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REVIEW ARTICLE

OVERVIEW OF DRUG INNOVATION TO COMMERCIALIZATION**Jaspreet Kaur^{*1}, Anil Kumar Sharma¹, Devesh Sharma²**¹Department of pharmaceutical management and Regulatory Affairs, CT Institute of Pharmaceutical Sciences, Jalandhar, India²Department of drug regulatory affairs, Ind Swift Laboratories, Mohali, India**Corresponding Author's email: jaspreet1602@gmail.com***ABSTRACT:**

The research, development, and approval of a drug product is a continuous but lengthy process involving drug discovery, laboratory development, animal studies, clinical trials, and regulatory registration. This lengthy process is necessary to assure the effectiveness and safety of the drug product. It takes about 10-15 years to develop one new medicine from the time it is discovered to when it is available for treating patients. The average cost to research and develop each successful drug is estimated to be \$800 million to \$1 billion. This number includes the cost of the thousands of failures: For every 5,000- 10,000 compounds that enter the research and development (R&D) pipeline, ultimately only one receives approval. These numbers defy imagination, but a deeper understanding of the R&D process can explain why so many compounds don't make it and why it takes such a large, lengthy effort to get one medicine to patients. Ultimately, though, the process of drug discovery brings hope and relief to millions of patients.

INTRODUCTION:

The drug discovery process was beginning in nineteenth century; by John Langley in 1905 when he proposed the theory of receptive substances. The first rational development of synthetic drugs was carried out by Paul Ehrlich (father of modern chemotherapy). Ehrlich was awarded by Nobel Prize in 1908. In 1960 Hansch & Fujita introduced the concept of QSAR (quantitative structure–activity relationship).¹ It is the mission of pharmaceutical research companies to take the path from understanding a disease to bringing a safe and effective new treatment to patients. Researchers work to:

- ❖ validate these targets,
- ❖ discover the right molecule (potential drug) to interact with the target chosen,
- ❖ test the new compound in the lab and clinic for safety and efficacy and
- ❖ Gain approval and get the new drug into the hands of doctors and patients.

This whole process takes an average of **10-15 years**. For every **5,000-10,000** compounds that enter the research and development pipeline, ultimately only one receives approval.²

DISCOVERY**Pre-discovery**

Goal: Understand the disease and choose a target molecule.

How: Scientists in pharmaceutical research companies, government, academic and for-profit research institutions contribute to basic research.

Discovery Goal: Find a drug candidate.

How: Create a new molecule or select an existing molecule as the starting point.

Perform tests on that molecule and then optimize (change its structure) it to make it work better.

Preclinical Goal: Test extensively to determine if the drug is safe enough for human testing.

How: Researchers test the safety and effectiveness in the lab and in animal models.

IND Goal: Obtain FDA approval to test the drug in humans.

How: FDA reviews all preclinical testing and plans for clinical testing to determine if the drug is safe enough to move to human trials.

Clinical Trials Goal: Test in humans to determine if the drug is safe and effective.

How: Candidate drug is tested in clinical setting in three phases of trials, beginning with tests in a small group of healthy volunteers and moving into larger groups of patients.

Review Goal: FDA reviews results of all testing to determine if the drug can be approved for patients to use.

How: The FDA reviews hundreds of thousands of pages of information, including all clinical and preclinical findings, proposed labeling and manufacturing plans. They may solicit the opinion of an independent advisory committee.

Manufacturing Goal: Formulation, scale up and production of the new medicine.

Ongoing Studies Goal: Monitor the drug as it is used in the larger population to catch any unexpected serious side effects.

TOTAL

How much: \$800 million – \$1 billion

How long: 10 – 15 years [3]

CURRENT TRENDS IN DRUG DISCOVERY

Drug discovery and development can broadly follow two different approaches: *structure based drug discovery and target-based discovery*. In structure based if the compound displays desirable pharmacological activity, it is refined and developed further where as in target based strategy putative drug target is identified first. The potential target could be a receptor thought to be involved in a disease process or a critical enzyme, or another biologically, important molecule in the disease pathway. Target validation requires the confirmation that whether the particular target is involved in the disease or not.

