2. DRUG EVOLUTION PROCESS: IND, NDA & ANDA

The path a drug travels from a laboratory to the medicine cabinet in the pharmacy or chemist shop is usually long and, every drug takes a unique jig-jag route. It has been estimated that the average cost to brand name companies of discovering and testing a new innovative drug (with a new chemical entity) may be as much as $800 million (Di Masi et al., 2003; Goozner, 2004). Most of drugs that undergo preclinical animal testing never even make it to human testing and review by the FDA.

The Federal Food, Drugs and Cosmetics Act, as regulated through Title 21 of the U.S. Code of Federal Regulations, requires a new drug to be approved by the Food and Drug Administration (FDA) before it may be legally introduced in interstate commerce. A schematic representation of the process for new drug development is shown in Figure 2.1 (Ansel et al., 2008).

In India, a new drug may be approved, as regulated by the requirements given in Schedule Y to the Rules of the Drugs and Cosmetics Act, 1940 and Rules 1945. The various steps in launching of a new drug in India are summarized in Figure 2.2 (Malik, 2010).

2.1 INVESTIGATIONAL NEW DRUG (IND)

2.1.1 IND PROCESS IN USA

Investigational New Drug has been defined under 21CFR 312.3(b) (US FDA) as ‘a new drug or biological drug that is used in a clinical investigation (www.accessdata.fda.gov/scripts/cdrh/cfdocs/CFR). The term also includes a biological product that is used in vitro for diagnostic purposes. The terms, ‘Investigational Drug’ and ‘Investigational New Drug’ are deemed to be synonymous. CFR 312.6 provides to label the IND as Caution: New Drug—Limited by Federal (or U.S.) law to investigational use.

Important information to be included in an IND includes: Cover sheet (name, address, etc. of the manufacturer, phase of the clinical investigation to be conducted, etc.); Table of contents; Introductory statement and general investigation plan; Investigator’ brochure; Chemistry; Manufacturing and control information; Pharmacology and drug disposition; Previous human experience with the investigational drug; and additional / relevant information.
During a new drug’s early pre-clinical development, the sponsor’s primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justify commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early stage clinical studies.

FDA’s role in the development of a new drug begins when the pharmaceutical industries, research institutions, and other organizations who take responsibility for developing a drug, having screened the new molecule for pharmacological activity and acute toxicity potential in animals, want to test its diagnostic or therapeutic potential in humans and submit the results of preclinical testing done in laboratory animals with their detailed proposal for human testing. The sponsor submits the application for conduct of clinical trial which is called Investigational New Drug (IND) application to the FDA. Once the IND is submitted, the sponsor must wait 30 days before initiating any clinical trials. FDA at this stage decides whether it is reasonably safe for the company to move forward with testing the drug in humans. The drug studies in humans (clinical trials) can begin only after an IND is reviewed by the FDA and a local institutional review board (IRB). IRBs approve the clinical trial protocols, make sure that participants have given consent and researchers take appropriate steps to protect patients from harm. Before the NDA is filed, an Investigational New Drug form (form FDA-1571) for the drug must be filed (www.fda.gov/forms/fdaforms.htm). If the FDA does not reject the IND request within 30 days of submission, clinical testing of the new molecule on human may begin by the investigator. The IND application must include proof of preclinical testing of the new drug on animals to substantiate the safety of clinical testing in humans. If during the clinical testing of a new drug, the data furnished to the FDA indicate that the drug is too toxic under the criterion of the FDA’s risk/benefit ratio, the FDA will terminate the IND approval and the FDA action is not subject to any judicial review. IND approval process is depicted in Figure 2.1.1.1.

**The IND application must contain following data/information:**

- Animal Pharmacology and Toxicology Studies: Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans.
Also included, are any previous experience with the drug in humans (often foreign use).

- Manufacturing information: Information pertaining to the composition, manufacturer, stability and control used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

- Clinical Protocols and Investigator information: Detailed protocol for proposed clinical studies to assess whether the initial phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators - professionals (generally physicians) who oversee the administration of the experimental compound - to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

The IND application contains data as under (http://www.cc.nih.gov):

1. Coversheet (Form FDA-1571)
2. A Table of Contents
3. Introductory Statement and General Investigational Plan
4. Investigator’s Brochure
5. Protocols
6. Chemistry, Manufacturing, and Control Information
7. Pharmacology and Toxicology Information
8. Previous Human Experience with Investigational Drug
9. Additional Information

**TYPES OF INVESTIGATIONAL NEW DRUGS IN USA:**

1. **An Investigator IND** submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
2. **Emergency Use IND** (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm) allows FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21 CFR, Sec.312.23 or Sec. 312.34. It is also used for patients who do not meet the criterion of an existing study protocol, or if an approved study protocol does not exist.

