Asian Journal of Medical and Pharmaceutical Sciences
ISSN: 2348-0165
Journal Home Page: www.pharmaresearchlibrary.com/ajmps

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

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A B S T R A C T

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. The aim of present research work Understand the requirements of the Regulatory Authorities governing the drugs in USA, European Union and Canada to register generic injectables in these regions. This study helped in 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. A comparison of regulatory requirements between US, Europe and Canada with respect to Module 1, 2, 3, 4 and 5are also discussed in the study.

Keywords: Regulatory affairs, Injectables, FDA, Drug development

A R T I C L E I N F O

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JOURNAL QR-CODE

A R T I C L E H I S T O R Y: Received 11 Nov 2019, **Accepted** 18 March 2020, **Available Online** 19 June 2020

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Citation: *Jaldu Praveen, et al.* An Evaluation and Comparative study of Regulatory Requirements for Registration of Generic Injectables in USA, European Union and Canada. *A. J. Med. Pharm, Sci.*, 2020, 8(1): 10-15.

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1. Introduction

Introduction to Regulatory affairs:

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.

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.A good regulatory professional must also be aware of the subtleties of regulations worldwide. Keeping up-to-date on regulations is essential in regulatory affairs; changes in regulations can affect the clinical trials process, regulatory strategy etc**.**

2. 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 shown in fig.1.

Detailed Stages of Drug Development:

- Discovery
- Product Characterization
- Formulation, Delivery, Packaging Development
- Pharmacokinetics And Drug Disposition
- Preclinical Toxicology Testing And IND Application
- Bioanalytical Testing
- Clinical Trials

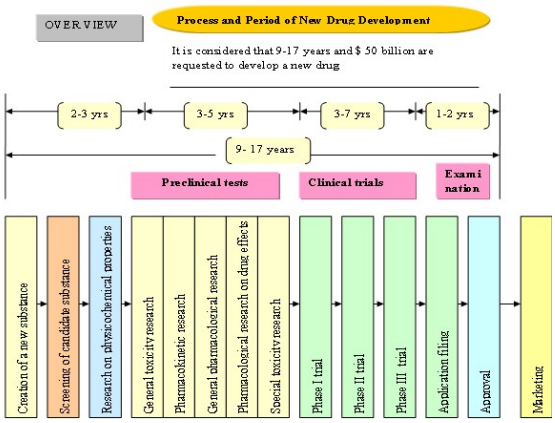

Fig 1: Flow chart of New Drug Development

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 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. Generic drugs are marketed under a non-proprietary or approved name rather than a proprietary or brand name.

Benefits of generic drugs:

- Reduced drug costs
- Increased drug use
- Prevent drug shortages- product rationalization and supply disruption.
- Increased bioavailability with respect to RLD.
- Reduced time of development

How do generics get into Market

To gain Regulatory Authority approval, all a company has to do is prove that its version of a drug is chemically equivalent to the original. If the chemical makeup is the same, it's assumed that the research and clinical trials are as applicable to the generic version as they were to the original. Also, generics manufacturers benefit from advertising of branded drugs, lowering their own marketing expenses. The process of generic entry begins when manufacturers submit an ANDA (Abbreviated New Drug Application) in USA, MAA (Marketing Authorization Application) in Europe and ANDS (Abbreviated New Drug Submission) in Canada.

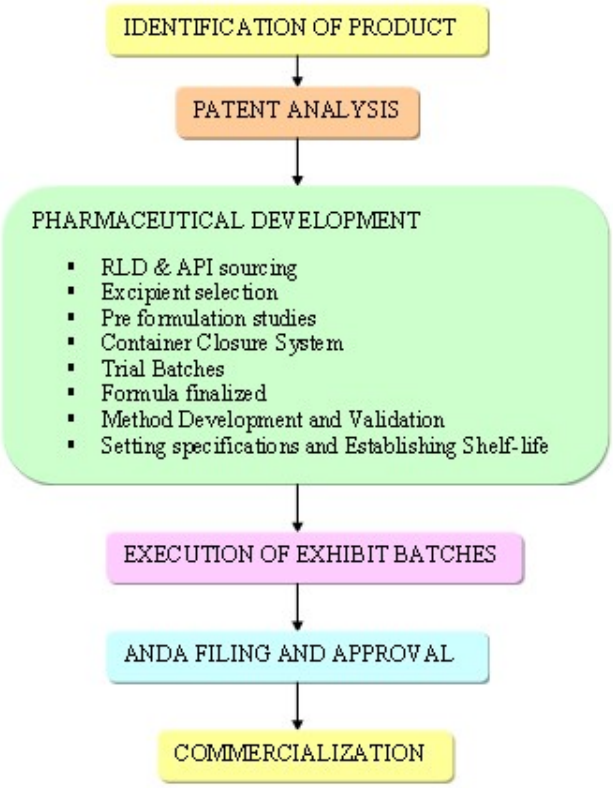

Fig 2: Flow chart of Generic Drug Development

Specific Registration procedures

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. 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.

