Chapter 1

Drug Discovery, Development and Approval Process: An Overview

LEARNING OBJECTIVES

To understand

- Drug Discovery
- Methods for Drug Discovery
- Drug Development
- Steps Involved in Drug Development
- Preclinical Evaluation (Animal Studies)
- Clinical evaluation (Human Studies)
- Clinical Pharmacology
- Clinical Trials
- Drug Approval Process
- Drug Approval Process in United States
- Investigational New Drug (IND) Application
- New Drug Application (NDA)
- Abbreviated New Drug Application (ANDA)
- Drug Approval Process in Europe
- Drug Approval Process in India
- A Comparision of Drug Approval Process in US, Europe and India.

Introduction

In ancient time most of the drug used in the treatment of disease were derived from naturally occurring substances of plant origin, e.g. Opium from poppy, Quinine from cinchona, digitalis from foxglove. Presently, the majority of new therapeutics agent are synthetic in

nature. Drug discovery and development is complex, time-consuming, costly process which carries commercial risk. Drug discovery and development is broadly divided into three main components:

i) drug discovery,
ii) preclinical evaluation,
iii) clinical trials.

Drug Discovery

Typically, researchers discover new drugs by the following methods:

i) Through new insights into a disease process that allow researchers to design a product to stop or reverse the effects of the disease.
ii) Through many tests of molecular compounds to find possible beneficial effects against a disease
iii) Through existing treatments that have unanticipated effects.
iv) Through new technologies that provide new ways to target products to specific diseases.

At this stage in the process, thousands of compounds may be potential candidates for development in to an effective and safe drug. After initial pharmacological and toxicity testing only a small number of compounds look promising and call for further studies.

Development: Once researchers identify a promising compound for development, they conduct experiments to gather information on: How it is absorbed, distributed, metabolized, and excreted. Its potential benefits and mechanisms of action. The best way to give the drug (such as by mouth or injection).

Side effects or adverse events that can often be referred to as toxicity. How it affects different groups of people (such as by gender, race or ethnicity) differently. How it interacts with other drugs and treatments. Its effectiveness as compared with similar drugs.

Methods for Drug Discovery

1. Random screening
2. Molecular manipulation
3. Molecular designing
4. Metabolites of drug
5. Serendipity

1. ***Random screening*:** In this procedure new chemical entities are subjected to battery of screening test designed to determine diff. types of biological activity. Such test include studies on animal behaviour. Isolated tissues, intact animal and sometimes even an animal models of disease. Such studies are time consuming, expensive and have a low yield. It is possible that the new drug thus found may be ultimately turn out to be similar in extraction to already existing drugs, with no added advantages.

2. ***Molecular manipulation*:** In this procedure analogues of existing drugs are synthesized and tested for their biological activity. This is more logical approach and may yield new compounds with certain advantages like better absorption**,** greater potency, more selective action, fewer side effects.
3. ***Molecular designing*:** This is the most rational form of drug R & D. It ends at designing of substances to fulfill of specific biological task. In its simplest form this may involve the synthesis of naturally occurring substance, a hormone, a vitamin o a precursor of a neurotransmitter. **e.g**. dopamine for cardiogenic shock, levodopa for parkinsonism.
4. ***Metabolites of Drug*:** Sometimes active metabolites of drug are found to posses therapeutic advantages over parent compound. e.g. Paracetmol is metabolite of phenacetin and it is effective as an analgesic but does not cause renal damage.
5. ***Serendipity*:** it means "happy observation by chance" and has led to introduction of many remedies in the past. *e.g.* use of organomercurials for cardiac oedema, penicillin as an antibacterial agent.

