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## **NEW DRUG DEVELOPMENT, APPROVAL AND REGISTRATION PROCEDURES: A REVIEW**

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### **ABSTRACT**

The global discovery and approval of new drugs, devices, and biologics will revolutionize the availability of health care products worldwide. The crucial areas of vaccines and blood safety, critical to our public health, coupled with such cutting-edge biologic scientific areas as gene therapy and tissue transplant will play a major part in these new product discoveries. These must be made available to the entire world population. The pharmaceutical industry's aggressiveness in marketing these products will also be a major factor in how fast these products become available internationally. Bureaucratic agencies regulating these products will also play a part in how fast they are approved for the global market. Pharmaceutical companies and related industries are actively seeking new ways to decrease the time and costs for the development and approval of new products. The ability to submit applications for new products simultaneously in more than one country would greatly ease these goals.

### **Keywords:**

Drug discovery, approval,  
registration, new drug

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## INTRODUCTION

The Food and Drug Administration (FDA) is responsible for assuring that foods and cosmetics are safe and that medicines and medical devices are both safe and effective. To carry out this responsibility, the FDA monitors more than \$1 trillion worth of products, representing about \$0.25 of every \$1.00 spent annually by American consumers.<sup>1</sup> balancing the efficacy and safety of these products is the core public health protection duty of the FDA. This mission requires examining efficacy as determined from well-controlled trials, effectiveness as determined from actual use in uncontrolled settings, and safety for both prescription and over the-counter pharmaceuticals before approving a medication for market. During the past decade alone, more than 500 new prescription drugs have been approved by the FDA. The global discovery and approval of new drugs, devices, and biologics will revolutionize the availability of health care products worldwide. The crucial areas of vaccines and blood safety, critical to our public health, coupled with such cutting-edge biologic scientific areas as gene therapy and tissue transplant will play a major part in these new product discoveries.<sup>1-3</sup> These must be made available to the entire world population. The pharmaceutical industry's aggressiveness in marketing these products will also be a major factor in how fast these products become available internationally. Bureaucratic agencies regulating these products will also play a part in how fast they are approved for the global market. Pharmaceutical companies and related industries are actively seeking new ways to decrease the time and costs for the development and approval of new products. The ability to submit applications for new products simultaneously in more than one country would greatly ease these goals. Bureaucratic agencies that approve these products are also cooperating by reviewing submissions more rapidly, with a new emphasis on accepting international data in order to avail new products to the world population. Personnel involved in new product development are working more closely with regulatory agencies to facilitate their needs and requests so that less time is involved in the approval process. Therefore a thorough understanding of all the regulations and guidelines and of how to effectively implement the intricate steps in new drug development is vital. There are many components in the drug, device, and biologic approval process that must be defined, documented, and understood. The knowledge one may gain from reading a book or taking a course can only be considered a basis of what is needed in getting a new product approved. It is only from experience of trial and error and constant training and retraining that one is capable of expressing enough understanding to hope for a successful product submission and approval.<sup>4</sup>

## **STAGES IN DRUG DEVELOPMENT<sup>5,6</sup>**

### **Drug Discovery Stage**

#### **A. Chemistry or Synthesis**

- Generate drug discovery lead(s) using rational approaches, such as random screening,
- Nonrandom screening, drug metabolism, or clinical observations, or using combinatorial chemistry libraries.
- Modify lead(s) by identification of pharmacophore and synthesis of analogues; functional group changes; SAR of lead candidate analogues; structure modification, such as homologation, chain branching, ring-chain transformation, and bioisosterism to increase potency and therapeutic ratio; and QSAR.
- Determine drug-receptor interactions using techniques like molecular modeling and X - ray crystallography.

#### **B. Pharmacology or In Vitro and Animal Model Efficacy**

- Using in vitro techniques, evaluate requirements for activation and dependency on dosing schedule and route of administration; calculate inhibitory concentrations, e.g., IC<sub>50</sub> and IC<sub>90</sub>, for each system evaluated; assess potential for resistance to lead candidate(s);
- determine synergistic, additive, or antagonistic drug-drug interactions during combination therapy, if appropriate; evaluate possible cytostatic or cytotoxic concentrations of lead candidate(s) on various cell types (bone marrow, stem cells, and immune system cells).
- Define and characterize an animal model(s) that mimics the human disease to be evaluated and determine appropriate end points for assessment of biological activity.
- Evaluate in vivo dose-response range, including dose-response comparison of lead candidates; determine pharmacologically active doses, e.g., ED<sub>50</sub> or ED<sub>10</sub>; and therapeutic ratio when combined with no-observable-toxic-effect or minimum-toxic-effect dose level.
- Conduct other in vivo evaluations including, but not limited to, dosing regimen dependency; route of administration and formulation dependency; and spectrum of activity, disease status, cross-resistance profile, combination therapy for synergy or antagonism, and special models.<sup>5</sup>

### **Drug Development Stage**

A. Preliminary formulation evaluation (may not be started until preclinical development is initiated).

- From pharmacology results and proposed clinical program, select route of administration (oral, pulmonary, intramuscular, subcutaneous, transdermal, ocular, vaginal, buccal, sublingual, etc.) and formulation type to be dosed (solution, suspension, tablet, capsule, granulation powder, microspheres, micro emulsion, depot drug, etc.).
- Evaluate excipients, including concentration and potential for interaction.
- Select and evaluate formulation process(es), such as tableting, granulation lyophilization, or microencapsulation.
- Prepare prototype formulation.
- Confirm formulation composition, including, but not limited to, drug substance content, drug substance stability, excipient levels, water, and residual solvents, using appropriately characterized methods.
- Measure formulation physical properties, such as hardness, size, size distribution, morphology.
- Measure formulation function, such as release or disintegration profile and nonrelease properties like taste-masking.
- Develop and characterize stability-indicating analytical chemistry method.
- Define and implement preliminary solubility and stability studies on drug substance and proposed drug product.<sup>6</sup>

#### B. Preliminary Bioanalytical Chemistry Method Development

- Select bioanalytical chemistry technique (LC/MS/MS, HPLC, GC, ELISA, etc.).
- Select physiological matrix (plasma, serum, whole blood, urine).
- Characterize bioanalytical chemistry method, including sample preparation procedure, for linearity, sensitivity, specificity, precision, and accuracy.
- Conduct preliminary stability study of drug candidate in selected physiological matrix.