3. **Treatment IND** is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

There are four phases of clinical trials which are conducted to investigate the safety and efficacy of drug in human being prior to its approval for use. Phase I studies are usually conducted in healthy volunteers with a goal to determine the common side effects of the drug and the emphasis in phase I is on safety. The primary objective of phase II studies is to evaluate the effectiveness of a drug for a particular indication while the phase III studies are undertaken on larger population, if evidence of effectiveness is shown in phase II. Phase IV involves post marketing surveillance of the approved drugs to detect adverse effects or other problems that were not encountered in the three prior phases of drug testing due to limited number of patients.

### 2.1.2 IND PROCESS IN INDIA

**Investigational New Drug** has been defined under explanation attached to Rule122-DA (3) of the Drugs and Cosmetics Rules 1945 wherein it means a chemical entity or a product having therapeutic indication but which have never been earlier tested on human beings (Malik, 2010). Clinical trials for the new drugs as well as investigational new drugs are mandatory before their manufacturing approvals. However, the clinical data as well as the requirement of Animal Toxicology, Reproduction Studies, Teratogenic studies, Perinatal studies, Mutagenicity and Carcinogenicity may be modified or relaxed in case of new drugs marketed in other countries and there is adequate published evidence of its safety (Malik, 2010).
CLINICAL TRIALS IN INDIA

No clinical trial for a new drug, whether for clinical investigation or any clinical experiment by any institute can be conducted except under, and in accordance with, the permission, in writing, of the Licensing Authority (DCGI). Two different types of provisions exist under the Indian drug regulations for conducting clinical trials. For new drug substances discovered in India, clinical trials are required to be carried out in India right from Phase I and are called domestic clinical studies while for those drugs which are discovered in countries other than India, Phase I data generated outside India may be submitted and direct Phase II trials may be permitted. Such studies are termed as global clinical trials (Malik, 2010).

Application for the purpose of conducting clinical trials in India is required to be submitted by the sponsors on Form 44 along with the requisite fee (Rupee fifty thousands) and documents as provided under Schedule Y appended to the Drugs and Cosmetics Act 1940. The sponsor is also responsible for implementing and maintaining quality assurance system to ensure that clinical trial is conducted and data generated and reported in compliance with the protocol and Good Clinical Practice guidelines issued by Central Drugs Standard Control Organization (CDSCO) (www.cdsco.nic.in) as well as all applicable statutory provisions of the Drugs and Cosmetics Act 1940 and Rules 1945.

- Status report is required to be submitted on clinical trials to the DCGI at prescribed periodicity.

- Summary report to be submitted within three month, if the studies are discontinued prematurely for any reason including lack of commercial interest.

- Summary report must specify brief description of study, number of patient exposed, drug dose, duration of exposure, details of adverse drug reaction if any and reason for discontinuation of study.

- Any serious adverse event (SAE) occurring during the clinical trial must be communicated promptly within 14 days by the sponsor.

Data to be submitted along with the application on Form 44 to conduct clinical trials (Two hard copies and two soft copies i.e., CD’s in PDF format).
1. Application on Form 44
2. Introduction of the drug
3. Fee Rupee fifty thousand through challan form
4. Chemical and Pharmaceutical Information as per Appendix I of Schedule ‘Y’
5. Animal Pharmacology as per Appendix IV of Schedule ‘Y’
6. Animal Toxicology as per Appendix III of Schedule ‘Y’
7. Human/Clinical Pharmacology data as per Appendix I of Schedule ‘Y’
8. Regulatory status in other countries as per Appendix I of Schedule ‘Y’

For new drug substances discovered in countries other than India, Phase I data as generated in other countries may be submitted along with the application. DCGI who is Licensing Authority may grant permission to conduct Phase II trials and Phase III trials or may direct to repeat Phase I trials. Phase III trials are to be conducted in India before permission to market the drug in India is granted.

**CLINICAL TRIAL REVIEW PROCESS**

After receiving the application for clinical trial, the CDSCO head quarter at New Delhi refer it to the new drug division where it is reviewed by the IND committee. The committee after completing the review process submits its report along with the recommendations to the DCGI. If the report of the committee is favorable, the DCGI approve the application. There is no time frame fixed for granting or rejecting the permission for clinical trials as on date. However, normally it takes from 4-6 months time to obtain approval but it is not documented. For international applicants import license to import the clinical trial samples and permission from Director General Foreign Trade to export blood samples for analysis is also needed. The Ethical Committee (EC) approval also require 1-3 month’s time. Thus, it takes almost 7-9 months after submission of the application to the DCGI to get the approval (www.expresspharmaonline.com).

