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THE APPROVAL OF DRUG PROCESS: A REVIEW

Gujral G.*[1], Kapoor D.[2] and Jaimini M.[3]

[1]Research Scholar Maharishi Arvind University Jaipur, Rajasthan.

[2]Dr. Dayaram Patel Pharmacy College Sardar Baug, Station Road, Bardoli Dist – Surat, Gujarat, India, Pin- 94601.

[3]Department of Pharmacy Maharishi Arvind University Jaipur, Rajasthan.

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***Corresponding Author**
Gujral G.
Research Scholar Maharishi Arvind University Jaipur, Rajasthan.

ABSTRACT

It takes on average 12 years and over US$350 million to get a new drug from the laboratory onto the pharmacy shelf. Once a company develops a drug, it undergoes around three and a half years of laboratory testing, before an application is made to the U.S. Food and Drug Administration (FDA) to begin testing the drug in humans. Only one in 1000 of the compounds that enter laboratory testing will ever make it to human testing.A new chemical entity means a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Act." The approval of NEW drug requires pre-clinical, Clinical studies (Phase I, II & III), Chemistry, Manufacturing and Control etc. data. Getting approval and successful launching of product into market is very difficult and success rate is very less. Pharmaceutical companies are investing reasonably good amount of money and time to get one drug approval and successful launch into the market.

KEYWORDS: Investigational new drug (IND)
Emergency use investigational new drug (EIND)
New drug application (NDA)
Abbreviated new drug application (ANDA)
Food and drug administration (FDA)
Reference listed drug (RLD)

INTRODUCTION

FDA History

The FDA is the oldest consumer protection agency in the United States, originating in the U.S. Patent Office in 1848, and later inherited by the Department of Agriculture in 1862.[1] The modern function of the agency in oversight of drug and medical device marketing was ultimately codified in the Pure Food and Drug Act of 1906[2-3], which was passed in response to a pressing need to curb interstate markets for adulterated and mishandled food and Pharmaceuticals. The Federal Food, Drug, and Cosmetics Act of 1938 required all drugs to be approved for safety by the FDA. This mission was expanded in 1962 by the Kefauver-Harris amendments that added the requirement that drugs be proven "effective" as well as safe, and placed strict controls on the use of investigational drugs. Regulations regarding drug safety oversight were expanded in 1976 to include medical devices. Over the course of the 20th century, the role of the FDA has undergone a significant metamorphosis due to expanding federal regulations, increasing complexity of drugs and devices, and the growth of the pharmaceutical industry into a major economic force in the United States. Today, the United States has among the most stringent regulations regarding medical drug and device development and marketing,

What is a Drug?

- A substance that is official in pharmacopoeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance (other than food) intended to affect the structure or any Function of the body.
- A substance intended for use as a component of a medicine but not a device or a component, part, or accessory of a device.

Prior to ever reaching a clinical researcher's hands, all new drug development follows a common pathway. Basic research leads to conceptualization, when a substance is ready for clinical study, but prior to any testing in human subjects, the drug developer must involve the FDA. This process begins when the drug's sponsor (usually the drug manufacturer or distributor) files an investigational new drug (IND) application with the agency. An approved IND application provides the developer with a technical exemption to this federal regulation, so that clinical investigators can distribute a drug to different study centres across the United States.[4]

"A new chemical entity means a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Act." The approval of NEW drug requires pre-clinical, Clinical studies (Phase I, II & III), Chemistry, Manufacturing and Control etc. data. Usually the development and approval of NEW drug will take 8-15 years and will cost at least $4 Billion and high as $11 Billion. Getting approval and successful launching of product into market is very difficult and success rate is very less. Pharmaceutical companies are investing reasonably good amount of money and time to get one drug approval and successful launch into the market.

THE IND APPLICATION

In many ways, the investigational new drug (IND) application is the result of a successful preclinical development program. The IND is also the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials (human trials). The sponsor has to verify whether the drug is safe for human use the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies. Data and information from 3 broad areas are included:

1. Animal Pharmacology and Toxicology Studies
2. Manufacturing Information
3. Clinical Protocols and Investigator Information

There are 3 basic pathways for IND approval which are as follows:

A- Pathway –I An investigator IND

Step 1: Contact the appropriate division of the FDA and set up a Pre-IND Consultation Program; check FDA guidance documents to be sure the new drug does not qualify for an exemption from IND application

Step 2: Submit the application (original and 2 copies) to Food and Drug Administration Center for Drug Evaluation and Research.

Step 3: If the FDA does not raise an objection within 30 days of submission of the application, the investigator may proceed

Step 4: If the FDA issues a "clinical hold," or responds with suggestions or mandatory changes, address these issues and resubmit the application.

