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# REGISTRATION PROCESS OF GENERIC DRUGS IN USFDA

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**ABSTRACT**

Regulatory involvement in the generic drug development hastens the drug approval process which directly or indirectly accelerated the launching of drug into the market. The regulatory documents whether in-house of documents to be submitted to regulatory authorities should be carefully reviewed by the skilled personal to minimize the queries raised by the regulatory agencies and speed up the approval process. Sponsors must ensure submissions meet the USFDA requirements for format and content.

**Key Words:** ANDA: Abbreviated new drug application, GDUFA: Generic drug user fee amendments, Generic Product

## INTRODUCTION:

***ICH (International conference on Harmonization of Technical requirements for registration of Pharmaceuticals for Human use):*** *(1,2)*

ICH is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration.Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development, so that the benefits of international harmonization for better global health can be realized worldwide. ICH's mission is to achieve greater harmonization to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. The purpose of ICH is to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines by recommending ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration. Harmonization would lead to a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety, and efficacy, and regulatory obligations to protect public health.

The ICH has four major parts:

1. ICH Steering Committee
2. ICH Coordinators
3. ICH Secretariat
4. ICH Working Groups

The Steering Committee, made of six ICH Parties, governs the ICH, determining the Policies and procedures, selecting topics for harmonization and monitoring progress of harmonization initiatives. The ICH consists of:

1. European Commission

2. European Federation of Pharmaceutical Industries and Associations (EFPIA)
3. Ministry of Health, Labor and Welfare (Japan)
4. Japan Pharmaceutical Manufacturers Association (JPMA)
5. Food and Drug Administration (FDA)
6. Pharmaceutical Research and Manufacturers of America (PhRMA)

The ICH Coordinators represents each ICH Party to the ICH Secretariat on a day-to-day basis. The ICH Secretariat is primarily concerned with preparations for, and documentation of, meetings of the Steering Committee as well as coordination of preparations for Working Group (EWG, IWG, and Informal WG) and Discussion Group meetings. The ICH Working Groups are created by the Steering Committee when a new topic is accepted for harmonization, and is charged with developing a harmonized guideline that meets the objectives outlined in the Concept Paper and Business Plan.

## INTRODUCTION TO FOOD AND DRUG ADMINSTRATION: [3, 4]

***Food and Drug Administration:*** The Food and Drug Administration (FDA or USFDA) is an agency of the United States Department of Health and Human Services, one of the United States federal executive departments.

It is a scientific, regulatory, public health agency. The agency grew from a single chemist in the US department of Agriculture in 1862 to a staff of approximately 9100 employees, staffing over 150 field officers, 5 regional offices and 20 district offices. Harvey Wiley arrived as a Chief chemist in 1883 and he unified a variety of groups in the federal law to prohibit the adulteration and misbranding of food and drugs. Head Quarter is situated in White Oak, Montgomery County, Maryland.

The FDA is responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), cosmetics and veterinary products.

Main mission of USFDA is to protect & promote public health and regulate medical devices.

The FDA also enforces other laws, notably Section 361 of the Public Health Service Act and associated regulations, many of which are not directly related to food or drugs. These include sanitation requirements on interstate travel and control of disease on products ranging from certain household pets to sperm donation for assisted reproduction. The FDA is led by the Commissioner of Food and Drugs, appointed by the President with the advice and consent of the Senate.

The Commissioner reports to the Secretary of Health and Human Services. The 21st and current Commissioner is Dr. Margaret A. Hamburg. She has served as Commissioner since May 2009.

The FDA has its headquarters in unincorporated White Oak, Maryland.[5] The agency also has 223 field offices and13 laboratories located throughout the 50 states, the United States Virgin Islands, and Puerto Rico.

In 2008, the FDA outsourced some jobs to foreign countries, including China, India, Costa Rica, Chile, Belgium, and the United Kingdom.

**Objectives of study:**

1. The objective of this review is to Understand the Regulatory Authority governing the drugs in USA.
2. Evaluate the Regulatory requirements for registration of the Generic drugs in USA.
3. Basic understanding on the "Regulatory requirements for Approval Changes of Generics in USA.

**Types of applications to be submitted at USFDA:**

The following applications were submitted at USFDA for registration of human drugs and for marketing of drugs at USA.
Five types of applications:

*1.* ***INDA (Investigational new drug application):*** The IND is the means through which the sponsor technically obtains this exemption from the FDA for conducting clinical trials and investigations in many states of US. And it was a legal support for sponsor.

The following are the sub types of the IND

a. An investigator IND
b. Emergency Use IND
c. Treatment IND

*2.* ***NDA (New drug application):*** The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA. The following 2 types of NDA are submitted at USFDA

a. 505 b (1): A normal NDA filing which requires clinical and preclinical testing done by applicant themselves during drug/ dosage from development. In such cases USFDA will give exclusivity of 14 years to the NDA applicant.

b. 505 b (2): In this type of application normally applicant can use clinical andpreclinical data done by others during their research (which is published in literatures) and USFDA findings NDA application with such data. USFDA will give mark exclusivity of 7 years only.