Various Steps involved in the ANDA Approval - from filing to approval:

ANDA can be submitted at any time if the listed drug's exclusivity for "New Chemical Entity' (NCE) has expired. If the listed drug's exclusivity for NCE, has not expired then the earliest possible date for ANDA filing is "expiry date of NCE exclusivity minus 1 year".

Example: If the NCE exclusivity expires on May 01, 2015, then the ANDA can be filed only on May 01, 2014 or after that.

1. Within 60 days after FDA receives an application, the agency will determine whether the application may be filed/received. The filing/receiving of an application means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review.
2. If FDA finds that none of the reasons for refusing to file/receive the application apply, the agency will file/receive the application and notify the applicant in writing.
3. If FDA refuses to file/receive the application, the agency will notify the applicant in writing and state the reason for the same. The applicant may then:
    i. Withdraw the abbreviated new drug application; or
    ii. Amend the abbreviated new drug application to correct the deficiencies; or
    iii. Take no action, in which case FDA will refuse to receive the abbreviated new drug application.

Some of the reasons for FDA to refuse to file/receive an application are provided below:

1. The application does not contain a completed application form.
2. The application is not submitted in the form required under CFR 314.50 or 314.94.
3. The applicant fails to submit a complete environmental assessment or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion.

Communications between FDA and applicants:

General principles: During the course of reviewing an abbreviated application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such communication may take the form of telephone conversations, letters, or meetings, whichever is most appropriate to discuss the particular issue at hand.

Notification of easily correctable deficiencies: FDA reviewers will make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an abbreviated application when those deficiencies are discovered, particularly deficiencies concerning chemistry, manufacturing, and controls issues. The agency will also inform applicants promptly of its need for more data or information or for technical changes in the application or the abbreviated application needed to facilitate the agency's review. This early communication is intended to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. Such early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application or abbreviated application by agency managers as well as reviewing staff. Instead, major scientific issues will ordinarily be addressed in a complete response letter.

Approval of an abbreviated application:

ANDA will be approved after the applicant has satisfactorily addressed the queries raised by the Agency and after the Agency determines that the drug meets the statutory standards for manufacturing and controls, labeling, and, where applicable, bioequivalence. The approval becomes effective on the date of the issuance of the agency's approval letter unless the approval is tentative.

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.

Applicant:

An Applicant means any person (usually a pharmaceutical firm) who submits an abbreviated new drug application (ANDA), or an amendment or supplement to them, to obtain FDA approval to market a generic drug product, and/or any person (or firm) who owns an approved application or abbreviated application.

Acceptable and Complete:

An application must contain sufficient information to allow a review to be conducted in an efficient and timely manner. Upon receipt of the application a pre-filing assessment of its completeness and acceptability is performed by a project manager within the Regulatory Support Branch, Office of Generic Drugs. If this initial review documents that the application contains all the necessary components, an "acknowledgment letter" is sent to the applicant indicating its acceptability for review and confirming its filing date.

Once the application has been determined to be acceptable for filing the Bioequivalence, Chemistry/Microbiology and Labeling reviews may begin.

Refuse to File Letter Issued:

If the application is missing one or more essential components, a "Refuse to File" letter is sent to the applicant. The letter documents the missing component(s) and informs the applicant that the application will not be filed until it is complete. No further review of the application occurs until the applicant provides the requested data and the application is found acceptable and complete.

Request for Plant Inspection:

Upon filing an ANDA an establishment evaluation request is forwarded to the Office of Compliance to determine whether or not the product manufacturer, the bulk drug substance manufacturer, and any of the outside testing or packaging facilities are operating in compliance with current Good Manufacturing Practice (cGMP) regulations as outlined in 21 CFR 211. Each facility listed on the evaluation request is evaluated individually and an overall evaluation for the entire application is made by the Office of Compliance. Furthermore, a preapproval product specific inspection may be performed on to assure data integrity of the application.

Labeling Review:

The labeling review process ensures that the proposed generic drug labeling (package insert, container, package label and patient information) is identical to that of the reference listed drug except for differences due to changes in the manufacturer, distributor, pending exclusivity issues, or other characteristics inherent to the generic drug product (tablet size, shape or color, etc.). Furthermore, the labeling review serves to identify and resolve issues that may contribute to medication errors such as similar sounding or appearing drug names, and the legibility or prominence of the drug name or strength.

Pre-approval Inspection:

A satisfactory recommendation from the Office of Compliance based upon an acceptable preapproval inspection is required prior to approval. The preapproval inspection determines compliance with current Good Manufacturing Practices (cGMPs) as well as a product specific evaluation concerning the manufacturing process of the application involved. If an unsatisfactory recommendation is received, a non approvable letter may be issued. In such a case, approval of the generic drug product will be deferred pending a satisfactory re-inspection and an acceptable recommendation.

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. 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.

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.

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 as shown in fig. 3. 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.