B- Pathway –II EIND (emergency use investigational new drug)

An EIND asks the FDA to approve use of an experimental drug in an emergency situation that does not allow time for a standard IND process or IRB approval[5]. This type of application may also be submitted to authorize use in a patient or patients who do not meet study criteria or if no approved study protocol exists. EINDs are initiated by direct contact with the appropriate division of the FDA.

C- The treatment IND

Treatment IND applications ask for approval to use an experimental drug that is showing promise in clinical studies before completion of the studies, FDA review, and final approval. These are also called "expanded use INDs".[6] Treatment IND regulations went into effect in 1987, largely as a response to public activism surrounding the limited availability of azidothymidine during the drug's development. After approval of an IND application, the FDA allows human Phase 0, I, II, and III studies, provided safety and efficacy are demonstrated at the appropriate clinical testing phase.

The Clinical Trials

Clinical trials establish the safety, efficacy, and effectiveness of new drugs and are divided into Phase 0, I, II, and III trials. Post-approval surveillance trials are generally termed Phase IV trials. The FDA encourages investigators and sponsors to communicate directly with the appropriate FDA review section during each phase of testing. The Tabulation below gives an idea about all the phases.

Table 1: Description of different phases.

	Phase 0	Phase I	Phase II	Phase III	Phase IV
Description	First-in-man early trial to determine if drug engages its expected target	Initial safety evaluations, determine safe dosage range, identify common side effects, study toxicity profile of the drug	Begin to explore efficacy while maintaining safety	Final confirmation of safety and efficacy	Any trials conducted after FDA approval of the drug
No of Subjects	10–15 healthy volunteers	20–80 healthy volunteers	100–300 volunteers with the targeted medical condition	1,000–3,000 subjects with the targeted medical condition	Number of subjects depends on trial endpoints
Doze	Single, low dose (<1% of dose calculated to produce a clinical effect)	Single dose, Single ascending Dose, Multiple ascending Dose	Multiple dose trials, often conducted against placebo	Multiple dose trials, ascending doses	Variable
End points	Not expected to show clinical effect or significant adverse Effects. Helps to choose between competing chemical analogs for further stud	Escalation of dose ends when unacceptable side effects occur; the previous dose is considered the maximum tolerated Dose.	Explores clinical effects against the targeted condition, and reveals the less-common side effects	Confirms clinical efficacy of the drug against the targeted condition and evaluates safety and side effects	Confirms clinical efficacy and safety and explores other possible drug uses; may be required as a condition of drug approval
Timing	Can be conducted with prior approval while final IND review is pending	Together with Phase 0 trials, first clinical trials conducted in an IND process	Conducted after report to FDA of results of Phase I trials	Conducted after report to FDA of results of Phase II trials	Conducted after release of the drug by the FDA for marketing

Following successful completion of Phase III clinical trials, the drug sponsor can file a New Drug Application (NDA) with the CDER of the FDA. This application constitutes a request by the sponsor to manufacture and sell the drug in the United States.

THE NDA (New Drug Application)

The NDA[7] includes all data concerning the drug; all information about the manufacturing process and facilities, quality control, and assurance; a complete product description (chemical formula, specifications, pharmacodynamic, and pharmacokinetics); indications; labelling; and proposed risk evaluation and mitigation processes if applicable. A typical NDA can run 100,000 pages, and according to the Office of the Federal Register, The FDA has 60 days to determine if they will file the application once it is received.

FDA reviewers will evaluate clinical data, analyse FDA review occurs within 180 days of receipt of a complete application. If the application is found to have deficiencies, the clock stops on review while the manufacturer is given an opportunity to respond to the deficiencies or withdraw the application. If approval of the NDA is denied, the FDA sends a complete response letter describing specific deficiencies and recommending ways for the applicant to make the application viable. Unsuccessful applicants may request a hearing. Upon review and approval of the NDA, the manufacturer is free to manufacture and market the drug. Approval may include specific conditions, such as requirements for post approval(Phase IV) clinical studies, distribution restrictions, changes to labelling, or other requirements.

ANDA (Abbreviated New Drug Application)

A written request to the U.S. Food and Drug Administration (FDA) to manufacture and market a generic drug in the United States. Abbreviated New Drug Applications are “abbreviated” since they do not require the applicant to conduct clinical trials and require less information than a New Drug Application. If an ANDA is approved, the generic drug will be listed in the Orange Book, which lists all medicines the FDA has found to be safe and effective. An ANDA contains the information the FDA needs to evaluate how safe and effective a proposed generic drug is compared with its brand-name equivalent. The FDA will not approve the generic unless it is equally safe and effective.