### 2.2 NEW DRUG APPLICATION (NDA)

#### 2.2.1 NDA PROCESS IN USA

New drugs simply refer to those that have not yet received general recognition by medical experts as being both safe and effective for the intended use. The official definition is in section 201(p) of the Federal Food, Drug, and Cosmetic Act,
(www.fda.gov/RegulatoryInformation/legislation/Federal) wherein the term “new drug” means-

1. any new drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a “new drug” if at any time prior to the enactment of this Act it was subject to the Food and Drug Act of June 30, 1906, as amended and if at such time its labeling contained the same representations concerning the conditions of its use; or

2. any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations been used to a material extent or for a material time under such conditions.

Applications for FDA approval to market a new drug are required to be submitted in triplicate: An archival copy, a review copy and a field copy. An application for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, medication guide. In addition, other information, including patent information, patent certification, claimed exclusivity, financial certification or disclosure statement, etc., are also included. The technical sections include information on Chemistry, Manufacturing and Control, Non-clinical Pharmacology and Toxicology, Human Pharmacokinetics and Bioavailability, Microbiology, Clinical data, Statistical data and Pediatric use data, if any.

A new drug may not be marketed in US unless it has been approved safe and effective. Such approval is based upon an NDA, which must contain acceptable scientific data, including the results of tests, to evaluate its safety. Newly discovered molecules are not the only subjects of NDAs. A drug may be legally regarded as a new drug if it is an
old, established drug which is offered in a new dosage form, with new medical claims, in new dosage levels or if the drug is to be used on a different patient population. An NDA may also be required if a new combination of old drugs is used.

New Drug Application is the formal step a drug sponsor takes to ask that the FDA consider approving a new drug for marketing in the US. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured. The application, if complete is then subjected to review by an FDA review team comprising of medical doctors, chemists, statisticians, microbiologists, pharmacologists, and other experts to evaluate if the drug is safe and effective as per the studies submitted by the sponsors. The FDA inspects the facilities where the drug will be manufactured as a part of approval process. After NDA is approved by FDA, the drug is marketed, but the FDA continues to track approved drugs for adverse events through a post marketing surveillance program.

In USA following four types of applications are submitted for the approval of a drug for marketing depending upon the type and nature of the drugs:

A. New Drug Application (NDA)
B. Biological License Application (BLA)
C. Application u/s 505(b)(2)- Paper NDA
D. Supplemental New Drug Application (sNDA)

A. NEW DRUG APPLICATION (NDA)

The application is submitted to the FDA for a drug that contains an active ingredient that has never been approved for marketing in the US (New Chemical Entity). The application is required to be submitted in common technical document format with 5 modules and contain information/documents as follows.

i. FDA Form 356h

ii. User Fee Cover Sheet (FDA Form 3397)

iii. Cover letter (Comprehensive table of contents for Modules 1-5)

iv. Administrative Information regarding sponsor, patent details, certification etc.
v. Chemical, nonproprietary, code and proprietary names of drug, the dosage form, the strength, and route of administration

vi. Statement regarding the applicant’s proposal to market the drug product as prescription only or as OTC product.

vii. Detailed summary of all aspects of the application, including the proposed text of the product’s intended labeling, chemistry, manufacturing and control, nonclinical and clinical pharmacology and toxicology, human pharmacokinetics and bioavailability, statistical analysis, clinical trial data, benefit and risk consideration, and proposed additional or planned post marketing studies.

viii. Detailed technical sections on the chemistry, manufacturing, and controls for the drug substance, including its physical and chemical characteristics, methods of identification, assay, and controls, and of the drug product, including its composition, specifications, methods of manufacture and equipment used, in-process controls, batch and master production records, container and closure system, stability, and expiration dating.

ix. Detailed technical sections for non-clinical pharmacology and toxicology in relation to the proposed therapeutic indication, including acute, sub acute and chronic toxicology, carcinogenicity, reproductive toxicology, and animal studies of absorption, distribution, metabolism, and excretion.

x. Detailed technical sessions for human pharmacokinetics and bioavailability along with microbiology for antibiotic applications.

xi. Detailed technical sections for clinical data for each controlled and uncontrolled study relating to the proposed indication, a copy of the study protocol, effectiveness and safety data including any updates on safety information, comparison of human and animal pharmacology and toxicology data, support for the dosage and dose intervals and modifications for specific sub groups, such as pediatric, geriatric, and renal impaired subjects.