Drug Development

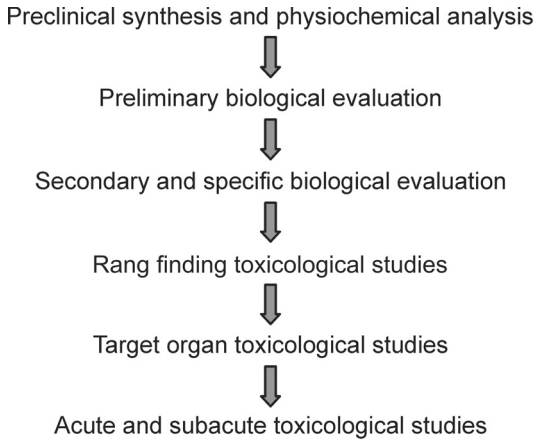
Once a new chemical entity is discovered it has to be subjected to the development process. Chemical synthetic activity is mostly carried out in R&D divisions of p'ceutical lab by synthetic chemistry. After synthesis the structure of new compound and its purity is determine and confirmed by analytical chemist.

Pharmacological evaluations can be divided into –

i) preclinical pharmacology and

ii) clinical pharmacology

Steps Involved in Drug Development



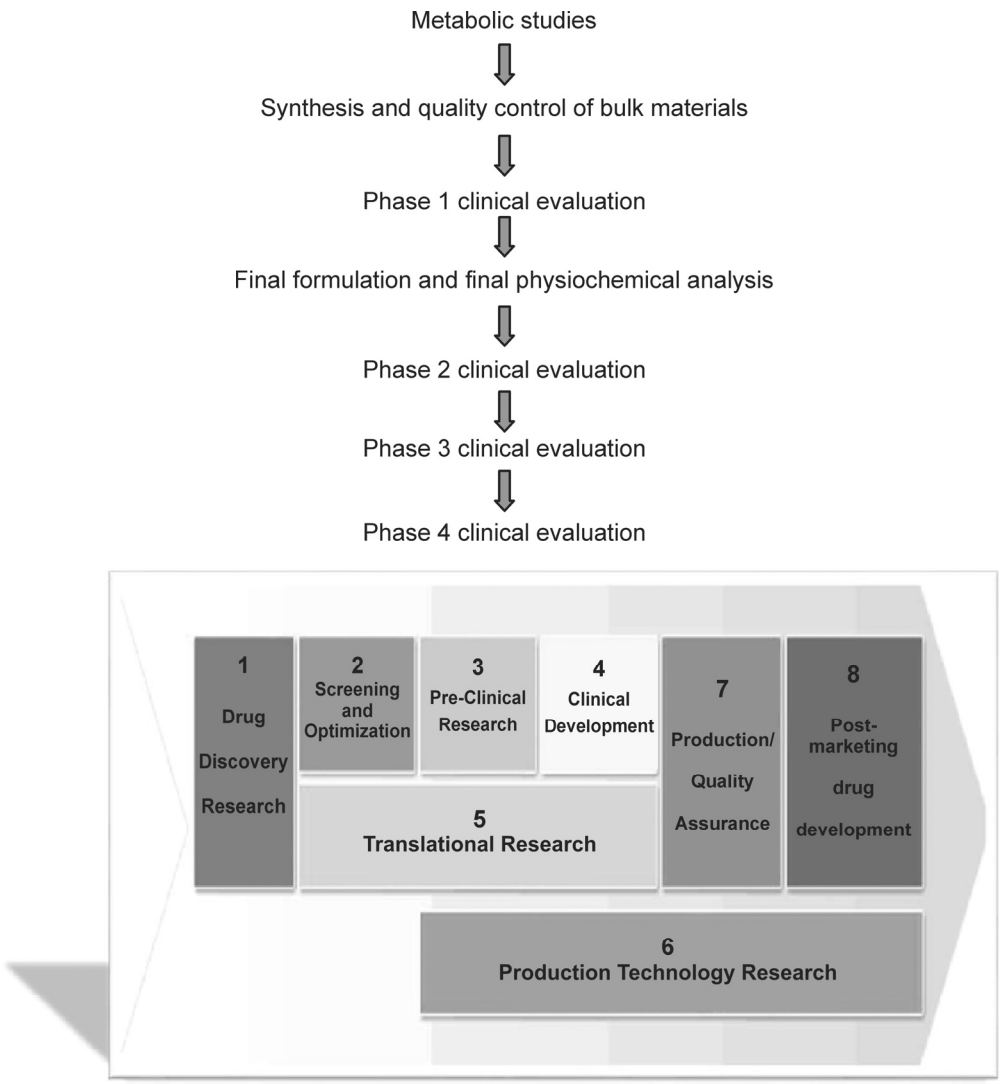


Fig.1.1 Various Stages in Drug Discovery Development and Approval Process.

