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New drug development process-Today: A review

Gowhar Ali*, Abuzar Khan, Samiullah
*Department of Pharmacy, University of Peshawar, Peshawar, Pakistan
email: gohar.pharmacist@gmail.com

Abstract

New drug development is an imperative biomedical research area and a key step towards maintenance of the public health. Since antique, maintenance of public health is a great challenge for health care professionals. Although new drug development is a tremendously strenuous, extremely technical, very costly ($800 million-$1billion) and a time consuming (15-20 years) process yet new drugs have transfigured the practice of modern therapeutics by controlling numerous serious diseases as a routine therapeutic practice. In general, globally new drug development program is processed as drug discovery, pre-clinical and clinical development.

Key words: New drug development, drug discovery, pre-clinical, clinical

Introduction

Drugs have the possibility to provoke desirable and undesirable effects when they are administered to animals or humans. Prior to the approval for marketing, a new drug must be shown to be safe and effective. It has been reported that over the past 30 years in the USA, mortality rate mainly due to cardiovascular and stroke diseases have been reduced by more than 50%, in part by new anti-hypertensive, anti-hyperlipedimic, anti-coagulant and thrombolytic drugs [1]. It has been estimated that a single new compound to receive approval for marketing is one of the 5,000-10,000 of compounds that have been extensively tested and a net cost of more than $800 million-$1billion and overall time may be more than 10 years[2-3]. Academic institutions neither have the incentive nor massive funds for such a tedious job. Therefore, most of the new drug development researches are conducted by leading pharmaceutical companies as shown in **Table 1**[4] while the academic institutions mainly committed to basic research [5]. In general, drugs existing today are prepared and developed in bulk scale from synthetic sources. The stages through which a new drug is discovered, developed and regulated are generally same in most countries of the world with minor differences. These include drug discovery, preclinical and clinical development [6] as shown in simplified form in **Figure 1** and a detail schematic diagram in **Figure 3.**

Drug discovery stage

During new drug development process, first of all a therapeutic need is identified and then a project is designed accordingly (pre-discovery study) [6-7]. After completion of human genome project in 2001, drug development has revolutionized the modern practice of pharmacotherapy. A multidisciplinary research areas are involved in the new drug development process including cellular biology, pharmaceutical organic chemistry, basic and clinical pharmacology, toxicology, pharmaceutical formulation, analytical research and regulatory sciences[8]. All these research areas work jointly to develop a new drug for marketing. These multidisciplinary research areas identify a therapeutic target (receptor, ion channel or enzyme), develop and optimize a potential drug candidate called lead compound.

The following general approaches are used for the new drug discovery or development irrespective of the source [1, 5, 9-13].

i. New biochemical target selection or identification e.g. enzymes, ionic channels or receptors. Drug discovery phase starts by targeting a particular clinical disorder to be treated [6].

ii. Based on extensive knowledge of molecular mechanisms, drug structure and drug receptor, development of a new drug as a rational drug design [14].

iii. Modification of the chemical structure of known compound with the plan of synthesizing a more effective or a less perilous drug (SAR study).

iv. Random screening of completely novel compounds for pharmacological activities.

v. Biotechnology and the cloning techniques using genes (genomics) to produce large peptides and proteins (proteomics) of crucial importance.

vi. Discovery of novel uses of drugs previously in use based either on discovery of mechanism of action or serendipity.

First of all a chemical with potential therapeutic benefits (lead compound/potential drug candidate) must be identified through various research techniques. Several techniques have been employed to obtain compounds for drug discovery including synthetic organic chemistry, drug modeling, combinatorial chemistry and natural sources [15-18]. Currently drug molecular docking, combinatorial chemistry,bioisosterism [19] and other synthetic chemistry techniques are widely used by leading R & D pharmaceutical organizations [18, 20]. Molecular modeling is a technique where computers are used to operate virtual chemical structures and compute protein binding capacities. Computer-assisted drug design (CADD) molecular modeling [21-23], have been tested in quantitative structure activity relationship