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". The overall organization of the Common Technical Document is presented on the following pages.

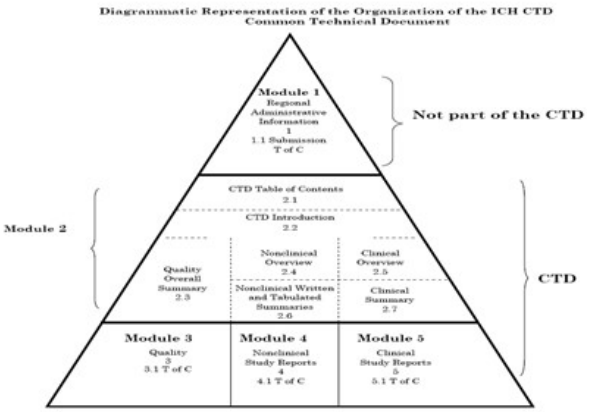

Fig 3: Organization of ICH

Quality Aspects:
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:

- Drug Substance
- Drug Product
- Regional Information

Drug Substance:
In this section, the applicant for generic drugs (applicant) provides the information related to the drug substance used in the manufacturing of the drug product. However, some information related to the drug substance is confidential and hence may not be available with the applicant unless and until the applicant is the manufacturer of both the drug substance manufacturer and the drug product.

General Information:

3.2.S.1.1 Nomenclature:
Information on the nomenclature of the drug substance has to be provided. For example:

- Recommended International Non-proprietary Name (INN)
- Compendial name, if relevant
- Chemical name(s)
- Company or laboratory code
- Other non-proprietary name(s) [e.g., national name, United States Adopted Name (USAN), British Approved Name (BAN))]
- Chemical Abstracts Service (CAS) registry number

Structure: The structural formula, the molecular formula, and the molecular mass should be provided.

General Properties: A list should be provided of physicochemical and other relevant properties of the drugsubstance. Physical and chemical properties of the drug substance such as the physical description, solubilities in common solvents (e.g., water, alcohols, chloroform, acetone, etc.), quantitative aqueous pH solubility profile, polymorphism, particle size distribution, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index, hygroscopicity, partition coefficient, etc., are few examples.

Manufacturer(s):
The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

Process Validation and/or Evaluation:

Presentation of this section in Dossier for USA:
A reference to the DMF number is provided in dossier for referring this section.

Presentation of this section in Dossier for Europe & Canada:
Sterility assurance discussions are provided. The following details which are shared in open part of the DMF of the drug substance to the generic applicant are covered in this section.

- Media Fill - Process Simulation
- Validation of Air Conditioning System and Environmental monitoring of the Manufacturing area
- Sterilization and Validation of Process Filters, Process Equipments, Container and Closures
- Validation of Process Filters
- Validation of Aseptic Filtration Process - Filter integrity validation and testing
- Sterility Testing
- Bacterial Endotoxin Testing

Elucidation of Structure and other Characteristics:
Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided. The structure is elucidated through Ultraviolet (UV) Spectroscopy, Infrared (IR) Spectroscopy, Nuclear Magnetic Resonance (NMR) Spectroscopy and Mass Spectroscopy. A description for Potential isomerism and Polymorphism should also provided in this section.

Impurities:
Information on impurities should be provided. The potential and actual impurities arising from the synthesis, manufacture, degradation and metabolite are discussed.

Drug Product

Description and composition of the drug product:
A description of the drug product and its composition should be provided in this section. Description of the dosage form: The description of the dosage form should include the physical description, available strengths, release mechanism, as well as any other distinguishable characteristics. Composition, i.e., list of all components of the dosage form, and their amount on a per unit basis (including overages) the function of the components, and a reference to their quality standards (compendia monograph or manufacturer's specification).The components should be declared by their proper or common names, Quality standards (e.g., USP, Ph.Eur. House, etc).

Pharmaceutical Development:
The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. The studies that are carried out during development are distinguished from routine control tests conducted according to specifications.

Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the pharmaceutical development section.

Regional information
Any additional drug substance or drug product information specific to each region are provided in section R of the application.

Presentation of this section in Dossier for USA and Canada: The Regional requirements for US are subdivided into the following sections.

Executed batch records: Copy of executed records with equipment specified, including packaging records. Batch reconciliation and label reconciliation, theoretical yield,

actual yield, packaged yield has are submitted in this section.

Comparability protocols: This section is applicable only for post approval changes and not for initial submission.

Methods validation package: List of Method Validation Reports for Drug substances and drug products are provided.

Presentation of this section in Dossier for Europe:

The Regional requirements for EU are subdivided into the following sections

Process validation scheme: Reference to the process validation Report submitted in 3.2.P.3.5 is provided.

Certificate of Suitability/European DMF: The name of manufacture of drug substance and a statement regarding the submission of Drug master file to the agency is provided.

Medicinal product containing or using in manufacturing process materials of animal or human origin: Details of products or human origin are provided, if they are used in the manufacturing process.

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.

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.

3. 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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