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Editorial

New Drug Approvals by FDA: An Update

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Abstract

Bringing a drug into the market is an arduous task, and involved testing from preclinical safety to clinical trials. With its understanding of the science used to create new products, testing and manufacturing procedures, and the diseases and conditions that new products are designed to treat, FDA (U.S. Food and Drug Administration) provides scientific and regulatory advice needed to bring new therapies to market. This article provides an overview of the steps involved during development of a drug and its launch into the market.

Key words: Drug Development; FDA; Clinical Trial; IND; NDA

Introduction

The pharmaceutical sector is a very challenging industry. It involves huge investments, strong regulations, and low output in terms of new drugs. During past 21 years (1997-2017), the U.S. Food and Drug Administration (FDA), has approved a total of 641 new entities, with 46 approvals in 2017 being the highest in last 21 years [1-3]. FDA's Center for Drug Evaluation and Research (CDER) supports development of new drugs at each and every step. This article provides an overview of the steps involved during development of a drug and its launch into the market.

Pre-clinical/Nonclinical Development

Before testing a drug in human population, researchers need to find out that whether it carries the potential to cause serious toxicity using in silico, in vitro and in vivo models. Different models available for testing preclinical safety of drugs and the translation value of preclinical models have been discussed elsewhere [4-5]. FDA necessitates use of good laboratory practices (GLP) for preclinical safety studies. ICH provides comprehensive safety guidelines to uncover potential toxicities associated with drugs [6]. GLP regulations for Nonclinical Laboratory Studies are defined in 21 CFR Part 58 [7]. Preclinical studies should provide comprehensive information on dosing and toxicity levels. This information is then reviewed to decide whether the drug should move forward for testing in humans. If the drug can move on, filing of IND

(Investigational New Drug) Application is performed.

IND (Investigational New Drug) Application

There are two types of INDs: 1) commercial, and 2) research (non-commercial). There are three types of IND applications: 1) investigator IND, 2) emergency use investigational new drug (EIND), and 3) treatment IND [8]. All drugs undergo review by a FDA committee, or "new drug division," which specializes in that particular class of drug i.e. renal/ cardiovascular/ anti-cancer etc. FDA encourages investigators for early consultation with appropriate division through the Pre-Investigational New Drug Application Consultation Program prior to submitting a formal IND application. Early collaborations can avoid clinical holds on the application later on [9]. FDA also provides guidance documents which can be helpful in preparing an IND application [10]. Information and contact numbers for submitting an EIND application are also provided. Submitting an IND application requires three types of information: 1) data regarding pre-clinical animal studies and any previous human experience with the drug; 2) manufacturing information, including composition, manufacturer, stability, and controls; 3) clinical protocols, information about investigators proving their qualification to conduct clinical trials, commitments to obtain informed consent from subjects, obtain institutional review board (IRB) approval, and adherence to regulations related to INDs [11].

Investigator IND

An investigator IND is submitted by a physician, sometimes on behalf of an institution or "sponsor" such as a pharmaceutical company. Investigator will initiate and conduct the investigation. Investigator must wait for at least 30 days after submitting an IND application to begin any clinical trials. If FDA does not object within 30 days, Phase I testing can begin [12].

Emergency use investigational new drug (EIND)

An EIND is to get approval for a drug in an emergency situation which does not allow time for a standard IND approval [13]. EIND application may also be submitted for approval of use in a patient or patients who do not meet study criteria or if no approved study protocol exists. In emergency cases, FDA can approve use of the drug in advance of a full IND, which must then be submitted later on at agreed time.

Treatment IND

Treatment IND application is for seeking approval for use of a drug that is showing promise in clinical studies before completion of the studies, FDA review, and final approval. They are also called "expanded use INDs" [14]. Following requirements must be met for a treatment IND: 1) drug is intended for treatment of a serious or immediately life-threatening disease; 2) no satisfactory alternative treatment available; 3) drug is already under investigation or trials are complete; 4) sponsor is actively pursuing approval. Process and timelines for treatment IND applications are similar to those of regular INDs, however, requirements for clinical evidence differ.

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 termed Phase IV trials. Characteristics of the different clinical trials phases are summarized in (Table 1).

Table (1): Characteristics of various phases of Clinical Trials

Phases	Phase 0 "Microdosing"	Phase I	Phase II	Phase III	Phase IV
Purpose	Initial PK	Safety and Dosage	Efficacy and Side Effects	Efficacy and monitoring of adverse reactions	Safety and Efficacy
Success Rate	Not Applicable	Approx. 70%	Approx. 33%	Approx. 25-30%	Not Applicable
Details	First-in-man early trial to Determine, 1) if drug engages its expected target, 2) PK – particularly, bioavailability and half-life of drug	Initial safety evaluations to, 1) determine safe dosage range, 2) identify common side effects, 3) 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	20–100 healthy Volunteers (Cancer patients for cancer drugs)	100–300 volunteers with the targeted medical condition	300–3,000 subjects with the targeted medical condition	Number of subjects depends on trial endpoints
Dose	Single, sub-therapeutic dose (<1% of dose calculated to produce a clinical effect)	• Often sub-therapeutic dose • Single dose • Single Ascending Dose (SAD) • Multiple Ascending Dose (MAD)	Multiple dose (therapeutic dose) trials, often conducted against placebo	Multiple dose (therapeutic dose) trials, ascending doses	Therapeutic dose
Endpoints	Not expected to show clinical effect or significant adverse Effects. Helps to choose between competing chemical analogs for further study.	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
Duration	1-2 weeks	Several months	Several months to 2 years	1-4 years	Not Applicable
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
Success Rate	Not Applicable	Approx.. 70%	Approx.. 33%	Approx. 25-30%	Not Applicable
Purpose	PK	Safety and Dosage	Efficacy and Side-effects	Efficacy and monitoring of adverse reactions	Safety and Efficacy