(QSAR) and computational chemistry to identify the shape of compounds [24-26]. In order to provide an insight as to the preferred conformation of a molecule, molecular mechanics and quantum mechanics calculations are conducted in conformational studies. Drug molecular modeling and molecular graphics have revealed spectacular development and are becoming an essential division of the drug-discovery development programmes [27]. Drug modeling is the creation, manipulation depiction of the three-dimensional shape of molecules and molecular graphic is the use of computer graphics to characterize the molecular structure [28-29]. Generally, all molecular structures having the capacity of binding to a single high efficiency site can be modeled. Combinatorial chemistry technique involves random addition of different functional groups to one compound, acting as a basic chemical to produce libraries or banks of all possible combinations [30]. Such compounds are initially assessed using automated robotic high-through put screening devices [31-32]. New drug development in most countries of the world has numerous features in common, starting with the discovery and characterization of a potential drug candidate [33]. Once a potential drug candidate is identified, it undergoes non-clinical, clinical and regulatory phases [34].

Non-clinical/preclinical stage

Non-clinical/preclinical or non-human study is the conduction of laboratory and animal testing to determine safety of new drug candidate. It involves both *in vitro* and *in vivo* (living cell cultures and animal models) testing. The US FDA requires that prior to proceed the clinical stage, it is mandatory to gratify all the essential requirements including physicochemical, pharmacokinetic, and pharmacodynamic and safety profile [5, 35]. Pre-clinical testing is carried out on laboratory animals including rodents like rabbits, mice, rats, guinea pigs etc and non-rodents like dogs, cats, monkeys etc [9]. The new drug is tested for the first time in a live biological system and useful predictive value can be obtained which can be further extrapolated to clinical studies. Among 5,000-10,000 compounds which enter the R & D channel, almost 250 compounds enter pre-clinical dynamic testing and then almost 5 compounds enter the clinical trials. Ultimately only one molecule receives marketing approval. The new compounds not qualifying the desirable results of preclinical testing, fail to progress the clinical development phase. The new drug must be produced in sufficient amount and at a high level of purity. Impurities, if exist more than 0.1%, must be identified and checked for toxicological property [2]. During preclinical stage, drug delivery system is developed for new chemical entity (NCE) and the physicochemical properties are identified. During the entire process of new drug development, the formulation development process is continued and the information's obtained both from non-clinical and clinical studies are used for the optimization of drug delivery system [2].

In general, the purpose of preclinical toxicity study is to determine the risk to benefit ratio of new drug. These studies also include determination of minimum lethal dose (LD_{50}), minimum effective dose (ED_{50}), minimum lethal dose and no-effect dose [1]. LD_{50} indicates that a dose which can cause death of the 50% of experimental animals. ED_{50} indicates a dose which is effective in 50% of experimental animals. Minimum lethal dose is the minimum dose which can kill any laboratory animal and no-effect dose is the maximum tolerated dose at which no obvious toxic effect can be observed. Clinical trial dose is based on this study and it is usually calculated as 1/100 to 1/10th of the no-effect dose of animals [1].

Aims and objectives of preclinical study

The pre-clinical study is conducted to achieve the following different objectives [1-2, 6].

A. Drug screening to establish pharmacological/biological activities profile through various biologic assays at the cellular (cell function), molecular (enzyme/receptor), organ system and even intact animals. Pharmacokinetic study (ADME) is also conducted on experimental animals.

B. Toxicological studies are designed as all chemicals including drugs are toxic at some dose

level (animal safety testing). This study is performed to determine any potential toxicity associated with new drug. The type of safety tests which are conducted at this stage include [1];

· Acute toxicity (single dose studies): It is the administration of a single acute dose to two species at two different routes to determine maximum tolerated dose.

· Sub-acute toxicity/intermediate (repeated dose studies): It is the administration of three doses to two species for four weeks to three months.

· Chronic toxicity/ long term (repeated dose studies): It is conducted for six months or longer both in rodents and non rodents. It depends on the expected duration of new drug to be used in humans and may continue during clinical development.