*3.* ***ANDA (Abbreviated new drug application):*** Is an application for a U.S. drug approval for an existing licensed medication or approved drug.

*4.* ***OTC (Over the counter*)**: For marketing the OTC drugs at US market. OTC drugs are defined as drugs that are safe and effective for use by the general public without seeking treatment by a health professional.

*5.* ***BLA (Biologics license application*)**: An application for approval of biological dugs approval and marketing at US market.

## METHODOLOGY

***Scope & Benefits of the Generic drugs*:** 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. Generic drugs are marketed under a non-proprietary or approved name rather than a proprietary or brand name. Generic drugs are usually cheaper than the innovator drugs because of the following Reasons

1. No cost of identification and isolation of New Chemical Entity (NCE),
2. No cost of research and development,
3. Minimum marketing cost because branded drug is already approved as safe and effective.

***Benefits of generic drugs*:**

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

***Safety and efficacy of generic drugs*:** Generic drugs are frequently as effective as, but much cheaper than, brand-name drugs. Generic drugs are just as safe as brand name drugs and clinical and pharmacological effects are same, expect to the same risks and benefits as brand name drug. Generic medicines play a key role in ensuring the affordability and sustainability.

***A generic drug can be produced/marketed for the drugs*:**
Where the patent has expired,
Which has never held patent,
In countries where a patent(s) is/are not in force,
Where the generic companies certify that the branded companies' patents are either invalid, unenforceable or will not be infringed. Hence, pharmaceutical companies may produce a generic drug when patent expires on the innovator drug. The expiration of a patent removes the monopoly of the patent holder on the drug.

**Generic Drug Development:** (5,6, 7,8)
Generics are copies of brand-name medicines whose patents have expired .That usually happens after a brand drug has been on the market for about 10 to 14 years.

***Before going to develop a new generic drug they are five key considerations should be kept in our mind.***

***Market size:*** Before going to the new generic drug development going for market research is very essential thing. They were

A. How much percentage of market shares was occupied by brand name drug?
B. How many opportunities are there for growing in market?
C. How many competitors are manufacturing the same product?

***Timing*:** Time also key consideration for new generic drug development. The proper time lines for developing and marketing drug are assessed. The 3 question that consider during this was:

A. How much of time will it take to develop a new drug?
B. How much of time it will take for approval of USFDA?
C. How long will it take to obtain provincial drug list?

***Development & Approval cost*:** An assessment made of the total cost associated with introducing new generic drug. These costs include R&D resources[15], product testing, legal and litigation fee, federal and provincial approval requirements. All of the costs are measured against the market size, & opportunities for growth.

***Specialization & Product portfolio*:** A manufacturer will review their specialization and portfolio in order to identify any benefits from economies of scale in their production. If a manufacturer specializes in drugs of a certain therapeutics or dosage forms the new drug might be complement their production. Alternatively, a manufacturer might want to expand their overall product portfolio to be a more attractive single source supplier to their customer.

***Legal challenges*:** Bringing a generic drug to market typically includes legal challenges to Brand-name drugs. Various patents which can be a costly and time consuming process. Contrary to popular belief, not all patents have merit or values. Brand – name companies routinely use strategic patenting to prolong their market monopolies and delay generic market entry.

**Generic product development stages according to regulatory perspective(9).**

***Stage 1: Identification of the Product:*** The commercial/Business Development team identifies the product based on the market potential and does the cost analysis

***Stage 2: Patent Analysis:*** The Intellectual Property Management (IPM) team does the patent analysis and proposes the path that needs to be followed. Generally in USA a orange covered book called "approved drug products with therapeutic equivalence evaluations" contains all the approved products and patents.

According to this book they are 4 types of patents certifications are there. They are

1. Paragraph 1 certification states that there is no patent listed.
2. Paragraph 2 certification states that the listed patent was expired.
3. Paragraph 3 certification states that FDA should approve ANDA after the last patent of pioneer drug get expires.
4. Paragraph 4 certificate state that its generic product does not infringe on the listed patents or that those patents are not enforceable (a "Paragraph 4" filing actually called a Paragraph IV filing.1. If the generic company files an ANDA with a Paragraph IV certification, then the branded company is notified. After the notice, the branded company has 45 days to file a patent infringement action against the generic company. After the suit has been filed, the FDA cannot approve of the application until the generic company successfully defends the suit or until 30 months, whichever comes first

***Stage3.Development:***

1. RLD Sourcing: RLD samples need to be sourced to determine the physic-chemical properties of the drug product
2. Identify the container closure system
3. Generate data to set specifications
4. To perform bio studies (if required)
5. Securing API and Excipients:
6. API is sources from an approved vendor, if he may be national or international.
7. The manufacturer conduct an assessment of any legal issues affects the availability of use of API in the USA market.
8. The API must be tested for its quality and consistency priority to formulation.
9. The suppliers manufacturing facilities and process must be inspected for checking the product quality.
10. The supplier's ability to guarantee a stable supply of the API is critical to the success of developing a generic drug.
11. Excipients Selection
12. Ensure that the excipients and their quantities comply with IIG (Inactive Ingredients Guide)
13. Ensure that the excipients selected is acceptable as per the regulations of the targeted market(s)
14. Establish Controls for the excipients.

