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Current regulatory requirements and regulation on submission of ANDA in India comparison with Singapore

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Abstract

Developing a new drug requires great quantity of research work in chemistry, manufacturing, controls, preclinical science and clinical trials. Drug reviewers in regulatory agencies around the world bear the liability of evaluate whether the research data support the safety, efficacy and quality control of a new drug product to serve the public health. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. This article focuses on history, regulatory policy and organization, and related issues with respect to different countries like, India and Singapore.

Keywords: Development; Drug; Generic; Global; Regulatory Authority

1. Introduction

The pharmaceutical industry is one of the highly in time 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 generic drug product which can be tailor made to meet the diverse market requirements. The pharmaceutical industry in India has shown an incredible growth which in turn has raised the economy of India. After the foreword of the product patent regime in India, there was a need for pharmaceutical companies both in India and abroad to explore newer markets. Ambitions, mergers and acquisitions are in focus with a reason to enter new market. For sustained growth over the next few decades, firms have to concentrate on generic drug products. "Diseases that cannot be cured, diseases that have to be managed, provide great opportunity for generic drugs." Government has the responsibility to protect their citizens. It is the responsibility of national governments to establish regulatory authorities with strong guidelines for quality assurance and drug regulations in the respective territories.

2. Generic Drug Development

To make a generic product, formulator must know in detail the exact regulatory requirements of each concerned country where the drug is intended to be filed. Generic drug product development uses a different approach and strategy compared to that used to develop an innovator drug product containing a new chemical entity. Generic drug product manufacturer must formulate a drug product that will have the same therapeutic efficacy, safety, and performance characteristics as of its branded counterpart.

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The key factor is that the generic drug product must meet all the necessary criteria to be therapeutically equivalent to the innovator drug product. Therapeutically comparable means that the drug product shows pharmaceutical equivalence as well as bioequivalence. Table 1 shows regulatory requirement for generic drug product development in some selected countries.

The decision to proceed with the development of a generic drug product should therefore be based on well-researched data that primarily indicate market value together with a sound knowledge of patent expiry dates, predicted market share, and growth rate for the product, amongst others. The predicted prosperity of the new generic product will require strategic planning for the subsequent launch timing, which must take into account the expected generic price and knowledge of predictable competitors, such as who they are and when they are expected.

According to Hamrell R. Michael "The Drug Price Competition and Patent Term Restoration Act" in 1984 changed the regulatory environment for generic drugs. This law allowed for the approval of generic "me-too" copies of many approved drug after the patent had expired. A liability to ensure that high-quality, safe, and effective medicines are made available to patients in a timely manner.

2.1. Filing a Generic Drug Application

Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceutical and Medical Devices Agency (PMDA), Therapeutic Goods Administration (TGA), Medicines Control Council (MCC), Tanzania Food and Drugs Authority (TFDA), Agência Nacional De Vigilância Sanitária (National Health Surveillance Agency) (ANVISA), Commonwealth Independent States (CIS), Department of Health (DOH), The Gulf Co-Operation Council (GCC).

2.1.1. India

The Drug and Cosmetic Act 1940 and Rules 1945 were passed by the India's parliament to regulate the import, manufacture, circulation and sale of drugs and cosmetics. The Central Drugs Standard Control Organization (CDSCO), and the office of its leader, the Drugs Controller General (India) [DCGI] were established. In 1988, the Indian government added Schedule Y to the Drug and Cosmetics Rules 1945.

Schedule Y provides the guidelines and requirements for clinical trials, which was further revised in 2005 to bring it at par with internationally accepted procedure. The changes include, establishing definitions for Phase I–IV trials and clear responsibilities for investigators and sponsors. The clinical trials were

- further divided into two categories in 2006. In one category (category A) clinical trials can be conducted in other markets with competent and mature regulatory systems whereas the remaining ones fall in to another category (category B) Other than A. Clinical trials of category A (approved in the U.S., Britain, Switzerland, Australia, Canada, Germany, South Africa, Japan and European Union) are eligible for fast tracking in India, and are likely to be approved within eight weeks.

The clinical trials of category B are under more scrutiny, and approve within 16 to 18 weeks. An application to conduct clinical trials in India should be submitted along with the data of chemistry, manufacturing, control and animal studies to DCGI. The date regarding the trial protocol, investigator's brochures, and informed consent documents should also be attached. Central Drug Standard Control Organization (CDSCO)

General Information Regarding Ctd Submission In India :

- Type of application: M&M
- CTD is the only data transfer format in CDSCO
- If the applicant has a license to manufacture bulk drugs provide a copy otherwise he or she can issue a permit from the authorized source regarding the supply of goods.
- Clear and accurate information should be provided
- Text and tables must be clearly printed, the left margin should be kept large and prepared using the border.
- Posted document printed on both sides of the page, for Times New Roman text with 12 point font as well as table content and 9-10 point font text.
- Page numbers should be at document level and numbered in the order of the page.
- All pages include a different header or footer and if a section contains more than 1 document a specific table of contents may be included.
- Send 1 hard copy and 3 soft copies namely Compact Disc (CD) in Portable Document (PDF) format.