· Reproductive performance: It is the determination of any detrimental effect on reproduction/fertility, teratogenic (birth defects), progeny, parturition, mating behavior and embryo toxicity etc.

· Carcinogenic activity: It is conducted in two species for two years when new drug is intended to be used chronically.

· Mutagenic activity: Any genetic changes (mutation) in prokaryotic or eukaryotic (mammalian) cell that is genotoxicity determination.

· Investigative toxicology: It is involved to determine toxicokinetic and toxicodynamic.

C. Chemical and pharmaceutical (pre-formulation and formulation) development for scale up synthesis, purity, stability and proper drug delivery.

Limitations of Preclinical testing

Although preclinical testing's are useful in many situations yet there are certain limitations as well [1, 9]. These limitations include;

a. The toxicological testing conducted during preclinical stage, is very expensive and lengthy procedures and may take 2-6 years to gain useful data for safety of new drug.

b. A huge quantity of experimental animals may be required to achieve statistically significant animal data. Currently in vitro cell and tissue culture techniques are progressively more used but their prognostic value is still inadequate [1].

c. Extrapolation of animal data to humans is not completely reliable in all cases. The therapeutic decisions cannot be absolutely extrapolated to use in humans [9].

d. Statistically, very rare adverse effects of drugs are implausible to be identified [2].

Although it is important to identify the limitations of animal testing yet a vigilantly and ethically designed animal study may have a predictive value for any new compound to be tested in humans. Animals studies generate for the first time pharmacokinetic, pharmacodynamic and toxicological data of the new drug and provide base for the clinical development stage [8].

Clinical development stage

Prior to the use of a new drug or new treatment in humans, it is essential that the new drug or new treatment should be warily and ethically evaluated first in animals (pre-clinical studies) and then in human beings for safety and efficacy (clinical studies). Such study in humans is referred to as clinical trials [36]. Clinical trials designing, controlling, conducting, reviewing, reporting and recording is under an international standard and ethical practice called good clinical practice (GCP). It makes sure that the data obtained from clinical trials is plausible and privacy of the subjects is cosseted.

Informed consent

Informed consent is essential before the initiation of a clinical trial. The research organization must obtain an informed consent [36]. It is a legally defined process in which the subjects are pre-informed about all aspects of the clinical trial like purpose, duration, required procedures and potential benefits to risks ratio etc. The subjects then make a decision to contribute or not. If subjects corroborate their willingness to participate, then the

consent form is signed and dated both by investigator and subject. If a subject is uneducated, his/her legal envoy will sign the form. In order to safeguard the human rights and welfare, an ethical committee periodically reviews the research methodology involving human beings [37]. A minimum of five members are necessary but maximum recommended members are 12-15 [36]. It is constituted as chairperson (administrator), one or two basic medical scientists (one preferably pharmacologist), one or two clinicians, one legal expert or retired judge, one social scientist, one philosopher/ethicist/theologist, one community lay person and a secretary member [36]. This committee monitors the ethical justification and scientific validity of research, review of informed consent, potential benefits to risks ratio, discuss any remuneration/pay, to safeguard confidentiality and blinding techniques.

Randomization

Randomization is a practice where the subjects are randomly allocated to receive either the test drug or a control in a clinical trial using a probability mechanism. This is generally done by a computer as depicted in **Figure 2**. The investigator has no part to decide the allocation of a particular treatment to a particular patient in the trial. This is done to prevent bias in the research e.g.

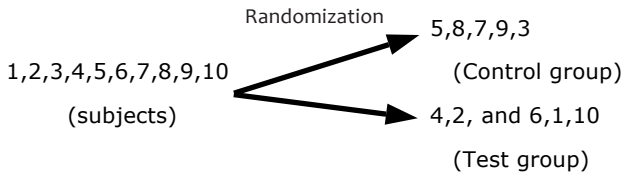

Figure 2: Randomization process during clinical trials

Clinical trial design

The rationale of blinding in clinical trial is to abolish bias (extra care of test group and no care of control or self-intentions).The subjects involved in the study don't know which study group they receiving. In case of single blind, only the subject is oblivious about the identity of drug, he/she is receiving while in double blind trial, both the investigator and subject are unaware about the group identity. Only a third party knows about identity. In most of the clinical trials, a randomized double blind trial is considered a standard design. Placebo is a dummy medicine like starch, lactose etc, having no pharmacological activity and is commonly used in clinical trials to curtail the bias.