xii. Statement regarding compliance to IRB and informed consent requirements.

xiii. Statistical methods and analysis of the clinical data.
xiv. Samples of the drug substance, drug product proposed for marketing, reference standards, and finished market package, as requested.

xv. Clinical case report forms for the archival copy of the application.

xvi. The FDA accepts foreign clinical data if they are applicable to the United States population and domestic medical practice; if the studies were by clinical investigators of recognized competence, and if the FDA considers the data to be valid without the need for an onsite inspection. Details of documents required for NDA, BLA and ANDA are given in Table 2.2.1.1. NDA approval and review process is depicted in Figure 2.2.1.1.

B. BIOLOGICAL LICENCE APPLICATION (BLA)

Biological license application is required under section 351 of the Public Health Services Act before a biological product is introduced into the interstate commerce. BLA is submitted to obtain a license. Granting of license certifies that the biological product is safe, pure and potent and the facilities where it is manufactured meet standards designed to ensure that it continue to be safe, pure and potent. Section 351 defines a biological product as a virus, therapeutic serum, toxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product. Biological products, subject to the PHS Act, also meet the definition of drugs under the Federal Food, Drug and Cosmetics Act (FDC Act). Therefore, such products following initial laboratory and animal testing (if found safe) can be studied in clinical trials like other drugs under an investigational new drug application (IND) in accordance with the regulations at 21 CFR 312. If the data generated by the studies demonstrate that the product is safe and effective for its intended use, the data are submitted as part of a marketing application. Whereas a new drug application (NDA) is used for drugs subject to the drug approval provisions of the FDC Act, a biological license application (BLA) is required for biological products subject to the licensure under the PHS Act. Details of documents/data required for submission of application for BLA is given in Table 2.2.1.1.

APPLICATION’S CONTENTS: (http:www.biotech.com/blaSubmissions.php)

1. Form FDA 356h
2. Manufacturer’s Information
3. Product/Manufacturing information
   i) Source material/raw material
   ii) Manufacturing process/ control
   iii) Formulation
   iv) Facilities information
   v) Contamination/ cross contamination information
   vi) Environmental assessment

4. Pre-clinical studies
5. Clinical studies
6. Labeling

C. APPLICATION U/S 505 (b) (2)-PAPER NDA

A 505 (b) (2) application is a new drug application (NDA) described in Section 505 (b) (2) of the Food Drug, and Cosmetics Act. It is submitted under Section 505 (b) (I) of the Act and approved under Section 505 (c) of the Act.

A 505(b) (2) application is one for which one or more of the investigations relied upon by the applicant for approval “were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted” [21 U.S.C. 355 (b) (2)].

Section 505(b) (2) was established by the 1984 Act to allow sponsors to obtain approval of the new drug applications (NDAs) based upon “full reports of investigations” establishing a drug’s safety and efficacy where such investigations were not conducted by or for the 505(b) (2) applicant and for whom the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

The 505(b) (2) application is one of three established types of new drug application (NDA), and it is a path way to approval that can potentially save Pharmaceutical sponsor both time and money. However, many sponsors are unsure how to evaluate the possible benefits of using this type of application. The 505(b) (2) regulatory pathway is defined in the Federal Drug and Cosmetics Act as an NDA containing investigations of safety and effectiveness that are being relied upon for approval and were not conducted by or for the applicant, and for which the applicant has not obtained a right of reference. These applications differs from the typical NDA [described u/s 505(b) (I) of the Act], in findings
of the safety and/or efficacy for a previously approved drug (the ‘reference drug’). Section 505 (b) (2) was added to the Act in 1984 with the goal of avoiding unnecessary duplication of preclinical and certain human studies. However, sponsor must still provide any additional preclinical or clinical data necessary to ensure that differences from the reference drug do not compromise safety and efficacy. Section 505(b) (2) differs from an abbreviated NDA [ANDA, described u/s 505 (j) of the Act], which is an application containing information to demonstrate that the proposed product is identical to a previously approved product. Identity is proven in an ANDA simply through chemistry and bioequivalence data, without the need for preclinical and clinical trials assessing safety and efficacy. In a sense 505(b) (2) application can thought of as a hybrid that contain more data than an ANDA, but less data than an NDA. The 505(b) (2) approval route can be utilized for a wide range of products, especially for those that represent a limited change from a previously approved drug.