#### C. Preliminary Pharmacokinetic and Bioavailability Assessments

- Evaluate distribution and disposition in pharmacology animal model species after intravenous and proposed clinical route of administration.
- Evaluate pharmacokinetics and bioavailability (drug delivery) in toxicology rodent and nonrodent animal species after intravenous and proposed clinical route of administration.<sup>6</sup>

#### D. Toxicology

- Evaluate single-dose or dose-escalation acute toxicity in rodent species.
- Evaluate single-dose or dose-escalation acute toxicity in nonrodent species.

- Conduct safety pharmacology studies, if appropriate.
- Conduct genotoxicity evaluations, if necessary.

#### E. Drug Metabolism

- Evaluate potential for drug metabolism by CYP450 isozymes and other enzyme systems.
- Study potential for conjugation, e.g., glucuronidation, sulfation, acetylation, etc.
- Determine extent of protein binding.

### **Preclinical Drug Development Stage<sup>6-8</sup>**

#### A. Drug Candidate Characterization

- Validate stability-indicating analytical chemistry method and other assays.
- Generate impurity profile and identify impurities in drug substance and proposed drug product.
- Study stress stability for drug substance and proposed drug product.

#### B. Formulation Development

- Review preliminary pharmacokinetics and histology (local reaction) results and modify formulation, if necessary, using GLP- or GMP-quality drug substance.
- Characterize and optimize modified formulation for excipients, pH, processing, etc.

#### C. Bioanalytical Chemistry Method Validation

- Validate developed method for specificity, sensitivity, range of reliable results, precision, and accuracy for each physiological matrix type and for each species.
- Evaluate protein binding in blood/plasma obtained from animal species and humans.
- Determine drug candidate stability in selected physiological matrices from time of collection to time of assay.

#### D. IND-Directed Toxicology Studies

- Determine safety pharmacology profile in CNS, cardiovascular, respiratory, renal, and gastrointestinal systems.
- Evaluate genetic toxicology.
- Conduct local irritation studies.
- Determine occupational toxicology (dermal, eye irritation, skin sensitization).
- Perform sub chronic (2- or 4-week) study in a rodent species using proposed clinical route of administration. Study should have a toxic kinetic component.
- Perform sub chronic (2- or 4-week) study in a non rodent species using proposed clinical route of administration. Study should have a toxic kinetic component.

- Perform sub chronic (13-week) study in a rodent species using proposed clinical route of administration. If appropriate, include a toxic kinetic component.
- Perform sub chronic (13-week) study in a no rodent species using proposed clinical route of administration. If appropriate, include a toxic kinetic component.
- Design and conduct additional confirmatory or specialized studies, as warranted.

#### E. Pharmacokinetics and Drug Metabolism

- Evaluate absolute bioavailability, distribution and disposition, and linearity of kinetics over toxicology dose range, i.e., dose proportionality, in pharmacology and toxicology in animal species.
- Synthesize and characterize radio labeled drug candidate.
- Using radio labeled drug candidate, determine mass balance, including metabolite profiling and route(s) of elimination, in toxicology animal species.
- Isolate and identify major metabolites and if appropriate, evaluate pharmacological and toxicological activity of metabolites.
- Correlate in vitro metabolism using liver and other appropriate enzyme systems from animal models and humans.
- Provide toxic kinetic support to toxicology studies.

#### F. Mechanism of Action Studies

- Study effect on cell cycle or replication cycle.
- Determine intra- or extracellular site of action.
- Evaluate requirements for enzyme activation or inhibition for desired
- Pharmacologic response.
- Perform enzyme-substrate kinetic studies, if appropriate.
- Assess intracellular site of action using compartmentalization experiments.

#### G. Manufacturing Program

- Obtain CO As on raw materials.
- Define, evaluate, and scale up manufacturing process for drug substance.
- Validate formulation process procedures such as mixing, sterilization, lyophilization, closure, resolubilization.
- Prepare various CMC sections for IND.
- Make phase 1 clinical supplies using GLP or GMP process.
- Test clinical supplies for composition, required characteristics, and function.

- Release phase 1 clinical supplies to clinic.

#### H. Quality Control Processes

- Validate analytical chemistry method(s) for drug substance, including identity tests and impurity profile.
- Validate analytical chemistry method(s) for drug product, including impurity profile.
- If appropriate, validate analytical chemistry method(s) for key intermediates in drug substance manufacturing process.
- Develop and validated analytical chemistry methods for excipients.<sup>8</sup>

#### I. Clinical

- Prepare phase 1 clinical protocol and outlines of phase 2 and 3 clinical programs.
- Prepare investigator's brochure.
- Prepare and submit IND to regulatory agency.

