market the generic drug product[9].

European Union- EMA

Types of application:

Applications for new active substances are described as 'full applications'. Applications for medicines containing existing active substances are described as 'abbreviated' or 'abridged applications'. The applications to market generic drugs come under abridged applications.

Full applications: Full applications must be accompanied by a dossier of information covering:

- Pharmaceutical (physico-chemical, biological or microbiological) tests
- Preclinical (toxicological and pharmacological) tests
- Clinical trials.
- Any relevant published literature should also be included.

Abridged applications:

Abridged applications do not require full preclinical or clinical dossiers. Applications for generic medicines are required to identify a 'reference medicinal product' from which the regulatory agency can determine the preclinical and clinical data[10]. The regulatory agency information centre can provide lists of products containing a particular active ingredient from which a suitable reference product can be identified.

Canada – TPD

Types of filing:

New Drug Submissions (NDS): This is required for all drug substances which is already not authorized for sale in Canada. All NDSs contain scientific information about the drug's safety, efficacy, and quality.

Abbreviated New Drug Submission (ANDS):

An Abbreviated New Drug Submission (ANDS) may be filed when the drug is the pharmaceutical equivalent of an existing drug, the Canadian Reference Product, to which a comparison can be made.

Introduction to Common Technical Document (CTD)

This document presents the agreed upon common format for the preparation of a well-structured Common Technical Document for applications that will be submitted to regulatory authorities. A common format for the technical documentation will significantly reduce the time and resources needed to compile applications for registration of

human pharmaceuticals and will ease the preparation of electronic submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements. In addition, exchange of regulatory information between Regulatory Authorities will be simplified[11,12].

Organization of the Common Technical Document:

The Common Technical Document is organized into five modules. Module 1 is region specific. Modules 2, 3, 4, and 5 are intended to be common for all regions. Conformance with this guideline should ensure that these four modules are provided in a format acceptable to the regulatory authorities.

Module 1. Administrative Information and Prescribing Information

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.

Module 2. Common Technical Document Summaries

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use. In general, the Introduction should not exceed one page[13].

Module 2 should contain 7 sections in the following order:

- ✓ CTD Table of Contents
- ✓ CTD Introduction
- ✓ Quality Overall Summary
- ✓ Non-clinical Overview
- ✓ Clinical Overview
- ✓ Non-clinical Written and Tabulated Summaries
- ✓ Clinical Summary

The organization of these summaries is described in ICH Guidelines for M4Q, M4S, and M4E.

Module 3. Quality

Information on Quality should be presented in the structured format described in ICH Guideline M4Q "CTD-Quality"

Module 4. Non-clinical Study Reports

The non-clinical study reports should be presented in the order described in ICH Guideline M4S "CTD-Safety"

Module 5. Clinical Study Reports

The human study reports and related information should be presented in the order described in ICH Guideline M4E "CTD-Efficacy"

Comparative study

Module 1. Administrative Information and Prescribing Information:

US: Generic application should include the following information in Module 1

- ✓ Signed and completed application form (356h)
- ✓ Cover letter
- ✓ Administrative information:
  - o Field Copy Certification
  - o Debarment Certification
  - o Financial Certification:
- ✓ Patent & Exclusivity

Europe:

- ✓ Cover letter
- ✓ Comprehensive table of contents
- ✓ Application form
- ✓ Product information
- ✓ Information about the experts
- ✓ Specific requirements for different types of applications
- ✓ Environmental risk assessment
- ✓ Information relating to orphan market exclusivity
- ✓ Information relating to pharmacovigilance
- ✓ Information relating to clinical trials
- ✓ Information relating to pediatrics

Canada:

- ✓ Correspondence
- ✓ Table of contents (toc)
- ✓ Administrative information
- ✓ Fee forms
- ✓ Product labeling
- ✓ Health canada summaries
- ✓ Environmental assessment statement

Module 2- Quality Overall Summary:

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD[14, 15]. The QOS should include sufficient information from each section to provide the Quality reviewer with an overview of Module 3. The QOS should also emphasize critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies discussed under the CTD-S module), including cross-referencing to volume and page number in other Modules. Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use. In general, the introduction should not exceed one page. Module 2 is divided into 7 sections[16].

a. CTD Table of Contents
b. CTD Introduction
c. Quality Overall Summary
d. Nonclinical Overview
e. Clinical Overview
f. 6Nonclinical Written and Tabulated Summaries
g. Clinical Summary

Note: QOS is submitted in the dossiers for Europe and Canada. For the dossiers of US, FDA has provided a Question-based Review (QbR) format.