Preclinical Evaluation (Animal Studies)

Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm, also called toxicity. The two types of preclinical research are: -*In Vitro, In Vivo*. FDA requires researchers to use good laboratory practices (GLP), defined in medical product development regulations, for preclinical laboratory studies.

Usually, preclinical studies are not very large. However, these studies must provide detailed information on dosing and toxicity levels. After preclinical testing, researchers

review their findings and decide whether the drug should be tested in people. The experimental animals used for preclinical testing include mice, rats, guinea pigs dogs, and sometimes monkeys.

The three major areas of preclinical evaluation are:

1. Acute, sub acute and chronic toxicity studies
2. Therapeutic index.
3. Absorption, distribution and elimination studies

Clinical Evaluation (Human Studies)

Preclinical data obtained from animal studies provide a general pharmacological, toxicological, and pharmacokinetic profile of a new drug. The New Drug application in the prescribed format, with all relevant literature and preclinical data must be submitted to Drug Control Authority for scrutiny, and sanction obtained before ***clinical evaluation*** studies are initiated.

Clinical Pharmacology

Clinical pharmacology deals with the effect of drugs on body and the effect of body on drugs in man, i.e. the *pharmacokinetic* and *pharmacodynamics studies in man.*

It has three distinct part:

1. Confirmatory pharmacology
2. Human biotransformation studies
3. Clinical trials.

Sir Bradford Hill (1966) defined a clinical trial as

"A carefull and ethnically designed human experiment with the aim of answering some precisely framed questions".

This definition is valid even today.

Clinical Trials

Here are some salient guidelines to design a perfect clinical trial:

1. **Ethics and patient selection:** Criteria for **selection of patient** should be well thought out and defined. Special care must be taken if more than one doctor is involved in the selection of patient in the trial specially in multicentric trials
2. **Response measurement:** The end point should be clearly defined. Side effect should be carefully observed and recorded.
3. **Experimental design:** For the design of an experimental design preferably a biostatistician should be consulted.

(a) In general, *controlled clinical trials* must include four safe guards against bias: double blind technique

(b) Randomization of treatment

(c) Matching of patient

(d) Cross over techniques.

Phases of Clinical Trials

- Phase I: Clinical pharmacologic Evaluation
- Phase II: Controlled clinical evaluation
- Phase III: Extended clinical Evaluation
- Phases IV: Surveillance during post marketing

Phase I:

Phase I are usually carried out on 20-50 healthy volunteers or patients, depending on class of drug and it's safety. This studies are mainly concerned with human toxicity, tolerated dosage range, pharmacological actions, and pharmacokinetics of drug.

Phase II:

These studies are carried out on 50-300 patients. These studies mainly aim to ascertain the safety and efficacy of the new drug, and are strictly controlled.

Phase III: Extended clinical Evaluation

These are formal therapeutic trials carried out in double blind Controlled manner in 250-100 patients. Efficacy and safety of the new drug is evaluated and even comparison with other drugs is undertaken.

Phase IV: Surveillance during Post marketing

After the drug release for general clinical use, certain unusual type of adverse reactions may be observed even after years of clinical usage. Thus, an adverse reaction monitoring is carried out in Phase IV evaluation.

For Further Reading

1. Pharmacology-I, Essential of pharmacotherapeutics, By F.S.K.Barar S.chand publication, 1st edition, 1985, Page no: 56-61 2
2. https://googleweblight.com/i?u=https://www.nature.com/subjects/drug discovery & grqid=DEji1MmA&hl=en-IN
3. https://googleweblight.com/i?u=https://www.slideshare.net/mobile/rahu l_pharma/drug discovery-and-development- 10698574&grqid=dRB10k76&hl=en-IN

DRUG APPROVAL PROCESS

Developing a new drug requires great amount of research work in chemistry, molecular biology, biochemistry, preformulation and formulation development, process development and manufacturing, quality control, preclinical and clinical studies. Drug regulatory agencies globally bear the responsibility of evaluating whether the research data support the safety, effectiveness 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. Different countries have different regulatory requirements for approval of new drug. For IND, NDA or marketing authorization application (MAA) a single regulatory approach applicable to various countries is almost a difficult task, not available at present. Therefore it is necessary to have knowledge about regulatory requirements for drug approval process of each country.