### **Nonclinical Drug Development Stage (Conducted Concurrently with Clinical Development)**

#### A. Chronic and Reproductive Toxicology

- Conduct chronic (9-month) no rodent toxicology study.
- Conduct chronic (6-month) rodent toxicology study or combined rat chronic toxicity/carcinogenicity (2-year) study.
- Perform mouse carcinogenicity study, if necessary.
- Evaluate reproductive toxicity in rats or other rodent species (Segments I, II, and III).
- Evaluate reproductive toxicity in rabbits or other appropriate no rodent species (Segment II).
- Design and conduct additional confirmatory or specialized studies, as warranted.

#### B. Pharmacokinetics and Drug Metabolism

- Using radio labeled drug candidate, perform tissue distribution, with whole body autoradiography, in rodents after single-dose, multiple-dose (if appropriate) administration.
- Provide toxic kinetic support as necessary, including, but not limited to, fetoplacenta transfer and lacteal secretion studies to support reproductive toxicology.
- Isolate and identify metabolite(s), if appropriate, in toxicology animal species and humans.
- Evaluate pharmacokinetics of metabolite(s) to support pharmacologic and toxicological evaluation of metabolites, if appropriate.
- Conduct in vitro and in vivo enzyme-induction and enzyme-inhibition studies in animal models, if appropriate.<sup>9</sup>

### C. Mechanism of Action

- Conduct additional mechanism of pharmacologic action studies, if necessary.
- Conduct additional mechanism of toxicological action studies, if necessary.

### **Clinical Drug Development Stage (Conducted Concurrently with Nonclinical Development)<sup>9-11</sup>**

#### A. Phase 1 Safety and Tolerance Study

- Obtain IRB approval for phase 1 study.
- Prepare and release clinical supplies.
- Develop and validate bioanalytical chemistry method for drug candidate and known metabolites in human physiologic fluid specimens.
- Conduct single-dose and multiple-dose escalation evaluation of drug candidate in normal human volunteers.
- Study pharmacokinetics of drug candidate and known metabolites in humans after single-dose and multiple-dose administration.
- Develop and validate surrogate and biochemical marker method(s), if appropriate.
- Design and conduct mass balance study in human volunteers using an appropriately labeled drug candidate.

#### B. Phase 2 Efficacy Studies

- Prepare phase 2 efficacy study protocols and obtain IRB approval.
- Conduct multiple-dose evaluation of drug efficacy in patients with disease indication.
- Determine surrogate and biochemical marker levels in human physiologic fluid specimens.
- Design and conduct relative bioavailability studies if drug product used in early phase 2 is changed for later phase 2 and 3 clinical trials.

#### C. Phase 3 Definitive Safety and Efficacy Studies

- Prepare phase 3 clinical protocols and obtain IRB and regulatory agency approvals.
- Conduct randomized, double-blind, placebo-controlled studies in patients with disease indication using at least two dose levels of proposed drug product.
- Perform pharmacokinetic studies in special population (geriatric or pediatric age groups, renal or hepatic impaired patients, various ethnic groups, and drug-drug interaction studies) groups, if appropriate.
- Determine surrogate or biochemical marker levels in human physiologic fluid specimens.
- Collate all information and prepare NDA for submission to regulatory agency.<sup>11-13</sup>



**D. Phase 4 Studies**

- Design phase 4 protocols for product extensions for new indications or improved/modified delivery profile/route and obtain appropriate approvals.
- Conduct double-blind, placebo-controlled studies in patients with new disease indication.
- Conduct bioequivalence/bioavailability comparison study for novel formulation assessment.

**INVOLVEMENT OF RESEARCH AT DIFFERENT STAGES<sup>9-13</sup>****Pharmacology**

Preliminary pharmacology evaluations in in vitro or animal models will have shown that a lead interacts with a biological process suggestive of human therapeutic benefit. Depending on the design and extent of these early studies, additional pharmacology studies may be needed to characterize further the dose, or physiological fluid concentration, response curve using the proposed clinical route and frequency of administration. If possible, these pharmacology studies should be conducted in at least two species to show that the biological response is not species dependent. The ED50 dose should be determined and that value, divided into the no-observable-toxic-effect dose in the same animal species, described in the section on toxicology, estimates a therapeutic ratio or index. If the therapeutic ratio is one or less, a lead will most likely elicit adverse effects in addition to the beneficial response.<sup>9</sup>

**Bio analytical Chemistry Method Development**

If not already available, a bio analytical chemistry method needs to be defined and characterized for the quantification of the lead in physiological fluids. This assay can then support experiments in some of the other scientific disciplines involved in assessing the develop ability of the lead and, after appropriate validation, the preclinical, nonclinical, and clinical development of a selected drug candidate. For preliminary studies, a bio analytical chemistry method should be characterized to demonstrate the range of reliable results, the lower and upper limits of quantification, specificity, accuracy, and precision. In addition, evaluations on the matrix to be used (blood, plasma, serum) should be conducted and the stability of the lead in each matrix should be determined. The first step in characterizing a bio analytical chemistry method is to select the analytical technique. For a compound with a molecular weight of less than 2000, instrumental methods such as LC/MS/MS (a very sensitive and specific technique and the most common method employed by the pharmaceutical industry), or HPLC and GC with a variety of detectors, including ultraviolet, fluorescence, flame ionization, and electron capture, may be used. A macromolecule (large peptide, protein, or oligonucleotide) may require an ELISA or RIA method.<sup>10</sup>