Module 3 – Quality:

As per the ICH, this module is divided into 3 sections and each section is subdivided to provide the Quality details of the drug products. The sections of this module are:

- 3.2.S Drug Substance
- 3.2.P Drug Product
- 3.2.R Regional Information

Module 4- Non clinical study reports:

In this module information related to Non clinical pharmacology, pharmacokinetic and toxicological study reports are provided.

For US and Canada: this section is not applicable.

For Europe: literature references are provided.

Module 5- Clinical study reports:

In applications for generic drugs BE studies are required. However, if the injectable product is in the form of solution prior to administration, BE studies are not required. For injections, in the form of Suspensions prior to administration, BE study is required. If such a BE study is performed, the information related to studies, literature references, etc., are provided in this section.

Table 1: List of Regulatory markets

S.No.	Region	Authority
1.	US	FDA [Food Drug Administration]
2.	EU	EMA [European Union Medical Agency] *EU has 27 countries
3.	CANADA	Health Canada
4.	AUSTRALIA	TGA [Therapeutic Good Administration]
5.	JAPAN	Pharmaceutical Medical Drug Administration [PMDA]

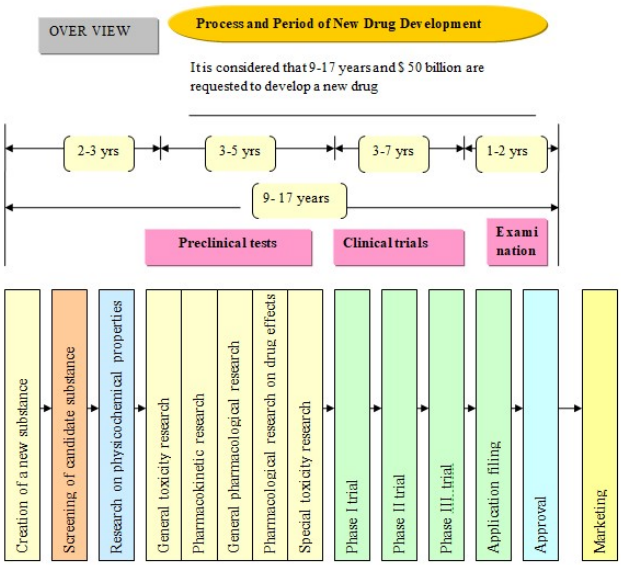

Fig 1: Flow Chart of New drug Development

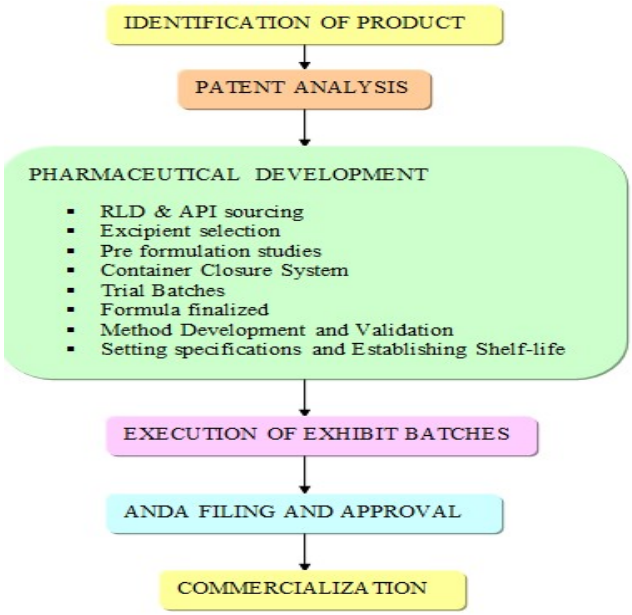

Fig 2: Flow chart of Generic drug development

Table 2: Comparison of Innovator and Generic Drugs