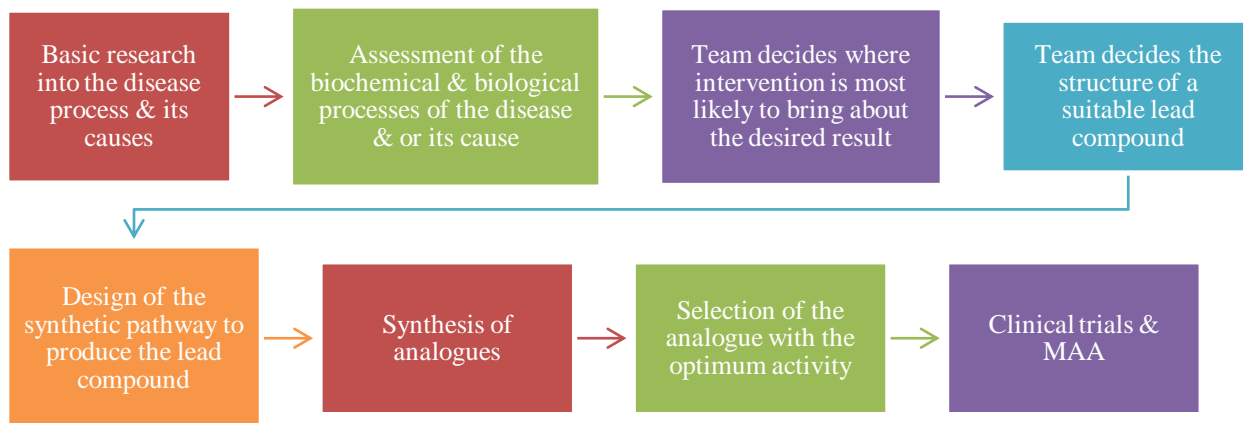


Fig1. Showing the general steps in the discovery of a new drug for a specific disease state[1]

DRUG DISCOVERY AND DEVELOPMENT

The process of drug discovery and development can be broadly categorized into two subclasses: drug discovery and drug development. The drug discovery process can be described as the identification and validation of a

disease target and the discovery and development of a chemical compound to interact with that target. Drug development involves satisfying all requirements that have to be met before a new compound can be deemed ready for testing in human subjects for the first time. Drug testing is achieved by preclinical and clinical trials.