**Early Non-clinical Formulation Development and Delivery**

Nonclinical formulation definition and the drug delivery characteristics of a lead are not usually studied in detail during the transition from discovery to development. The experiments necessary to define an acceptable formulation depend on the proposed clinical route of administration and usually require substantial quantities, i.e., milligram or gram amounts, of the lead. For a compound to be administered by intravenous injection or infusion, the formulation needs to be compatible with blood so that the compound does not precipitate when administered and has minimal local toxicity. Leads that are highly lipophilic or have limited aqueous solubility are the most likely compounds to have these types of problems. A low extent of, or a high variability in, absorption can cause problems for leads administered by other routes, such as oral, subcutaneous, and dermal. For compounds that are poorly absorbed, the amount reaching the site of action may be insufficient to elicit or to maintain a desired pharmacological response. If the absorption is variable and the therapeutic ratio is low, a toxic response may be observed in some animals.<sup>11</sup>

**Preliminary Animal Pharmacokinetics**

The first animal pharmacokinetic study confirms that the bio analytical chemistry method is useful in characterizing the absorption and disposition profiles of the lead. The animal species for this study is usually the same as that used in pharmacology evaluations, most likely a rodent. A study design for a lead that has pharmacological activity when administered orally to rats may consist of dosing at least two rats with intravenous bolus injections at a dose level between 25% and 50% of the pharmacologically active dose and dosing at least two rats orally at the pharmacologically active dose. Serial blood samples, collected from each rat and processed to obtain the desired physiological fluid, are analyzed by the bio analytical chemistry method. The plasma concentration versus time profiles after intravenous dosing provide preliminary information on the distribution and disposition kinetics of the lead. These intravenous results certify that the assay method is useful for quantifying the lead in specimens obtained from animals, predict the concentration range that can be expected in animal specimens, and assist in determining the sampling times to be used in more definitive animal pharmacokinetic experiments. The plasma concentration versus time profiles after oral dosing provide preliminary information on the absorption kinetics and the absolute bioavailability of the lead.

The design of additional animal pharmacokinetic studies depends on the results of the preliminary animal pharmacokinetic study, the theoretical kinetic profile needed to produce the desired pharmacology response, and the results from preliminary toxicology experiments. For

most drug development programs, toxicology studies in two or more species are necessary. In this case, preliminary animal pharmacokinetic studies should be conducted in each species projected for use in animal safety studies.

### **Preliminary Drug Metabolism**

The number and design of drug metabolism studies needed to characterize the fate of a lead or drug candidate in the body depend on the results from preliminary animal pharmacokinetic and toxicology studies. Commonly, the results from these in vivo experiments are not available during earlier development ability assessments, and in vitro drug metabolism evaluations are utilized to determine the metabolic stability and the extent of metabolism of a lead and to compare the extent of metabolism among various species, including humans. These in vitro experiments can be conducted in a variety of systems, including CYP450 isozymes (the enzymes responsible for most oxidative metabolism of drugs), microsomes, hepatocytes, or liver slices. Since hepatocytes contain both phase 1 (oxidative, hydrolysis, and reduction) and phase 2 (conjugation) metabolism systems and can be relatively easily obtained from pharmacology and toxicology animal species and from humans, many researchers select this model for the first assessment of metabolism. If the results from hepatocytes show extensive metabolism, additional in vitro experiments are usually conducted first in microsomes to ascertain if oxidative metabolism is present and then in isolated CYP450 isozymes to determine which enzyme or enzymes are responsible.<sup>13</sup>

### **Acute Toxicology Studies**

Toxicology studies are conducted to define the safety profile of a candidate and include definition of the no-observable-toxic-effect dose, maximum tolerated dose or MTD, potential organs of toxicity, and potential biochemical markers to detect and track toxic events. Most developmental compounds that do not become therapeutic products have unacceptable toxicity in animals and/or humans. Before the definitive toxicology studies needed to support an IND submission are initiated, a number of in vitro and animal experiments can be conducted to characterize the potential toxicity of the candidate. These early toxicology evaluations are usually conducted in the same species as used in pharmacology evaluations. As mentioned earlier, the lowest dose that has no toxicity, or an acceptable level of toxicity, is compared with the dose that gives the desired pharmacological response in the same animal species to obtain a therapeutic ratio or index for that species.<sup>11-13</sup>

### **PROCESS OF NEW DRUG REGISTRATION**

Track 1 : Standard Review - 210 - 280 working days

Track 2 : Accelerated or Priority Review (Drugs for public health problems / life threatening)  
100-130 working days

### **Drug Development**

Drug development can generally be divided into phases. The first is the preclinical phase, which usually takes 3 to 4 years to complete. If successful, this phase is followed by an application to the FDA as an investigational new drug (IND). After an IND is approved, the next steps are clinical phases 1, 2, and 3, which require approximately 1, 2, and 3 years, respectively, for completion (Table 1). Importantly, throughout this process the FDA and investigators leading the trials communicate with each other so that such issues as safety are monitored. The manufacturer then files a new drug application (NDA) with the FDA for approval. This application can either be approved or rejected, or the FDA might request further study before making a decision. Following acceptance, the FDA can also request that the manufacturer conduct additional post marketing studies. Overall, this entire process, on average, takes between 8 to 12 years. It is not surprising that from conception to market most compounds face an uphill battle to become an approved drug. For approximately every 5,000 to 10,000 compounds that enter preclinical testing, only one is approved for marketing.<sup>8</sup> A 1993 report by the Congressional Office of Technology Assessment estimated the cost of developing a new drug to be \$359 million. Newer figures place the cost at more than \$500 million.<sup>12,13</sup>

### **Preclinical research**

When a new drug compound is discovered the drug manufacture and sponsored carries out a series of experiment to establish safety of compound by federal law experimental drug must be tested in animals before clinical trials. For pre clinical testing animals, cell culture, tissue culture, computer data are used.