S.No.	Parameters	Innovator Drug	Generic Drug
1.	Active ingredients	Same	Same
2.	Safety and efficacy	Same	Same
3.	Quality and strength	Same	Same
4.	Performance and standards	Same	Same
5.	Costs/prescription	Highly expensive	Less expensive
6.	Inspection of manufacturing facilities	Yes	Yes
7.	Reviews reports of adverse reactions	Yes	Yes
8.	Review on Drug Labelling	Yes	Yes
9.	Extensive research and development investments	Yes	No
10.	Clinical trials(4 phases)	Yes	No
11.	Review to show active ingredient is equivalent to original	---	Yes
12.	Extensive marketing and advertising	Yes	No
13.	Patent protection	Yes	No
14.	Product development time	~12 to 15 yrs	2 to 4 yrs

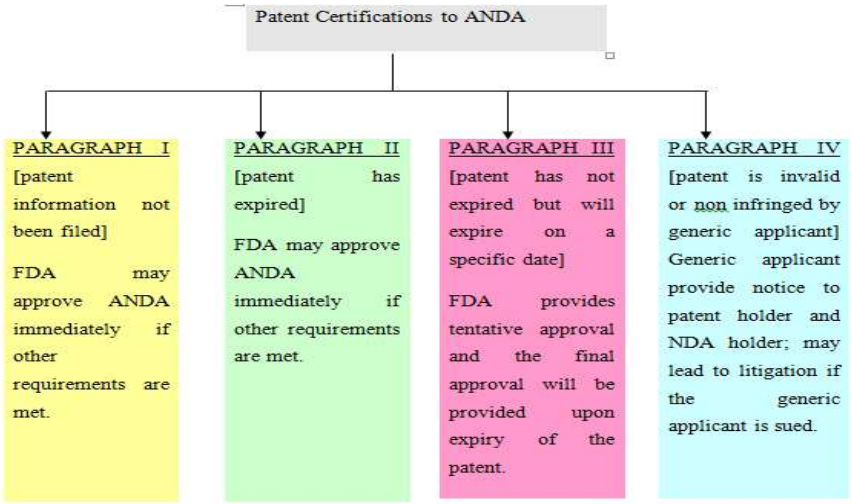

Fig 3: Flow chart of Patent Certification

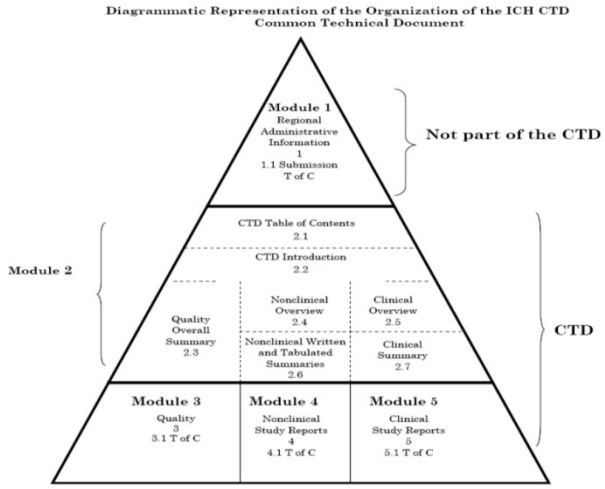

Fig 4: Organization of ICH

4. Conclusion

Based on the study, it is understood that the ICH –template on Module 2 through Module 5 is common for all regions (i.e., US,EU and Canada). However Module 1 is regional specific and information provided in this module varies from country to country. This template avoids need to generate and compile different registration dossiers for the three regions with the exception of Module 1.This template will facilitate the regulatory reviews and communication with the applicant and in addition exchange of regulatory information between regulatory authorities will be simplified.

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