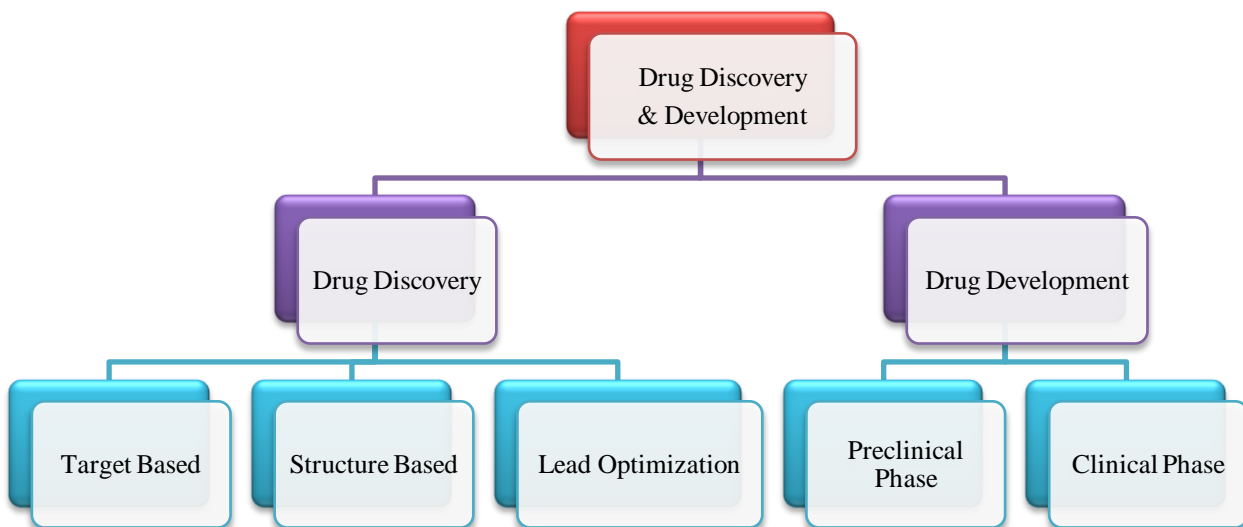


Fig 2: Steps for Drug discovery to development

BRANCHES OF SCIENCE IN VARIOUS STEPS OF DRUG DISCOVERY

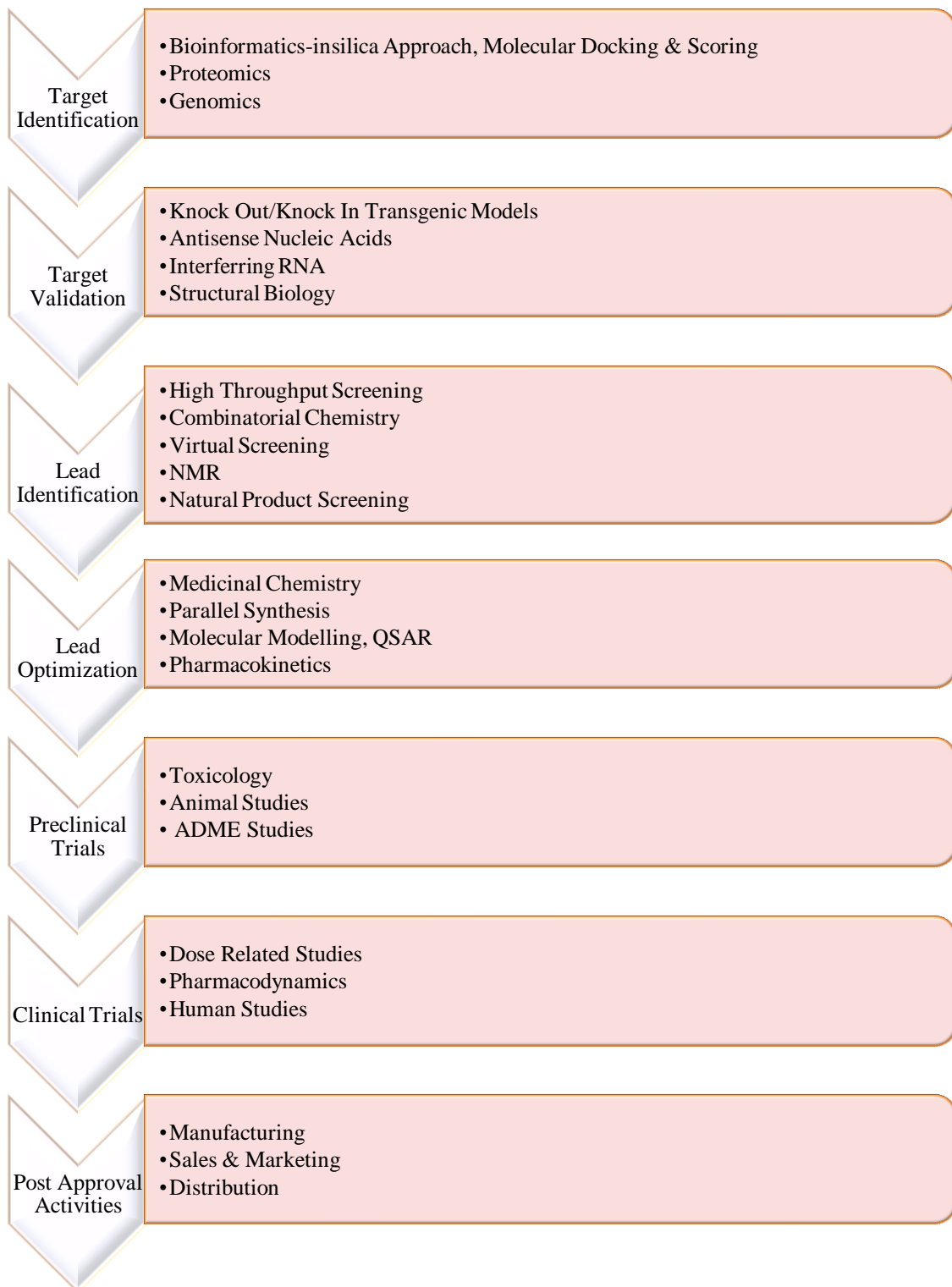


Fig 3: Showing the involvement of different topics and branches of science in various steps of drug discovery