Data collected is:

- 1) LD 50 (Lethal dose) Upper limit establishment.
- 2) ED 50 (Effective dose) Minimum limit establishment.
- 3) Rate of drug absorption, metabolism, and elimination.
- 4) Drugs nature for carcinogenicity, nutagenisity,teratogenesisity.
- 5) IND Applications:- Before starting clinical trial in humans the manufacture must file and IND application in regulatory agency of the particular country. FDA in USA, EMEA in Europe, TGA in Australia and CDSCO in India.

For filling the following data must be submitted:-

- 1) All information and data from pre clinical trials.

- 2) Information about drug production and dosage.
- 3) Medical use for the drug.
- 4) Route of drug administration.
- 5) Full description of clinical trial protocol.
- 6) Chemical composition of the drug.
- 7) Name and qualification of clinical investigator.

= Regulatory agency usually review the IND with in 30 days.

=Regulatory authority in USA that is FDA provides two types of IND approval.

- 1) Commercial IND
- 2) Treatment IND

### **Clinical trials<sup>13-15</sup>**

#### **Phase 1**

Drug is tested on small group of people 20-80. Phase 1 studies focus on the safety and pharmacology of a compound. During this stage low doses of a compound are administered to a small group of healthy volunteers who are closely supervised. In cases of severe or life-threatening illnesses, volunteers with the disease may be used. Generally, 20 to 100 volunteers are enrolled in a phase 1 trial. These studies usually start with very low doses, which are gradually increased. On average, about two thirds of phase 1 compounds will be found safe enough to progress to phase 2.

#### **Phase 2**

This is the phase to determine the effectiveness and safety of drug. They are carried out 100-300patient. These are well controlled blind trials. For determining effectiveness the subjects are divided into treatment and controlled group. Treatment group subject are given investigational drug and control group subject are given a placebo (dummy drug). Phase 2 studies examine the effectiveness of a compound. To avoid unnecessarily exposing a human volunteer to a potentially harmful substance, studies are based on an analysis of the fewest volunteers needed to provide sufficient statistical power to determine efficacy. Typically, phase 2 studies involve 100 to 300 patients who suffer from the condition the new drug is intended to treat. During phase 2 studies, researchers seek to determine the effective dose, the method of delivery (ex, oral or intravenous), and the dosing interval, as well as to reconfirm product safety.<sup>2,7,11,12</sup> Patients in this stage are monitored carefully and assessed continuously. A substantial number of these drug trials are discontinued during phase 2 studies. Some drugs turn out to be ineffective, while others have safety problems or intolerable side effects.

### Phase 3

Large no of people 1000-4000 this is carried out to confirm drug safety, side effect and interaction. Phase 3 trials are the final step before seeking FDA approval. During phase 3, researchers try to confirm previous findings in a larger population. These studies usually last from 2 to 10 years and involve thousands of patients across multiple sites. These studies are used to demonstrate further safety and effectiveness and to determine the best dosage. Despite the intense scrutiny a product receives before undergoing expensive and extensive phase 3 testing, approximately 10% of medications fail in phase 3 trials. If a drug survives the clinical trials, an NDA is submitted to the FDA. An NDA contains all the preclinical and clinical information obtained during the testing phase. The application contains information on the chemical makeup and manufacturing process, pharmacology and toxicity of the compound, human pharmacokinetics, results of the clinical trials, and proposed labeling. An NDA can include experience with the medication from outside the United States as well as external studies related to the drug. After receiving an NDA, the FDA completes an independent review and makes its recommendations. The Prescription Drug User Fee Act of 1992 (PDUFA) was designed to help shorten the review time. This act allowed the agency to collect user fees from pharmaceutical companies as financial support to enhance the review process. The 1992 act specifies that the FDA reviews a standard drug application within 12 months and a priority application within 6 months. Application for drugs similar to those on the market are considered standard, whereas priority applications represent drugs offering important advances in addition to existing treatments.<sup>13</sup> If during the review the FDA staff feels there is a need for additional information or corrections, they will make a written request to the applicant. During the review process it is not unusual for the FDA to interact with the applicant staff.

### Phase 4

Post marketing surveillance. Post marketing surveillance is important, because even the most well-designed phase 3 studies might not uncover every problem that could become apparent once a product is widely used. Furthermore, the new product might be more widely used by groups that might not have been well studied in the clinical trials, such as elderly patients.

A crucial element in this process is that physicians report any untoward complications. The FDA has set up a medical reporting program called Med watch to track serious adverse events (1-800-FDA-1088). The manufacturer must report adverse drug reactions at quarterly intervals for the first 3 years after approval,<sup>10</sup> including a special report for any serious and unexpected adverse reactions.<sup>15</sup>

**NDA filing**

When phase 3 clinical trial is confirm the investigation drug is safe and effective NDA filing is done. NDA filing is the request from manufacturer to manufacturer and sell the drug in market.<sup>15-17</sup>

NDA file must include

- 1) Complete data of animal and human studies.
- 2) Information about drug chemistry and pharmacology.
- 3) Purposed packaging design and material used in packaging.
- 4) Details about facility of premises where drug will be manufacture.
- 5) Assurance that drug will be made according to CGMP guidelines.

**CTD OVERVIEW**

The ICH M4 guideline provides the agreed-upon common format for the preparation of a well-constructed Common Technical Document (CTD) for applications that will be submitted to regulatory authorities for marketing approval. The goals of using a common format for the technical documentation are<sup>18,19</sup>

- To reduce significantly the time and resources needed to compile applications for registration of human Pharmaceuticals.
- To ease the preparation of electronic submissions.
- To facilitate regulatory agency reviews and communications with the sponsor.
- To simplify the exchange of regulatory information between regulatory agencies.