The new drug approval process consists of two stages, the first stage is for IND and the second stage is for NDA and marketing authorization of dr**u**g. Firstly, non-clinical studies of drug are completed to ensure safety and efficacy. The next step is the submission of application for conduction of clinical trials to competent authority of respective country. In next step, clinical trials are carried out in four phases i.e. phase 1 to phase 4 study. These studies are carried out for the assurance of safety, efficacy and for optimization of dose of drug in human being. Then application for marketing of drug is verified by competent authorities. The competent authority review the application and approve the drug for marketing purpose, only if that drug is found to be safe and effective with desired therapeutic effect. The drug approval process in various countries is reviewed below.

Drug Approval Process in United States

The United States has the world's most stringent standards for approving new drugs. Drug approval standards in the United States are considered to be the most demanding in the world.[1-3]

Investigational New Drug (IND) Application

It's an application filed to the FDA in order to start clinical trials in humans if the drug was found to be safe from the reports of Preclinical trials. A firm or institution, called a Sponsor, is responsible for submitting the IND application.[4] A pre - IND meeting can be arranged with the FDA to discuss a number of issues like the design of animal research, which is required to lend support to the clinical studies, the intended protocol for conducting the clinical trial, the chemistry, manufacturing, and control of the investigational drug. Such a meeting will help the Sponsor to organize animal research, gather data, and design the clinical protocol based on suggestions by the FDA.

New Drug Application (NDA)

If clinical studies confirm that a new drug is relatively safe and effective, and will not pose unreasonable risks to patients, the manufacturer files a New Drug Application (NDA), the actual request to manufacture and sell the drug in the United States.[5-6]

Abbreviated New Drug Application (ANDA)

It's an application made for approval of Generic Drugs. The sponsor is not required to reproduce the clinical studies that were done for the original, brand name product. Instead, generic drug manufacturers must demonstrate that their product is the same as, and bioequivalent to, a previously approved brand name product.[7]For human testing in clinical trials Phase 1 studies (typically involve 20-80 people) Phase 2 studies (typically involve a few dozen to about 300 people). Phase 3 studies (typically involve several hundred to about 3,000 people). The pre-NDA period, just before a new drug application (NDA) is submitted, is a common time for the FDA and drug sponsors to meet Submission of an NDA is the formal step the FDA takes to consider a drug for marketing approval 8. After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed 9. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness. The FDA reviews information that goes on a drug's professional labeling (information on how to use the drug). The FDA inspects the facilities where the drug will be manufactured as part of the approval process. FDA reviewers will approve the application or find it either "approvable" or "not approvable"

Preclinical: Computer simulations, experimental animal studies, or *in vitro* studies are performed to identify a promising drug, test for promising biologic effects and test for adverse effects. A drug company may test many related compounds to identify 1 or 2 to take further in development. The FDA is not involved in this aspect of drug development but will review the study results for any compounds that are planned for clinical (human) testing.

New Drug Application (NDA): The IND is the formal process by which a sponsor requests approval for testing of a drug in humans and includes information developed during preclinical testing regarding safety and effectiveness. There are 3 phases in clinical testing of a new drug

Phase I studies are usually conducted in healthy volunteers. The emphasis in Phase I is on safety. The goal is to determine what the drug's most frequent side effects are often, to determine how the drug is absorbed, distributed, and excreted. The number of subjects typically ranges from 20 to 80.

The emphasis in Phase II is on effectiveness. The goal of a Phase II study is to obtain preliminary data on whether the drug works in people who have a specific disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a placebo or a different drug. Safety continues to be evaluated and short-term side effects are studied. Typically, the number of subjects in Phase II studies ranges from a few dozen to about 300 after Phase II.

At the end of Phase II, the FDA and sponsors negotiate about how the large-scale studies in Phase III should be done. The FDA usually meets with a sponsor several times, including prior to Phase III studies, and pre-NDA right before a new drug application is submitted.