Drug Discovery Pipeline: The process by which a new drug is brought to market stage is referred to by a number of names – most commonly as the development chain or “pipeline”. The process of drug discovery takes

about 15 years to complete, and the interesting feature is that it is complete only for few drug candidates as large number of parameters has to follow in order to pass from each and every step.



Fig 4: Showing the drug discovery pipeline and reveals that how different process are interlinked.

TARGET IDENTIFICATION – DISEASE MECHANISM

Choose a molecule to target with a drug. Once they have enough understanding of the underlying cause of a disease, pharmaceutical researchers select a “target” for a potential new medicine. A target is generally a single molecule, such as a gene or protein, which is involved in a particular disease. Target selection by the pharmacist depends on the disease on which he focused. Presently, G-protein coupled receptors (GPCR) are the predominant families addressed and more than 600 genes encoding GPCR have been identified. In humans, GPCR are responsible for about 30 disease including Diabetes insipidus, hypo and hyperthyroidism, retinis pigmentosa, several fertility disorders and even carcinoma. Approximately, 150 GPCRs found in human have unknown function. For the identification of target, In Silica approach is widely used, it’s a computer based technique to study the specific chemical responses in the body or target organism and tailoring combination of these to fit a treatment profile. Molecular Docking and Scoring techniques are also widely used; it involves computationally placing a virtual molecular structure into a binding site of a biological macromolecule. Various software has been developed-Auto Dock, Zdock, Dock & Docking Server.¹

Pre-discovery: Understand the disease. Before any potential new medicine can be discovered, scientists work to understand the disease to be treated as well as possible, and to unravel the underlying cause of the condition. They try to understand how the genes are altered, how that affects the proteins they encode and how those proteins interact with each other in living cells, how those affected cells change the specific tissue they are in and finally how the disease affects the entire patient. This knowledge is the basis for treating the problem.

Target Validation: Test the target and confirm its role in the disease. After choosing a potential target, scientists must show that it actually is involved in the disease and can be acted upon by a drug. Target validation is crucial to help scientists avoid research paths that look promising, but ultimately lead to dead ends. Researchers demonstrate that a particular target is relevant to the

disease being studied through complicated experiments in both living cells and in animal models of disease.

Lead Compound Identification: Find a promising molecule (a “lead compound”) that could become a drug. Armed with their understanding of the disease, scientists are ready to begin looking for a drug. They search for a molecule, or “lead compound,” that may act on their target to alter the disease course. If successful over long odds and years of testing, the lead compound can ultimately become a new medicine.

There are a few ways to find a lead compound:

Nature: Until recently, scientists usually turned to nature to find interesting compounds for fighting disease. Bacteria found in soil and moldy plants both led to important new treatments, for example. Nature still offers many useful substances, but now there are other ways to approach drug discovery.

De novo: Thanks to advances in chemistry, scientists can also create molecules from scratch. They can use sophisticated computer modeling to predict what type of molecule may work.

High-throughput Screening: This process is the most common way that leads are usually found. Advances in robotics and computational power allow researchers to test hundreds of thousands of compounds against the target to identify any that might be promising.

Based on the results, several lead compounds are usually selected for further study.

Biotechnology: Scientists can also genetically engineer living systems to produce disease-fighting biological molecules.

Early Safety Tests: Perform initial tests on promising compounds. Lead compounds go through a series of tests to provide an early assessment of the safety of the lead compound. Scientists test Absorption, Distribution, Metabolism, Excretion and Toxicological (ADME/Tox) properties, or “pharmacokinetics,” of each lead.