From the standpoint of telling the story of the discovery and development of a drug candidate and integrating the results from the various research studies conducted to define manufacturing processes and to characterize the physiochemical properties, pharmacology or efficacy, pharmacokinetics, and toxicology or safety of the drug candidate in animal models and in humans, Module 2 is by far the most important module of a CTD. This module provides summary information on all aspects of the discovery and development processes, including CMC information and nonclinical and clinical evaluations. The writers of each of these summaries need to have a good understanding of the overall story so that each author can compare, contrast, and integrate the results in his/her summaries with the information in the summaries prepared by other authors. Most large pharmaceutical corporations have trained and experienced scientific and medical writing groups who have as one of their primary functions the drafting of these quality, nonclinical, and clinical summaries for regulatory agency submissions. Smaller pharmaceutical firms and some larger biotechnology companies may have



a few science writers on the staff and when the time comes to prepare a marketing application, these writers may be asked to draft summaries both inside and outside their areas of expertise. Most small biotechnology firms do not have the resources to have an independent scientific writing staff; they frequently rely on partners (i.e., large pharmaceutical companies who have licensed or are co developing a drug candidate with the discoverer) to perform these important aspects of the drug development process.<sup>19-22</sup>

The following need to be properly documented:

### **Quality overall summary (QOS)**

The QOS is a summary that follows the scope and outline of Module 3 and should not include information, data, and/or justifications that are not included in Module 3 or in another part of a CTD. The primary purpose of a QOS is to provide sufficient information so that a reviewer is given an overview of the data in Module 3. A QOS should emphasize key parameters of a drug substance (or a drug candidate, as a compound under development is commonly referred to in nonclinical and clinical research efforts; both designations are utilized throughout this chapter) and a drug product and should include discussions of issues that integrate information from sections in Module 3 with supporting information from Modules 4 and 5. The length of a QOS (excluding tables and figures) should generally not exceed 40 pages of text. However, for most biotechnology drug candidates and for candidates manufactured using more complex processes, a QOS may be longer but should not exceed 80 pages of text.<sup>21</sup>

### **Nonclinical Overview**

A Nonclinical Overview is to present an integrated and critical assessment of the pharmacological, pharmacokinetic, and toxicological evaluations of a drug candidate in in vitro systems and animal models and should not exceed about 30 pages of text. Where relevant guidelines (e.g., ICH safety guidelines) on the conduct of nonclinical studies exist, these guidelines are to be taken into consideration and any deviations are to be discussed and justified. In addition, the nonclinical testing strategy (i.e., the nonclinical drug development plan) should be discussed and justified and comments included on the status of compliance with GLP Regulations for the research studies being submitted. Where appropriate, any association between nonclinical findings and the quality characteristics of a drug candidate, the results from clinical trials, and/or the effects seen with related drug products is to be described.<sup>23</sup>

### **Clinical overview**

A Clinical Overview provides a critical analysis of the clinical data generated during the development of a drug candidate and is to reference appropriately the information in the more



detailed Clinical Summary and in the individual clinical study reports in Module 5 and other relevant study reports. A primary purpose of this overview is to present the conclusions and implications of the clinical results and to provide a succinct discussion and interpretation of these findings in conjunction with other relevant information, such as nonclinical data or quality issues that may have clinical implications.

### **Non-clinical Written and Tabulated Summaries**

The information presented in the Nonclinical Written and Tabulated Summaries section of the ICH CTD guideline is intended to assist sponsors and authors in the preparation of nonclinical pharmacology, pharmacokinetic, and toxicology summaries in a format acceptable to the various ICH regions and is not intended to indicate what nonclinical research studies are required or how these studies are to be designed or conducted. Since no guideline can cover all possibilities, a sponsor can modify, if needed, the format to provide the optimal presentation of the generated results in order to facilitate the understanding and evaluation of the information.<sup>24</sup>

### **Drug registration process**

Applicants: Only authorized licensees are qualified to apply for product registration.

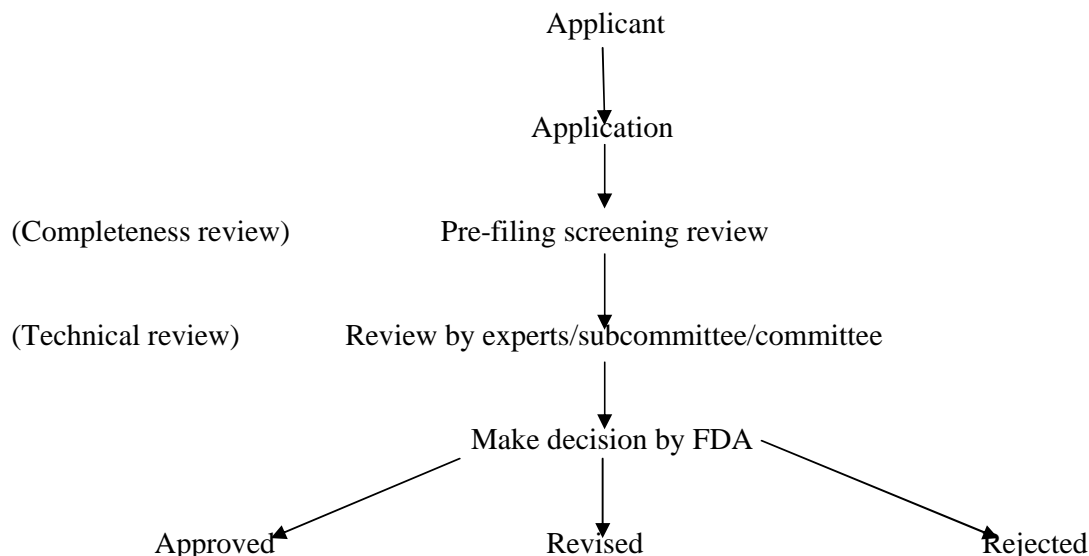
Manufacturing plants : GMP compliance

2 steps:

Step 1: Application for permission to manufacture or import of drug samples – One Stop Service Center

Step 2: Application for product registration approval

### **Flow chart of drug review process**



**THE INVESTIGATIONAL NEW DRUG APPLICATION (IND)**

An IND may be submitted to the FDA by a commercial organization (the “sponsor”) or by a clinical investigator (the “investigator”). The sponsor or investigator may not commercially distribute or test market an investigational new drug, nor may an investigation be unduly prolonged after the finding that the results of the investigation appear to establish sufficient data to support a marketing application. Under certain defined circumstances described in 21 CFR Part 312.7, a sponsor may charge the patient for an investigational drug, but this is atypical and can be done only after written approval from the FDA. The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of an IND providing all of the following apply: (1) the investigation is neither intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor to be used to support any other significant change in the labeling for the drug, if the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product, the investigation does not involve a route of administration nor dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product, and the investigation is conducted in compliance with the requirements for institutional review approval and the requirements for informed consent as discussed elsewhere in this book.<sup>22-25</sup>

**Labeling Requirements for an Investigational New Drug**

Labeling for a drug covered by an IND will be discussed under the Chemistry, Manufacturing, and Control requirements for part 7 of the IND; however, independent of the use or indication for the drug and independent of the dosage form, all immediate packages of drug product supplied to a patient involved in an investigational trial require the following statement: “Caution: New Drug—Limited by Federal (or United States) law to investigational use.” Additionally, the label or labeling (including the investigator’s brochure) shall not bear any statement that is false or misleading possibly to represent the investigational new drug as being safe or effective for the purposes for which it is being investigated.<sup>26</sup>

**NEW DRUG APPLICATION (NDA)**

An NDA is an application submitted to the United States FDA for permission to market a new drug product in the United States. The content of an NDA is designed to answer several questions: Does the new product provide a proven medical benefit? Are the associated risks acceptable compared to the benefits? Can the product be manufactured reproducibly and

reliably? Are the data in the NDA reliable? Since 1963, new drug products introduced into commerce in the United States have been the subjects of NDAs approved by the FDA, with some exceptions. For the approval of vaccines, traditional biological products (such as blood fractions), and genetically engineered biotechnical products, Biologics License Applications are used. They answer the same questions as NDAs about medical benefit, acceptable risks, and reliability of manufacturing and data. Generic drug products, which are designed to be equivalent to products already on the market, are subjects of ANDAs. An ANDA is designed to provide data that show the new product to be equivalent to the existing product, the method of manufacture to be reliable, and the information in the ANDA to be reliable. However, an NDA is needed if the route of administration is changed for a previously approved drug. For example, if the proposed product is a nasal spray and the previous product was an orally administered tablet, an NDA is needed. The forms, regulations, and guidelines needed for assembling an NDA are available from the FDA's website on the internet, [www.FDA.gov](http://www.FDA.gov). The regulations, Title 21 of the Code of Federal Regulations (21 CFR), can also be purchased from government bookstores located in major cities or from the Government Printing Office; however, recently the bookstores have been closing due to the ability to order books online from the Government Printing Office. Copies of the various guidelines are available from the FDA Drug Information Branch, 5600 Fishers Lane, Rockville, MD 20857; phone (301) 827– 4573. Form FDA 356h, "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use," is the form that needs to accompany an NDA, a BLA, or an ANDA. Form FDA 356h and Form FDA 3397, "User Fee Cover Sheet," are available from the Forms Distribution Page of the CDER part of the FDA website. Both forms request the name, address, and phone number of the applicant or owner of the NDA.<sup>26-28</sup> If the applicant is a foreign corporation or other entity, it is necessary to list an agent in the United States with legal authority to represent the foreign applicant. Product information such as the generic name, chemical or biochemical name, dosage form, strengths, route of administration, and proposed indications for use are to be entered on Form FDA 356h. For new drugs, a name approved by USAN is needed. The regulations governing NDAs for new drugs are in 21 CFR Part 314, and those for biologicals are in 21 CFR Part 601. These describe the content of an NDA and also the legal and administrative procedures connected with an NDA. The regulations describing the bioavailability and bioequivalency testing needed for approval of an NDA are in 21 CFR Part 320. The proposed labeling for the new drug needs to be included in the NDA, and 21 CFR Part 201 contains these regulations. The manufacturing facilities for the new drug product and for the active pharmaceutical ingredient