Clinical trial Phases

During this stage, the new drug is tested in human beings to determine safety and efficacy and then approved for therapeutic purpose. After conclusion of preclinical study, the research organization files an investigational new drug (IND) application with the regulatory authority for approval to test the new drug for the first time in humans. This application is accompanied all the previously collected and justified data. It includes data regarding source, chemistry and all animal data. A clinical trial design is a well defined protocol with clear aims and objectives, prescribed inclusion and exclusion criterion for subjects with respect to age, sex, disease; defined experimental groups, randomization, blinding techniques, panel of investigators and center(s) of study. Depending upon the type of phase of clinical trials, investigators enroll either healthy volunteers or patients and the results obtained with new drug are compared with already existing standard therapy. A clinical trial is one of the steps needed to introduce a new drug or therapy. Clinical trials are conducted in four distinct phases, each having definite objectives [4, 6].

Phase-I clinical trials

A small group of healthy volunteers (20-80) are used in this phase. Volunteer may be paid. The purpose of this phase is to determine safety, maximum dose tolerability, pharmacokinetics (ADME) and pharmacodynamic of new drug for the first time in humans. This phase normally involves to determine safe clinical dose range called dose escalation through single and multiple ascending techniques for determination of therapeutic dose range. Although healthy volunteer are used in this phase but drugs with significant toxicity as in anti-

cancer and anti- HIV therapy, then such trials could also be conducted on terminal cancer or HIV patient which lack other treatment options. Fasting and full stomach study is also carried out to determine food effect on absorption. These trial are non-blind or open trial that is both the investigators and the subjects are aware that what is being given. Predictable toxicities of drugs are also detected. Such study is performed in research centers by specially trained clinical pharmacologists.

Phase-II clinical trials

The main purpose of this phase is to assess the effectiveness of drug in patients with targeted disease for which the drugs is developing. Such trials are performed on a larger number of patients (100-200 and even up to 300). This phase provide information about**,** efficacy**,** therapeutic dose range, P.K, P.D and a broader range of toxicities data. A single blind is often used, with inert placebo medication and an established active drug (positive control) and investigational new drug (IND). Such trials are usually performed in special clinical centers e.g university hospitals. When the development process for a new drug fails, this occurs usually in this phase.

Phase-III clinical trials

Such trials are performed further on larger number of patients (1000-3000) with targeted disease. The main objective of this phase is to verify the results of phase I and II trials that the drug is safe and effective for intended use. This phase also involves special population study like pediatrics, geriatric, patients with renal failure etc. Also provide information about dosage schedule, frequency, duration, drug interaction and ADRs. These are double blind randomized and cross over trials and performed in multicentres by specialist in diseases. Certain toxic effects, especially those caused by immunologic processes, may first become apparent in this phas. In this phase, the IND efficacy is compared with already existing standard treatment. Phase-III trials are the most expensive, time consuming and difficult to run as a large number of subjects are involved and long duration especially in chronic disease management.

After completion of phase-III, the organization files an application called new drug application (NDA) with the regulatory authority to get approval for marketing the drug. This application contains often in hundreds of volumes, full deposits of pre-clinical and clinical data of IND.

Phase-IV post- marketing surveillance study

Once get approval for marketing a new drug; it is called post- marketing surveillance study. It comprises further corroboration of efficacy and safety of the new drug under actual conditions of use in a large number of patients[38]. It presents information's regarding potential drug interactions, identification of new indication, evaluation of different formulations, to estimate incidence of adverse reactions, detect previously unknown ADRs and identity risk factor for ADRs. The drug company collects the data form ADR monitoring centre's and submit post marketing data regularly to the regulatory agency to continue its use. Some drugs are withdrawn from the market after analyzing post marketing data by FDA due to their life threatening ADRs e.g roziglitazone, cenvastatin, terfenadine, rofecoxib etc.