- Copy on paper: The sides and front of the file should include the applicant's company name, drug name, and delivery date and file number.
- Volumes should not be more than 3 inches in size, the CD should be marked using a marker pen with the applicant's company name, delivery date and drug name.
- The requester should keep a copy of the dose for further reference.

During the various references from module 1 to another specify volume, page number and target identifier for the target text.2

Send the application to the office

- Government of India Directory of Health and Family Welfare

Indian Council of Medical Research (ICMR)

2.1.2. Ministry of Health and Family Welfare

ANDA Regulatory Review Process

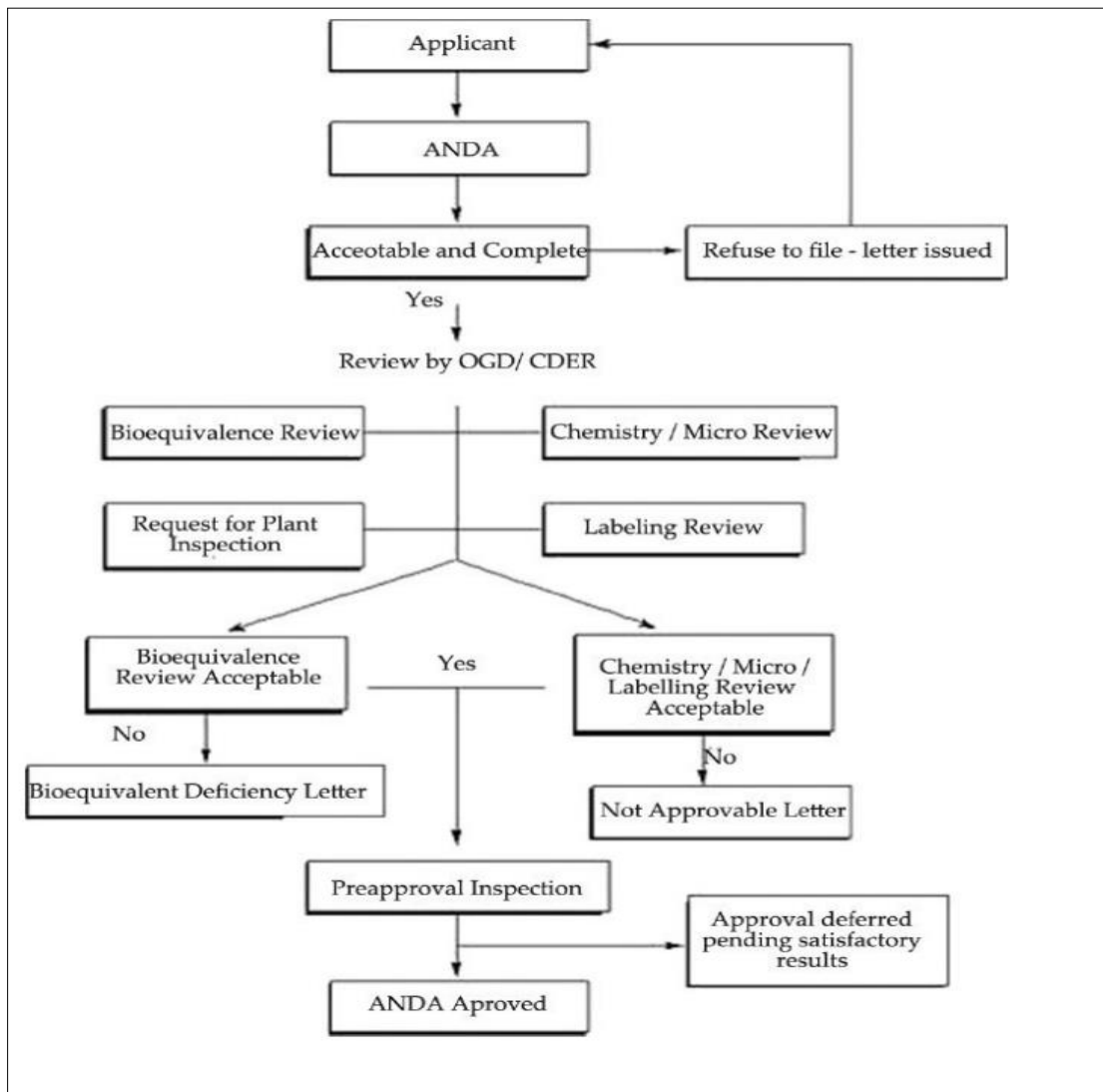


Figure 1 ANDA Regulatory Review Process

2.1.3. Singapore

Health Sciences Authority (HSA) is the regulatory authority for regulating pharmaceutical products in Singapore. For new product licenses, Singapore has a new drug application (NDA) and a generic drug application (GDA) for products already approved by certain regulatory agencies submitting an

abridged dossier is possible. Applicants submit an online application through PRISM (Pharmaceutical Regulatory and Information System) and also submit a CTD dossier.