All biologic agents or other products made using high-technology procedures. Products for HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions and viral diseases. Products for orphan conditions.

Drug Approval Process in Europe

National authorization procedure: Each country within the EU has its own procedures for authorizing a marketing application for a new drug. A sponsor can consult the website of the regulatory agency in each country in which it is interested in obtaining marketing approval to obtain details of the approval process. A sponsor can also seek approval of several EU countries simultaneously using the decentralized or mutual recognition procedure.

Decentralized procedure: For products that fall outside the scope of the European Medicines Agency (EMA) with regard to centralized procedures, a sponsor can submit under the decentralized procedure. Using this process, a sponsor can apply for simultaneous authorization in more than one EU country for products that have not yet been authorized in any EU country. Mutual recognition procedure. With the mutual recognition procedure, a product is first authorized by one country in the EU in accordance with the national procedures of that country. Later, further marketing authorizations can be sought from other EU countries, who, rather than conducting their own review, agree to recognize the decision of the first country.

Centralized procedure: European drug approvals are overseen by the European Medicines Agency. The EMA is a decentralized body of the EU, with headquarters in London, England. It is responsible for the scientific evaluation of applications for authorization to market medicinal products in Europe (via the centralized procedure). Marketing applications for drugs for use in humans are evaluated by the Committee for Medicinal Products for Human Use (CHMP). Products that are eligible for review under the centralized procedure must meet the following criteria.

1. Biologic drugs developed by recombinant technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, and hybridoma and monoclonal antibody methods medicinal products containing new active substances for the following indications: AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions, and viral diseases
2. Orphan medicinal products other new active substances may, at the request of the applicant, be accepted for consideration under the centralized procedure when it can be shown that the product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a Community authorization is in the best interests of patients at the Community level.

Pre-submission process: At least seven months prior to submitting a marketing authorization application (MAA), a sponsor must notify the EMA of their intention to submit and the month of submission. This pre-submission involves a variety of information including a document outlining the reasons the sponsor believes the application should fall under the centralized procedure. The EMA will consider the pre-submission and notify the sponsor of its decision regarding acceptance of the MAA.

Selection of rapporteur/co-rapporteur: The rapporteur is a country-specific regulatory authority within the EU. The rapporteur (reviewer) and co-rapssporteur (if needed) are identified from the CHMP members. The selection of the rapporteur is based on objective criteria, to ensure objective scientific opinion and the best use of available expertise at the EMA. The role of the rapporteur is to perform the scientific evaluation and prepare an assessment report to the CHMP. If a co-rapporteur is involved, the co-rapporteur will prepare an independent assessment report, or provide a critique of the rapporteur's report, at the discretion of the CHMP. The process for assigning the rapporteur/co-rapporteur is usually initiated at the CHMP meeting following the receipt of a letter of an intention to submit. The sponsor is notified of the rapporteur/co-rapporteur once the EMA has deemed a submission admissible.

Product naming: A sponsor's name for the drug product should be the same in all countries within the EU, except where it violates trademark rules. The sponsor should submit the proposed name in advance (usually four to six months, and not more than 12 months) of the marketing authorization application.

Drug Approval Process in India

Passed by the India's parliament to regulate the import, manufacture, distribution 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] was 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 includes, 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. A copy of the application must be submitted to the ethical committee and the clinical trials are conducted only after approval of DCGI and ethical committee. To determine the maximum tolerated dose in humans, adverse reactions, etc. on healthy human volunteers, Phase I clinical trials are conducted. The therapeutic uses and effective dose ranges are determined in Phase II trials in 10-12 patients at each dose level. The confirmatory trials (Phase III) are

conducted to generate data regarding the efficacy and safety of the drug in ~ 100 patients (in 3-4 centers) to confirm efficacy and safety claims. Phase III trials should be conducted on a minimum of 500 patients spread across 10-15 centers, If the new drug substance is not marketed in any other country. The new drug registration (using Form 44 along with full pre-clinical and clinical testing information) is applied after the completion of clinical trials. The comprehensive information on the marketing status of the drug in other countries is also required other than the information on safety and efficacy. The information regarding the prescription, samples and testing protocols, product monograph, labels, and cartons must also be submitted. The application can be reviewed in a range of about 12-18 months. Figure represents the new drug approval process of India. After the NDA approval, when a company is allowed to distribute and market the product, it is considered to be in Phase IV trials or pharmacovigilance.