Thus, Section 505(b) (2) application permits a sponsor to rely upon the FDA’s findings of safety and efficacy for a previously approved drug product without requiring the sponsor to obtain a right of reference from the original applicant. The 505 (b) (2) applicant must provide any additional clinical data required to demonstrate the safety and efficacy of differences between the original drug and the 505(b) (2) drug, so while unnecessary duplication of preclinical and certain human studies is avoided, specific studies may be required to establish the relevance and applicability of prior findings for your particular product formulation (21 C.F.R. 314.54).

In addition to permitting reliance upon the FDA’s prior finding of safety and efficacy for previously approved drugs, Section 505 (b) (2) continues to allow reliance on third party data that is available in published literature and which establishes the safety and efficacy of a drug. Section 505(b) (2) and (j) together replaced FDA’s paper NDA policy, which had permitted an applicant to rely upon published studies published in scientific literature to demonstrate the safety and efficacy (Srivastava, 2004).

**EXAMPLES OF 505(b) (2) APPLICATION**

1. Changes in dosage form, strength, formulation, route of administration, dosage regime, change in formulation etc.
2. New indications.
3. New combination product including substitution of active ingredient.
4. Different salt, ester, chelate, racemate, enantiomer of an active ingredient.
5. Switching from prescription drug to OTC drug.
6. Drugs with naturally derived or recombinant active ingredients where limited additional clinical data is required to show that the ingredient is same as the ingredient in reference drug.

Section 505 describes three types of New Drug Applications (NDA):

i) Application with full report of investigations [Section 505(b) (I)].

ii) Application containing full report of investigation but where some of the data required for approval comes from the studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference [Section 505(b) (2)].

iii) Application for the product showing that the product is identical in active ingredient, dosage form, strength, route of administration labeling, quality, performance and intended use to a previously approved product [Section 505(j)].

D. SUPPLEMENTAL NEW DRUG APPLICATION (SNDA)

Supplemental New Drug Application is submitted by the marketing authorization holder of the drugs. The application is submitted to the FDA for approval of the changes after approval of drug by the FDA. There may be changes in the indications of the drug or new dosage form of an already approved drug product or use of new salt, etc (http://www.fda.gov). Depending on the changes proposed, some require FDA approval before implementing; others do not. Among the changes requiring prior approval are as below: (Ansel et.al., 2008).

i) Approval of already approved drug for new indication.

ii) Approval of new ester, new salt and new dosage form of an already approved drug and drug product.

iii) A change in the method of synthesis of the drug substance.
iv) Use of a different facility to manufacture the drug substance where the facility has not been approved through inspections for Current Good Manufacturing Practices standards within the previous 2 years.

v) Change in the container and closure system for a product.

vi) Extension of the expiration date for a drug product based on new stability data.

vii) Change in the formulation, analytical standards, method of manufacture, or in process controls of the drug product.

viii) Use of a different facility or contractor to manufacture, process, or package the drug product.

**REVIEW OF NEW DRUG APPLICATION (NDA)**

On receipt of the application, the central document room of the CDER stamps with a receipt date to enable the FDA to forward action within 180 days to the applicant. The FDA assigns the application to the appropriate therapeutic review division for review. The FDA has to intimate the applicant if it is incomplete or inadequate within 60 days from the receipt of the application. If the application is incomplete FDA can refuse to file it and the sponsor can resubmit it later. If it is complete, FDA notifies the sponsor and secondary review process starts. The review committee consists of scientific experts from outside FDA and may also have consumer, patient, and industry representatives. The review is usually in a public forum and advises FDA on scientific issues related to the application.

Throughout the process FDA and the sponsor communicate through in person meetings, telephone conferences, letters, e-mails, and faxes to seek clarification, wherever necessary. FDA also inspects the manufacturing facilities for the drug. It may also inspect a sample of clinical trial locations to verify the accuracy of the data submitted. Once all reviews are complete; the divisional director evaluate the reviews and make FDA’s decision. The FDA may:

1. Approve the drug, so that it can be marketed in the US.
2. Approve the drug with condition when problem exist with the application, that need to be addressed before the drug may be approved.
3. Refuse to approve the drug, when it may require additional research or reformulation of the drug product.
2.2.2 NDA PROCESS IN INDIA

In India, the term ‘new drug’ has been defined under Rule 122-E of the Drugs and Cosmetics Rules, 1945, as a drug which has not been used in the country to any significant extent under the conditions prescribed, recommended or suggested in the labeling thereof and has not been recognized safe and effective by the Drugs Controller General India (DCGI) for the proposed claims (Malik, 2010).