(API) need to be in compliance with GMP regulations, 21 CFR Parts 210 and 211. For non-clinical safety studies, the GLP regulations are in 21 CFR Part 58. For clinical studies in the NDA, the applicable regulations are those for informed consent, 21 CFR Part 50, institutional review boards, 21 CFR Part 56, the Declaration of Helsinki, 21 CFR Part 312.120, investigational new drug exemptions, 21 CFR Part 312, and the financial disclosure by clinical investigators, 21 CFR Part 54. An NDA also requires an environmental impact statement covering the manufacture of the proposed product, and the regulations covering this are in 21 CFR Part 25. The FDA has issued a series of guidance documents for the preparation and assembly of an NDA.<sup>27</sup> A complete list of available guidance documents covering all aspects of drug development is available at the FDA website. Guidelines do not have the same force as regulations, so it is not absolutely necessary to follow them. However, it is recommended that guidelines be followed, if possible. If there is a deviation from a guideline, a clear explanation of the reason for the deviation should be provided. The FDA has issued specifications for the color-coded binders that are needed for the volumes of an NDA. The binders can be ordered from the U.S. Government Printing Office, Washington, DC 20404-0001 [Phone (202) 512-1800]. Alternatively, applicants can have the binders made and printed according to the FDA specifications. The specifications for the binders for NDAs, including specifications for IND and Drug Master File binders, can be found on the FDA website. The binders for an NDA have been assigned form numbers, Form FDA 2626 and Forms FDA 2626a through h. These numbers are useful for ordering from the Government Printing Office. The NDA Summary provides the FDA with a good general understanding of the specific drug product. It must state conclusions that can be derived from the most important data within the NDA submission. The information should be written as required for a publication in a medical journal with the results, where possible, reported in graphic and tabular form and must never be promotional in nature. The components of the summary are as follows:<sup>28</sup>

- Pharmacological Class, Scientific Rationale, Intended Use, and Potential Clinical Benefits
- Foreign Marketing History

#### **ABBREVIATED NEW DRUG APPLICATION (ANDA)<sup>26-30</sup>**

An Abbreviated New Drug Application (ANDA) is specifically designed for an approval of a generic drug product. When data within an ANDA are submitted to the Food and Drug Administration's Center for Drug Evaluation and Research (CDER), Office of Generic Drugs, the applications are reviewed and approved from that division. On approval of the application

the applicant may manufacture and market the generic drug product with the purpose of providing consumers with a safe, effective, and low cost alternative of the generic form of a brand name drug. A generic drug must be a drug product that is comparable to an innovator drug production dosage form, strength, route of administration, quality, performance characteristic, and intended use. The Waxman-Hatch Act, also known as the Drug Price Competition and Patent Term Restoration Act of 1984, established bioequivalence as the basis for approving generic copies of drug products. This act permits the FDA to approve ANDAs submitted to market generic versions of brand-name drugs without conducting costly and duplicative preclinical and clinical trials. To access additional information on the bioequivalence review of generic products, the Office of Generic Drugs provides a home page to generic drug developers including an interactive flowchart presentation of an ANDA focusing on how CDER determines the safety and bioequivalence of generic drug products prior to an approval for marketing. The term *abbreviated* is used in generic drug applications because, as stated above, they are usually not required to include preclinical and clinical data to establish safety and efficacy. However, a sponsor of a generic drug must scientifically demonstrate that the product is bioequivalent. Bioequivalent, for the purpose of this submission, refers to having the generic product perform in the same manner as the innovator drug. A way scientists demonstrate bioequivalence is to measure the time it takes the generic drug, to reach the bloodstream in 24 to 36 healthy volunteers. The rate of absorption is determined or the bioavailability of the generic drug, which then can be compared to the innovator drug. It must be shown that the generic drug version delivers the same amount of active ingredients into a subject's bloodstream in the same amount of time as the innovative drug.<sup>31,32</sup> The detailed components described in this chapter, Specific Requirements, Content, and Format of an NDA, detail how the content of the ANDA might be approached. With the exception of the preclinical and nonclinical sections and the clinical section, an ANDA should follow the items in Application Form 356h (see chapter 5, p. 168). The guidance documents that have been developed by the FDA to assist applicants in preparing ANDAs are listed together on CDER's Guidance Document Index webpage. The guide-lines to assist in preparing ANDAs include

1. Format and content for
  - a. Application summary
  - b. Chemistry, manufacturing, and controls section
  - c. Nonclinical pharmacology and toxicology section
  - d. Human pharmacokinetics and bioavailability section

e. Clinical and statistical section

f. Microbiology section

2. Guideline for postmarketing reporting of adverse reactions

3. Guideline for the submission in microfiche of the archival copy of an application

4. Guideline for submitting supporting documentation for the manufacture of drug substance

5. Guideline for submitting supporting documentation for manufacture of finished dosage forms

6. Guideline for submitting supportive analytical data for methods validation in NDAs

7. Guideline for submitting supporting documentation for stability studies of human drugs

8. Guideline for packaging

### **APPROVAL TIME**

The reviews times for NDAs for new molecular entities have dropped in 1993 the median total approval time was 23 months of which 21 months were used by the FDA and 25 new molecular entities were approved.<sup>33,34</sup> By 1996 the median time had dropped to 14.3 months for total time, with a median of 12 months for FDA review, and 53 new molecular entities were approved in 2001, 7 new molecular entities that were classified as priority were approved with a median review time of 6 months and 17 new molecular entities that were classified as standard were approved with a median FDA review time of 15.7 months.

### **CONCLUSION**

The Food and Drug Administration Modernization Act of 1997 (FDAMA) extended the use of user fees and focused on streamlining the drug approval process.<sup>11,13</sup> In 1999, the 35 drugs approved by the FDA were reviewed in an average of 12.6 months, slightly more than the 12-month goal set by PDUFA.<sup>10</sup> This act also increased patient access to experimental drugs and facilitated an accelerated review of important new medications. The law ended the ban on disseminating information to providers about non-FDA-approved uses of medications. A manufacturer can now provide peer reviewed journal articles about an off-label indication of a product if the company commits to filing a supplemental application to establish the use of the unapproved indication. As part of this process, the company must still conduct its own phase 4 study. As a condition for an accelerated approval, the FDA can require the sponsor to carry out post marketing studies to confirm a clinical benefit and product safety.

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