**Pre formulation Studies:**
These studies need to be done to
Determine the compatibility of the Active Pharmaceutical Ingredient and each of the excipients
Determine compatibility of the Active Pharmaceutical Ingredient and container closure system

**Formulation:**
Various formulations are laboratory tested against the brand-name drug. Development of a quality control matrix for formulation to be integrated into the manufacturing process.

**Method Development and Validation:** Develop a suitable method for testing of drug substance (if required) and drug product. Ensure that the method is specific, rugged, accurate, precise, robust, linear etc.

**Container Closure System:** Finalize based on the RLD samples (do any modifications that are specific to the site, proposed generic product etc.) and pre-formulation studies. Establish the controls and test procedures for container closure system.

**Trial Batches:** Execute trial batches of the drug product, varying the quantity of the excipients and modifying the manufacturing process if required

**Finalization of the drug product formula:** Finalize the formula and the container closure system of the drug. product based on the studies performed on RLD samples, pre-formulation trials, trial batches etc.

**Establishing Shelf-life:** Perform stability studies as per the regulations of the targeted market(s) to establish the shelf-life of the drug product

**BE studies**: In case of Generic Injectabels manufacturer did not go for the bioequivalence studies. Because of their 100% bioavailability of dosage inside the body manufacturer did not go for bioequivalence studies. Instead of these studies they provide BIOWAVIER[14] statement. This states that the product was comparable with RLD in releasing drug into body.

***Stage 4: Exhibit batches***
Execute the submission batch (es) and generate stability data as per the regulations of the targeted market(s) and proceed for filing the dossier.

**TYPES OF STUDY**: The study was conducted with an objective to sketch the regulatory frame work for generic drug approval process in USA and mainly emphasising on the application form, approval timelines and sequence of steps in the generic drug approval .The literature was collected using numerous search engines like pharma knowledge base, centre for pharmaceutical information and engineering research (CPIER) and official govt. website like FDA, EMEI,HMA and CDSCO. The patent information which is included in this work is obtained for the country specific patent organisations and world intellectual property organisation

**Hatch-Waxman Act: (16)**

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman

Amendments) amended the Federal Food, Drug, and Cosmetic Act (the Act). The Hatch-
Waxman Amendments created section 505(j) of the Act which established the Abbreviated

New Drug Application (ANDA) approval process, which in turn allows lower-priced generic versions of previously approved innovator drugs to be approved and brought on the market. ANDA is filed for the approval of a generic version[11] of an already approved innovator drug; the ANDA should have same ingredient(s), route of administration, dosage form, strength, conditions of use as that of already approved drug. The application for marketing of a generic drug is called an abbreviated application because some studies need not be performed by the applicant of the generic drug.

**ANDA APPROVAL PROCESS IN USA:**
Intially, an ANDA filer must show that the conditions of use identified in its proposed labelling have been previously approved for the listed drug on which the ANDA is based. According to the statute , ANDA must incorporate the same labelling as that of previously approved for the listed drug except for any changes require because of the differences are approved on the basis of a suitability pitition[12].

**WITHDRAWAL OF AN ANDA:**
FDA may withdraw/ suspend approval of an ANDA when the approval of the listed drug on which the ANDA relies is either a withdrawal/suspended. futher, an approval of an ANDA or 505(b) (2) application contains any untrue statement of material fact [7].FDA must withdraw approval of an ANDA if it finds that the approval "was obtained, expicted or otherwise facilitated through bribery[13],payment of an illegal gratuity, or fraud or material for statement", or may withdraw approval of an ANDA if it finds that the applicant has "repeatedly demonstrated a lack of ability to produce drug, and has introduced or attempted to introduce ,such adultrated or misbranded drug into commerce".

**CONCLUSION:** The decision to proceed with the development of a generic drug should be made on the basis of well researched data that primarily indicate the marketing share and annual sales of the innovator

drug in the respective country where the generic manufacturer is planning to launch ,together with the sound knowledge of patents and marketing exclusivities ,availabilities of API or pharmaceuticals materials formulation and BE considerations .The predicted profit of the generic product requires a stratergic planning for submission of dossier to the regulatory authority shortly prior to the patent expiry such that generic product is ready to enter into market immediately after the innovator drug patent expiry. Before approving the ANDA the USFDA team inspects the manufacturing plant, after completion of plant only they approve the application.If any deficiencies found during the GDUFA payment, during inspection or in application the USFDA refuse to review the ANDA. Once our ANDA approved we market the product into USA. After that if any changes occur to registered ANDA they filled as supplements to the ANDA. For PAS we pay $29,370 for GDUFA. For moderate changes and minor changes no fee. And minor changes were submitted as annual reports.

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