Four possible outcomes of clinical trials

a. Positive Trials: It shows that the new treatment /drug has a large beneficial shape and is considered superior than already existing standard treatment /drug.

b. Non-Inferior Trials: It shows that the new treatment /drug has equivalent to standard treatment.

c. Inconclusive Trial: It shows that the new treatment is neither clearly better nor clearly inferior to standard treatment.

d. Negative Trails: It shows that the new treatment/drug is inferior to standard treatment.

A new drug is protected by a patent for 14-20 years. During this period the new can be marketed

only by that pharmaceutical company manufacturer that develops it for the first time. This is because of company huge investment, in millions of dollars to develop a new drug which require years of work. Other pharmaceutical companies cannot manufacture and market this drug. However after the expiration of patency, other companies then submit an abbreviated NDA (ANDA) to the FDA, with the equivalency data and then this can be marketed as a generic product.

Conclusion

In summary, modern drug discovery and new drug development process is the product of a series of events which may takes an average 10-15 years and an approximate cost of $800 million-$1 billion. These events include pre-discovery phase for identification of a therapeutic need; discovery phase for target identification, target selection, lead finding and lead optimization; pre-clinical development for safety prior to be tested in humans; IND application; clinical development for testing in humans including clinical trials FDA; approval and an ongoing marketing monitoring.

"This is a fantastic time to be doing drug discovery. We have an incredible wealth of knowledge that has been generated over the past few years." (Thomas Hughes, Ph.D., Novartis)

"Some ideas may just stay on paper forever, but others have a way forward to make it into a pill, into a bottle at the pharmacy." (Debra Luffer-Atlas, Ph.D., Eli Lilly and Company)

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Pharmaceutical company	R&D spending	Pharma sales	R & D as % of sales
Pfizer	4,847	25,518	19
GlaxoSmithKline (GSK)	3,694	24, 791	14.9
AstraZeneca	2,687	16,183	16.6
Aventis	2,574	14,879	17.3
Johnson & Johnson	2,465	14,851	16.6
Merck & Co	2,456	19,732	12.4
Eli Lilly	2,235	10, 856	20.6
Pharmacia	2,085	11,970	17.4
Bristol-Myers Squibb (BMS)	2,066	15,300	13.5
Novartis	2,046	11,963	17.1

Table 1. 2001 ranking of leading pharmaceutical companies by R & D spending [US $ in millions] [4]