DEFINITION OF ‘NEW DRUG’ AS PER RULE 122-E:

i) A drug as defined in the Act including bulk drug substance which has not been used in the country to any significant extent under the conditions prescribed, recommended or suggested in the labeling thereof and has not been recognized as effective and safe by the Licensing Authority for the proposed claim: Provided that the limited use, if any has been with the permission of the Licensing Authority.

ii) A drug already approved by the Licensing Authority for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration.

iii) A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz., indications, dosage, dosage form (including sustain released dosage form) and route of administration.

iv) All vaccines are considered as new drugs, unless notified otherwise by the DCGI.

v) A new drug continues to be considered as new drug for a period of four year from the date of its first approval or its inclusion in the Indian Pharmacopoeia, whichever is earlier.

After successful finishing the clinical trials, the applicant seeking for approval to manufacture a new drug is required to submit application on Form 44 along with the data as given in Appendix 1 to the Schedule Y of the Rules, 1945, including the results of clinical trials carried out in the country, Bio-availability/ Bio-equivalence, Regulatory
status in other countries, Prescribing information, Samples and testing protocols, etc., to the Drugs Controller General of India, who grants its approval in form 46 or 46-A.

Further, the applicant is required to submit evidence that the drug for the manufacture of which application is made has already been approved by the DCGI in his name while applying to manufacture a new drug to the State Licensing Authority. Thus the applicant is required to obtain necessary approval from the DCGI as well as the State Licensing Authority (SLA) for manufacturing a new drug for sale purposes in India. New Drug Application filing in India has also been allowed through common technical document (CTD) since November 2010. The approval issued is ‘manufacture for sale’ rather than ‘marketing approval’ as per the practice world over. Brief detail of the documents/ information required along with the application on Form 44 for different categories of New Drug Applications (NDA) is as under:

A. PERMISSION TO MANUFACTURE A NEW DRUG:

- Brief introduction of the new drug
- Chemical and pharmacological information
- Animal Pharmacology
- Animal Toxicology
- Human/ Clinical Pharmacology (Phase I)
- Exploratory Clinical trials (Phase II)
- Confirmatory Clinical trials (Phase III)
- Bio-Availability, dissolution and stability study data
- Regulatory status in other countries
- Application for test license
- Marketing information:
  i) Proposed product monograph
  ii) Draft of labels and cartons

B. SUBSEQUENT APPROVAL/PERMISSION FOR MANUFACTURE OF ALREADY APPROVED NEW DRUG:

I. Formulations

- Bio-availability/ bio-equivalence protocol
• Name of the investigator/ centre
• Source of raw material and stability study data

II. Raw Material (Bulk drug substance)
• Manufacturing method
• Quality control parameters and/or analytical specification, stability report
• Animal toxicity data

C. APPROVAL/ PERMISSION FOR FIXED DOSE COMBINATION:
• Therapeutic justification
• Data on pharmacokinetics / pharmacodynamics combination (authentic literature in peer reviewed journals / textbooks)
• Any other data generated by the applicant on the safety and efficacy of the combination

D. SUBSEQUENT APPROVAL OR APPROVAL FOR NEW INDICATION-NEW DOSAGE FORM:
• Number and date of approval already granted
• Therapeutic justification for new claim. Modified dosage form
• Data generated on safety, efficacy and quality parameters

2.3 ABBREVIATED NEW DRUG APPLICATIONS (ANDA)

2.3.1 ANDA PROCESS IN USA

Generic drug applications are referred to as Abbreviated New Drug Applications (ANDA). Pharmaceutical companies must submit ANDAs and receive FDA’s approval before marketing new generic drugs [21 CFR 314.105(d)]. A generic drug is the same as a reference-listed (i.e., brand name) drug with respect to conditions of use, active ingredient(s), route of administration, dosage form, strength, and labeling [21 CFR 314.92 and 314.105(c)] (www.fda.gov/cder/regulatory/applications/anda.htm). In addition, the generic drug must be bioequivalent to (i.e., perform in the same manner as) the brand name drug. A generic drug that is therapeutically equivalent is expected to have the same clinical effect and safety profile as the brand name drug when administered under the
conditions specified in the labeling. If generic drugs are determined to be therapeutically equivalent, physicians and pharmacists can substitute them for brand name drugs.