A Comparision of Drug Approval Process Requirements in US, Europe and India

A comparision of Drug approval process requirements in US, Europe and India is shown in Tables 1-5.

Table 1.1 Comparison of Drug Approval Process Requirements in US, Europe and India (Administrative Requirements)

S.No.	REQUIREMENT	US FDA	EUROPEAN	INDIA
1.	Application	ND/NDA/ANDA	MAA	IND/MAA
2.	Number of copies	3	1	1
3.	Approval Timeline	18 months	12 months	12 months
4.	Fees	No Fees	10-20 Lakh	Rs 50,000
5.	Presentation	e CTD , Paper	e CTD, Paper	Paper

Table 1.2 Comparison of Drug Approval Process Requirements in US, Europe and India (Finished Product Control Requirements)

S.NO	REQUIREMENT	US FDA	EUROPEAN	INDIA
1.	Justification	ICH Q6A	ICH Q6A	-
2.	Assay	90-100%	95-105%	90-110%
3.	Disintegration	Not Required	Required	Required
4.	Color Identification	Not Required	Not Required	Required
5.	Water Content	Required	Not Required	Required

Table 1.3 Comparison of Drug Approval Process Requirements in US, Europe and India (Manufacturing and Control Requirements)

S.NO	REQUIREMENT	US FDA	EUROPEAN	INDIA
1.	Number of batches	1	3	3
2.	Packaging	A minimum of 1,00,000 units	Not Required	Not Adressed
3.	Process validation	Not required at the time of submission	Required	Required
4.	Batch size	Minimum of 1,00,000 units	Minimum of 1,00,000 units	3 pilot scale

Table 1.4 Comparison of Drug Approval Process Requirements in US, Europe and India (Stability Requirements)

S.NO	REQUIREMENT	US FDA	EUROPEAN	INDIA
1.	Number of batches	1	2	3
2.	Condition	25^0/60-40^0/75 RH	25^0/60-40^0/75 RH	30^0/35-30^0/75 RH
3.	Date & time of Submission	3 months accelerate &3 months long term	6 months accelerate& 6 months long term	6 months accelerate & 3 months long term
4.	Container Orientation	Inverted & upright	-------	Packing which simulate the final packaging for storage &distribution
5.	Clause	21 CFR part 210&211	Guidelines for medicinal products	ICH QF

Table 1.5 Comparison of Drug Approval Process Requirements in US, Europe and India (Bioequivalence Requirements)

S.NO	REQUIREMENT	USFDA	EUROPEAN	INDIA
1	CRO	Audited by FDA	Audited by MHRA	Audited by CDSCO
2	Reserve Sample	5 times the sample required for analysis	No such requirement	-----
3	Fasted/Fed	Must be as per OGD recommendation	No such requirement	As per CDSCO recommendation
4	Retention of samples	5 years from date of filling the application	No such requirement	3 years from the date of filling the application

For Further Reading

1. Rick NG, Drugs from discovery to approval. 2nd ed., John Wiley & Sons, Inc., (Hoboken, New Jersey). p.201.
2. Rick NG, Drugs from discovery to approval. 2nd ed., John Wiley & Sons, Inc., (Hoboken, New Jersey). p.202.
3. IRA R Berry, Robert P Martin, Editors, The Pharmaceutical Regulatory Process. 2nd ed., Informa Healthcare. p.45.
4. Rick NG, Drugs from discovery to approval. 2nd ed., John Wiley & Sons, Inc.,(Hoboken, New Jersey). p.203-4.
5. Rick NG, Drugs from discovery to approval. 2nd ed., John Wiley & Sons, Inc.,(Hoboken, New Jersey). p.205-7.
6. Rick NG, Drugs from discovery to approval. 2nd ed., John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 208-10.
7. IRA R Berry, Robert P Martin, Editors, The Pharmaceutical Regulatory Process, 2nd ed., Informa Healthcare. p.46.