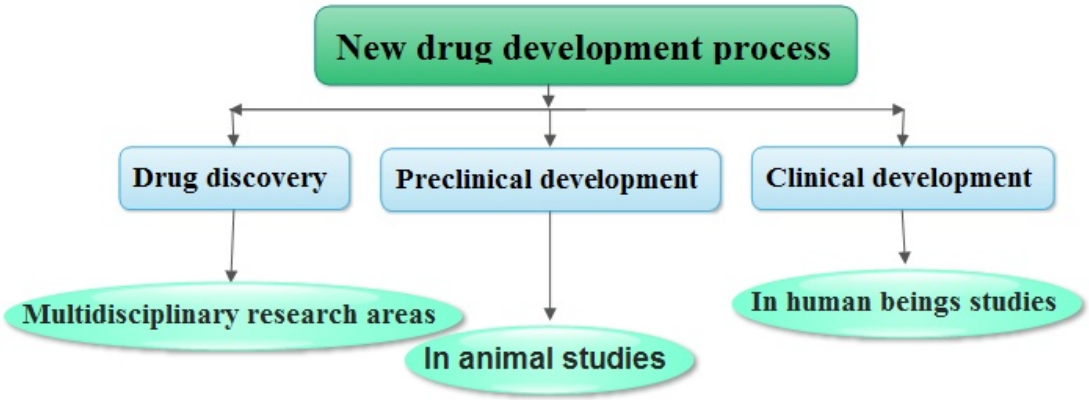

Figure 1: A simplified sketch of new drug development process

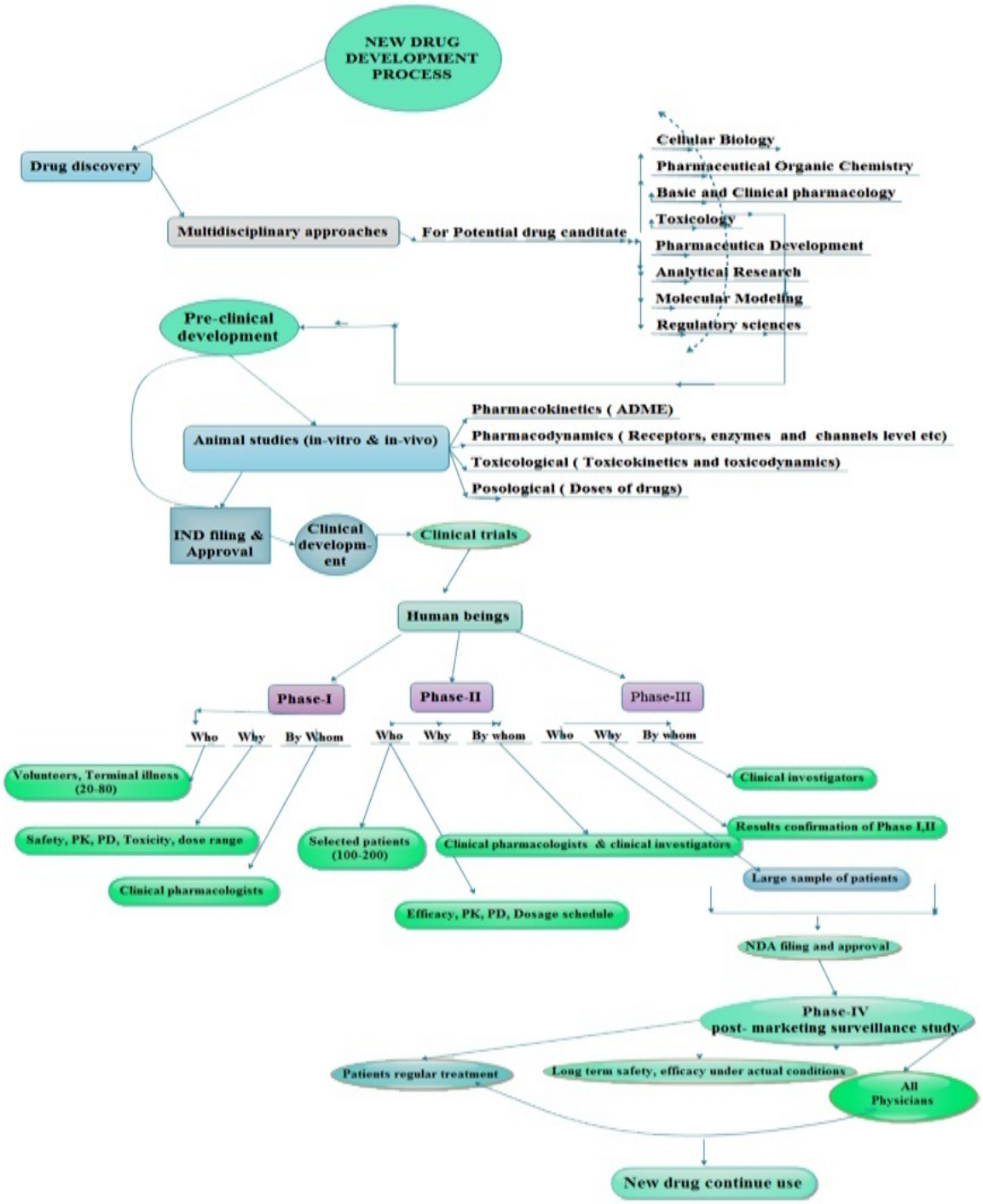

Figure 3: A detail sketch of new drug development process