Sometimes generic versions of a drug have different colors, flavors or inactive ingredients and also do not look alike the branded one because of trade mark laws (www.fda.gov/cder/ord). In most cases generics are available once the patent protection available to the original developer expires. When a patent expires, firms offering the generic substitutes may enter the market and start selling the copies of original drug. As the generic contains exactly the same active ingredients, these are certified to be the perfect substitute for the innovators at lower cost. The generics are cheaper because; (i) the generic manufacturers do not have to incur the costs of searching and finding a new drug to treat a particular illness. (ii) The generic manufacturers do not require to carryout clinical trials, only bioequivalence is mandatory to prove their equivalency to the innovator. (iii) These companies get the advantage of marketing established by innovators, as the drug is usually in the market for a decade or so. (iv) They are also not required to spend much on the sales promotion. The research and developmental costs incurred by the innovators is cited as the major reason for citing their high cost which they recover before expiry of their patent. The generic firms do not incur such costs as bioequivalence testing is much cheaper.

**GENERIC DRUG APPROVAL PROCESS**

In 1970 FDA established the Abbreviated New Drug Application (ANDA) as a mechanism for the review and approval of generic versions of drug products approved during 1938 and 1962. For drugs approved after 1962, complete safety and efficacy through clinical trials were mandatory for generic applicants. After 1978, however, manufacturers were required to cite published reports of such trials documenting safety and efficacy. Enacted in 1984, the U.S. Drug Price Competition and Patent Term Restoration Act, popularly known as the “Hatch- Waxman Act”, standardized U.S. procedures for recognition of generic drugs. A generic applicant is required to demonstrate therapeutic equivalence to a specified previously approved “reference listed drug” without the submission of clinical studies and other data required in a full NDA (http://www.worldtradelaw.net/uragreements/tripsagreement.pdf).
An Abbreviated New Drug Application (ANDA) contains data that, when submitted to FDA’s Centre for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of generic drug product as shown in Table 2.2.1.1. The application for generic approval is required to be submitted in CTD format to the FDA.

Under Section 314.94, three copies of an abbreviated application are required to be submitted: an archival copy, a review copy and a field copy. An archival copy shall include the following information: Application form; Table of contents; Basis for ANDA submission (giving reference to the reference listed drug); Conditions of use; Active ingredients; Route of administration; Dosage form and strength; Bioequivalence; Labeling; Chemistry, Manufacturing and Controls; Samples; Other information; Patent Certification; Financial certification or disclosure statement, etc.

Under Section 314.94 (a) (12), the Patent Certification includes one of the following:

- That the patent information has not been submitted to FDA – Paragraph I Certification.
- That the patent has expired – Paragraph II Certification.
- That the patent will expire (on the date of marketing) – Paragraph III Certification.
- That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use or sale of the drug product for which the abbreviated application is submitted – Paragraph IV Certification.

**REVIEW AND APPROVAL / DISAPPROVAL OF ANDA**

Three divisions within FDA’s Centre for Drug Evaluation and Research (CDER), and Office of Generic Drugs (OGD), review all ANDAs (http://www.oig.hhs.gov). On receipt of the application a pre-filling assessment of its completeness and its acceptability is performed by a project manager within the regulatory support branch. If the initial review is found in order, then acceptability letter is sent to the applicant. The application is
reviewed at bioequivalence division, chemistry division, microbiology and division of labeling and program support. The applicant is intimated to provide information or data if any deficiency is found at any review division to address the deficiency (Kshirsagar et al., 2009). After all components of the application are found to be acceptable, an approval or tentative letter is issued to the applicant.

EXCLUSIVITY

Exclusivity is a statutory provision and is granted to an NDA applicant if statutory requirements are met. This was designed to promote a balance between an innovator and generic drug competitor. For as long as a drug patent lasts, a brand name company enjoys a period of “market exclusivity” or monopoly, in which the company is able to set the price of the drug at a level which maximizes profitability. Expiration of a patent removes the monopoly of the patent holder on drug sales licensing. Patent life time differs from country to country, and typically there is no way to renew a patent after it expires. Before General Agreement on Tariffs and Trade (GATT), patent term used to be different (or less than 20 years) in several countries (other than USA), including India. However, after GATT, patent term in most countries (including India) is 20 years and typically there is no way to renew a patent after it expires.

Hatch-Waxman Act 1984 has limited the ability of pioneers to have exclusive rights to certain data that demonstrated the safety and efficacy of the approved drugs which was not limited in duration prior to 1984 Act. For an NCE drug, an applicant cannot submit an ANDA or a paper NDA application for a generic version of the drug to the FDA until 5 years after the date of approval of the pioneer NDA, or until 4 years if a Paragraph IV certification was made. For non-NCE drugs, the FDA cannot approve an ANDA or a paper NDA application for a generic version of a non-NCE drug for 3 years after the date of approval of a pioneer NDA (Glover, 2007).