ANDA Approval Pathway[10]

The process for obtaining approval to market an innovator drug approved under a new drug application (NDA) differs from that for obtaining approval to market a generic drug under an

ANDA. A sponsor of an innovator drug must submit an NDA, which must contain, among other things, a demonstration of the safety and effectiveness of the drug for the conditions of use for which approval is sought. In its application, an NDA applicant must submit information for each patent that claims the drug or method of using the drug and for which a claim of patent infringement could reasonably be asserted against a person engaged in the unlicensed manufacture, use, or sale of the drug product. Upon approval of an NDA, FDA publishes this patent information in its publication Approved Drug Products with Therapeutic Equivalence Evaluations, known as the Orange Book.

To obtain approval of a generic drug, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug. Instead, the applicant relies on FDA's previous finding that the reference listed drug (RLD) relied upon by the ANDA applicant is safe and effective. The ANDA applicant must identify the RLD on which it seeks to rely and, among other things, demonstrate, with limited exceptions, that the proposed generic drug has the same active ingredient(s), route of administration, dosage form, and strength as the RLD. A generic drug also must have the same conditions of use and the same labelling as the RLD (except for certain permissible labelling differences), and the applicant must demonstrate that its proposed generic drug is bioequivalent to the RLD.

Exclusivity[8-9]

To provide pharmaceutical companies with an opportunity to recover their investment in drug research and development and to incentivize continuing innovation, the United States Food and Drug Administration (USFDA), European Medicines Agency (EMA) and various other agencies have implemented numerous provisions to extend the period during which companies can market their drugs free of generic competition. USFDA provides 5 years data exclusivity for the new chemical entity and apart from this incentive the Patent term may be extended maximum of 5 years, so that the patent term for New Drug will have a term of up to 25 years. During this 5 years exclusivity period no other company should use the same NCE data for commercial purposes. In Europe, it is given as 10 years of data exclusivity and also one year additional exclusivity if any new therapeutic indication is registered before 8 years of first approval. Patent term can also be extended maximum of 5 years through Supplementary Protection Certificate. During 10 years of data exclusivity period agency will not approve any generic products.

A first applicant is an ANDA "applicant that, on the first day on which a substantially complete application containing a [paragraph IV] certification is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a [paragraph IV] certification for the drug." An applicant that previously submitted a substantially complete ANDA that did not contain a paragraph IV certification may become eligible for 180-day exclusivity. The listed patent or patents to which an ANDA applicant submitted a paragraph IV certification that gives rise to the eligibility for 180-day exclusivity is referred to as the qualifying patent(s).[10]

Generic Drugs

A generic drug product is considered to be essentially similar or bioequivalent to an innovator product. Due to high costs of the innovator drug products, which are not affordable to the common people, regulatory authorities permit manufacture and market the generic versions of the innovator drugs after the exclusivity period of innovator drug expires. Generally these generic drug products are typically sold at substantial discounts from their brand name counterparts. Generic companies are not needed to conduct non-clinical studies and Phase I, Phase II and Phase III clinical studies to explicit safety and efficacy of the drug products. Instead generic companies need to show that their generic product is bioequivalent to that of the innovator drug product through bioequivalence studies, thereby making medicines more affordable and more accessible to wider populations preventing drug shortages.

Development of Generic formulations particularly modified release dosage forms becomes very difficult, as the innovator companies used to protect the Modified release dosage forms technology, composition, polymers on very brand range, dissolution profile & Bio data through patents. So the generic companies cannot use the same technology/composition/polymer for development of modified release dosage forms till the patent expiries that is generally 20 years from the date of filing. So it is very difficult and becomes challenge for development of generic modified release dosage forms. The main challenge is developed formulation should pass Bio-equivalency studies in Fasting & fed conditions and also the product should be stable and should meet ICH guidelines. The Bio-equivalency will depend on the polymer used and percentage of polymer. So choosing of non-infringing polymer & composition which is able to control the drug release, passing Bio with respect to Reference product & stable during entire shelf-life of product is becomes

more difficult. Below is comparative chart of documents/data required for approval of new drugs/ dosage forms and generic drugs in most of the regulated markets:

Table 2: NDA vs. ANDA Review Process in USA.

S.No	NDA	ANDA
1	Applicable for new drug	Applicable for generic drug
2	Takes longer time(12-15years)	Takes 2-3 years
3	High expenditure involved	Comparatively less
4	Non clinical and clinical investigation is essential	Bio availability and Bioequivalence studies essential

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