PK: Pharmacokinetics

Phase 0 trial

Also termed as "Phase 0," or "exploratory" trials [15]. Phase 0 trials represent the earliest, first-in-man use of a proposed drug therapy [16]. Phase 0 clinical trial requires submission of an exploratory IND followed by a full IND. It is carried out in very small cohorts (10 to 15 patients), with dose levels of less than 1% of the dose calculated to produce a clinical effect [17], with administration schedules not expected to produce any clinical toxicity. Duration of dosing is less than 1 week. This trial can help determine whether a drug engages to its expected target and will likely have the anticipated clinical effect in human subjects. It can also help to study the pharmacokinetic and pharmacodynamic characteristics of the drug. It may also help to remove ineffective drugs early and help the investigator to choose between contending analogue drugs for further clinical development. Approval for a Phase 0 trial requires less preclinical toxicity testing than for full Phase I trials. Phase 0 trials can also be carried out while awaiting FDA review of a standard IND application, thus providing valuable information regarding human effects.

Phase I trial

Exploratory (Phase 0) INDs progress to "full" Phase I clinical trials if early results are encouraging. Purpose of a Phase I trial is to provide initial safety evaluation, determine safe dosing range, and identify common side effects and toxicity profile of the drug. Number of subjects is usually between 20 to 80 [18], subjects being generally healthy because clinical effectiveness is not an endpoint in this trial.

Single-dose studies are the usual beginning point of Phase I trials. Subject is given a single dose of drug no greater than one-tenth the highest dose associated with no adverse effects in the most sensitive animal safety studies. Single-dose trials are followed by single and multiple ascending-dose trials (Phase Ia and Ib trials, respectively). In Phase Ia trials, a small number of subjects (typically 3) are given a single, higher dose. If no adverse effects observed, another small set of subjects are given a further escalated dose, and this procedure continues until either pre-calculated pharmacokinetic safety levels are reached or until adverse effects start appearing. If at a particular dose level, a subject reports an unacceptable side effect, and then further subjects (e.g., 3 more) are dosed to confirm the effect. When unacceptable side effects appear, drug has reached its maximum tolerated dose (MTD). MTD is the dose preceding the one with intolerable adverse effects. Multiple ascending-dose (Phase Ib) studies assess pharmacokinetics and pharmacodynamics of multiple doses of the drug. Patients are administered multiple low doses of the drug, and biological samples (blood, urine etc.) are collected and analyzed. Dose is then further escalated on the basis of results obtained.

Phase II trial

Phase II trial is conducted to explore efficacy of the drug while continuing with establishing safety. It is larger (100 - 300 subjects), so that less-common side effects can be seen, involving patients suffering with an ailment which is a therapeutic target of the drug. Testing is often done in comparison to placebo. Dose escalation may be incorporated to explore therapeutic range of the drug.

Phase III trial

Phase III trials are the final confirmation of safety and efficacy and carried out in large cohorts (1,000 - 3,000 subjects). These trials evaluate effectiveness, monitor side effects, and compare the drug with commonly used alternative treatments. Following its successful completion, a New Drug

Application (NDA) can be filed. NDA constitutes a request by the sponsor to manufacture and sell the drug in United States.

New Drug Application (NDA): NDA includes information about manufacturing process and facilities, quality control, and assurance; a complete product description (chemical formula, specifications, pharmacodynamics, and pharmacokinetics); indications; labeling; and proposed risk evaluation and mitigation processes, if applicable [19]. A typical NDA can be of 100,000 pages, and application fee for an NDA that requires clinical data is $2,421,495 for financial year 2018 [20]. FDA has 60 days to determine if they will file the application once received [21].

Phase IV trial

Despite rigorous testing in the process of drug development, limitations exist to get the information regarding safety of a drug at the time of approval. Complete information regarding drug's safety actually keep coming over the months and even years it remains in market. FDA reviews reports of problems with prescription and over-the-counter drugs, and adverse effects observed. It can then decide to supplement cautions to dosage or usage information, as well as other measures e.g. adding warning in label for more serious issues.

FDA reviewers evaluate clinical data, analyze drug samples, inspect production facilities, and check proposed labeling. Approval may include specific conditions, such as requirements for post-approval (Phase IV) clinical studies, distribution restrictions, changes to labeling, or other requirements. FDA review occurs within 180 days of receipt of a complete application. If application is found to have deficiencies, review process is kept on hold, while the manufacturer is given an opportunity to respond to deficiencies or withdraw the application. If NDA approval is denied, FDA sends a complete response letter describing specific deficiencies and recommending ways for the applicant to make the application viable. Upon review and approval of the NDA, manufacturer is free to manufacture and market the drug in United States.

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