TERMS OF EXCLUSIVITY

<table>
<thead>
<tr>
<th>Orphan Drugs</th>
<th>7 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Chemical Entity</td>
<td>5 Years</td>
</tr>
<tr>
<td>Pediatric Exclusivity</td>
<td>6 Months additional</td>
</tr>
<tr>
<td>Patent Challenge</td>
<td>180 Days</td>
</tr>
</tbody>
</table>
180-DAYS EXCLUSIVITY

The first successful company to submit a Paragraph IV certification to the FDA has the exclusive right to market the generic drug for 180 days as per 21 U.S.C.355(j) (5)(B)(iv). This provision was made to encourage generic companies to invest in the required product testing and to cover expensive legal challenges to pioneer products. The FDA is precluded from approving subsequent ANDA before expiration of the first filer’s 180 days exclusivity period. The 180-days exclusivity period begins at the earlier occurrence of the either of the two instances:

“When the first successful applicant initiate commercial marketing of its generic drug or after the decision of a court holding the patent which is the subject of the certification to be invalid or not infringed” [21 U.S.C. 355(j)(5)(B)(iv)(I) and (II)].

REFERENCE LISTED DRUGS (RLD)

Under the 1984 Act manufacturers seeking approval to market a generic drug must submit data demonstrating that the drug product is bioequivalent to the pioneer (innovator) drug product. This drug is referred to as the ‘reference listed drug’ (21 CFR314.94 [a][3]) and is identified by the FDA as the drug product upon which an applicant relies in seeking approval of its ANDA (Ansel et al., 2008). In most countries, the RLD is generally innovator drug product (Brand) which is marketed on the basis of a full dossier that includes chemical, biological, safety, clinical efficacy, labeling, etc. A standard RLD may avoid possible significant variations among generic drug products and their brand name counterparts. Reference Listed Drugs are listed in Approved Drug Products with Therapeutic Equivalence Evaluations, popularly known as “Orange Book” (www.fda.gov/cder/orange/default.htm). Some examples of reference listed drug of Nifedipine Tablet Extended Release 90mg are Adalat CC (Bayer Pharma), Procardia XL (Pfizer) (http://www.accessdata. fda. gov/scripts /cder/ob /docs/tempai.cfm).

2.3.2 ANDA PROCESS IN INDIA

The Indian Drugs and Cosmetics Act, 1940, defines the term ‘drug’ under section 3(b) of the 1940 Act which also include the term ‘generic drug’ as well (Malik, 2010). No separate definition for this term has been given in the statute. Therefore, Indian laws provide similar regulations for both, the branded as well as generic medicines.
The license/approval for manufacture of drugs (both branded as well as generic) other than the ‘new drugs’ is granted by the respective State Licensing Authorities under the Drugs and Cosmetics Rules, 1945. The applicant is required to submit the application for grant of license or approval to manufacture for sale of drug product (s) to the concerned SLA, with the required fees, composition of the formulation, pharmacopoeial status( if applicable), packing/ labeling details and test procedure (in case of non-pharmacopoeial drugs). The State Licensing Authority, after causing its inspection (if required) and satisfying that the requirements of the Rules under the Act have been complied with and that the conditions of the license and the Rules under the Act will be observed, shall issue a license. Bio-equivalence studies are not required for approval of generic or branded drug; however, such studies are mandatory for approval of new drug.

There is no concept like abbreviated application for generic approval in India as the patent regime has just started. Normally approval of generic or branded drug does not require inspection of the facilities and is granted spontaneously. There exists a system of dual approval/licensing in some critical products like large volume parenterals, vaccines, sera, blood, blood components and blood products etc., where the approval/license is approved by the SLA as well as the DCGI.

Section 107-A of the Indian Patents Act, 1970, is the equivalent of the “Bolar Provisions”, which allows a generic manufacturer, to start working on the generic drug development, even before the expiry of the drug patent (Garg, 2008). However, the various court rulings in India have established that there exists no linkage between a “drug approval process” and “patent certification”, so far as the launch of a generic is concerned (Mathew, 2009).

CONCLUSION

Although, the Indian drug laws define the terms ‘drug’ and ‘new drug’ yet it does not provide any definition for the terms ‘generic drug,’ ‘innovator/branded drug’ and ‘Investigational New Drug’ while the US and other overseas countries provide definition of ‘generic drug’ which differentiate it from its counterpart branded one. Similarly Indian drug regulations do not provide for ANDA or ANDS as prevalent in overseas countries. There is an immediate need for providing definition as well as appropriate approval process exclusively for generic drugs to promote them in the country.