Application types:

- In applying for a new Product License for a medicinal product in Singapore, there are two categories
- of applications: a new drug application (NDA) and a generic drug application (GDA):
- GDA-1: For the first strength of a generic chemical product.
- GDA-2: For subsequent strength(s) of the generic chemical product that has been registered or has been submitted as a GDA-1.
- The product name and pharmaceutical dosage form shall be the same as that for the GDA-1.

2.1.4. Technical documents required

Administrative documents:

- Comprehensive Table of Contents
- Introduction
- Application
- Labeling, Package Insert and Patient Information Leaflet
- Approved Summary Product Characteristics (SPC) / Patient Information Leaflet (PIL)
- Assessment Report from Reference Agencies
- Description of Batch Numbering System
- Proof of Approval
- Authorization Letters
- GMP Certification/Proof of GMP Compliance
- Patent declaration
- Declaration on rejection, withdrawal and deferral
- Declaration for GDA verification
- Registration status in other countries

2.1.5. ACTD & ICH CTD overview and summaries

The overview and summary documents are to be inserted into Module 2 of the ICH CTD or into the relevant sections in Part II, III and IV of the ACTD. A completed Singapore Quality Overall Summary (SQOS) must also be inserted into Module 2, section 2.3 of the ICH CTD or Part II, section B of the ACTD, irrespective of whether an ICH or ACTD QOS has been included in the application dossier. SQOS must be named and dated by the applicant prior to submission. The electronic copy of the Singapore QOS should be in Microsoft Word format

Quality document

- Body of Data:
- Drug Substance
- Drug Master File (DMF)
- Certificates of Suitability (CEP)
- Control of Drug Substance (3.2.S.4)
- Stability Data of Drug Substance (3.2.S.7)

Body of Data

- Drug Product
- Pharmaceutical Development (3.2.P.2)
- Process Validation (3.2.P.3.5)

- Control of Excipients (3.2.P.4)
- Control of Drug Product (3.2.P.5)

Table 1 Comparison of regulatory requirements of ANDA in India with Singapore

SL NO:	Requirements	INDIA	SINGAPORE
1	Regulatory authority	CDSCO	HAS
2	Data requirements	Extensive data required	More reliance on reference agencies
3	Bioequivalence studies	Often mandatory	Generally required
4	Application submission	Submit application to CDSCO	Submit application to HSA
5	Clinical trials	May require local clinical trials	May accept foreign clinical data
6	Review time	Variable, can be lengthy	Generally faster process
7	Inspection and audits	Regular inspections of facilities	Quality audits conducted
8	Approval criteria	Safety, efficacy, quality, and price	Safety, efficacy, quality
9	Pricing and reimbursement	Regulated by national pharmaceutical pricing authority (NPPA)	Managed by the ministry of health
10	Generic drug launch	Can be launched after approval	Requires regulatory approval
11	Market size	Large market, high demand for generics	Smaller market, niche opportunities
12	Intellectual property	Stringent IP protection	Strong IP protection
13	Manufacturing	The manufacturer can begin production and distribution of the generic drug	After approval, the manufacturer can start manufacturing and distributing the generic drug

3. Conclusion

Generic Pharmaceutical companies bring to the market a generic version of a new drug product in a faster time and lower cost, compared to inventive drugs, thus benefiting a community and making health care more accessible. These drugs introduce an equally safe and effective alternative to established products, which contain well-known, well-tested active ingredients. Generic drugs are strictly controlled by Regulatory Authorities and are only licensed through a comprehensive authorization process. There are rules they require medicines to be made, tested, followed and made in accordance with the instructions to be safe and to protect the patient's health. These include a discussion of the ANDA format, the review process, information on the introduction of generic drugs on the market, obtaining approval on regulatory issues and a list of regulatory authorities around the world who are responsible for protecting public health. Each regulatory authority has its own system of reviewing drug trafficking in various countries. These comparisons help different pharmaceutical companies and professionals to understand the introduction of generic drugs and the differences in meeting requirements between HSA and CDSCO.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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