Successful drugs must be:

- ❖ absorbed into the bloodstream,
- ❖ distributed to the proper site of action in the body,
- ❖ metabolized efficiently and effectively,
- ❖ successfully excreted from the body and

❖ demonstrated to be not toxic.

These studies help researchers prioritize lead compounds early in the discovery process. ADME/Tox studies are performed in living cells, in animals and via computational models.

Lead Optimization: Alter the structure of lead candidates to improve properties, Lead compounds that survive the initial screening are then “optimized,” or altered to make them more effective and safer. By changing the structure of a compound, scientists can give it different properties. For example, they can make it less likely to interact with other chemical pathways in the body, thus reducing the potential for side effects.

Hundreds of different variations or “analogues” of the initial leads are made and tested. Even at this early stage, researchers begin to think about how the drug will be made, considering formulation, delivery mechanism and large-scale manufacturing.

Preclinical Testing: Lab and animal testing to determine if the drug is safe enough for human testing With one or more optimized compounds in hand, researchers turn their attention to testing them extensively to determine if they should move on to testing in humans.

Scientists carry out *in vitro* and *in vivo* tests. *In vitro* tests are experiments conducted in the lab, usually carried out in test tubes and beakers and *in vivo* studies are those in living cell cultures and animal models.

Preclinical Toxicology Testing and IND Application: Preclinical testing analyzes the bioactivity, safety, and efficacy of the formulated drug product. This testing is critical to a drug’s eventual success and, as such, is scrutinized by many regulatory entities. During the preclinical stage of the development process, plans for clinical trials and an Investigative New Drug (IND) application are prepared.

The main stages of preclinical toxicology testing are:

Acute Studies: Acute tox studies look at the effects of one or more doses administered over a period of up to 24 hours. The goal is to determine toxic dose levels and observe clinical indications of toxicity. Usually, at least two mammalian species are tested. Data from acute tox studies helps determine doses for repeated dose studies in animals and Phase I studies in humans.

Repeated Dose Studies: Depending on the duration of the studies, repeated dose studies may be referred to as sub-acute, sub-chronic, or chronic. The specific duration should anticipate the length of the clinical trial that will be conducted on the new drug. Again, two species are typically required.

Genetic Toxicity Studies: These studies assess the likelihood that the drug compound is mutagenic or carcinogenic. Procedures such as the Ames test (conducted in bacteria) detect genetic changes. DNA damage is assessed in tests using mammalian cells such as the Mouse Micronucleus Test. The Chromosomal Aberration Test and similar procedures detect damage at the chromosomal level.

Reproductive Toxicity Studies: Segment I reproductive tox studies look at the effects of the drug on fertility. Segment II and III studies detect effects on embryonic and post-natal development. In general, reproductive tox studies must be completed before a drug can be administered to women of child-bearing age.

Carcinogenicity Studies: Carcinogenicity studies are usually needed only for drugs intended for chronic or recurring conditions. They are time consuming and expensive, and must be planned for early in the preclinical testing process.

Toxicokinetic Studies: These are typically similar in design to PK/ADME studies except that they use much higher dose levels. They examine the effects of toxic doses of the drug and help estimate the clinical margin of safety.

Pre Clinical Evolutions (Animal Studies)

The candidate drug is subjected to extensive pharmacological testing *in vitro* and *in vivo* on animal models (mice, rats, pigs, dogs). Major areas of research are:

1. Acute, substance and chronic toxicity studies (toxicity profile)
2. Therapeutic index (safety and efficacy evolution): it is the ratio of median lethal dose (LD50) for a drug to the median effective dose (ED50).
3. Absorption, Distribution, Metabolism & Elimination ADME studies (Pharmacokinetics)

Pharmacokinetics and Drug Disposition

Pharmacokinetic (PK) or ADME (Absorption/Distribution/Metabolism/Excretion) studies provide useful feedback for formulation scientists. PK studies yield parameters such as AUC (area under the curve), C_{max} (maximum concentration of the drug in blood), and T_{max} (time at which C_{max} is reached). Later on, this data from animal PK studies is compared to data from early stage clinical trials to check the predictive power of animal models.

Drug development phases

There are three major phases in drug development:

1. Pre-clinical research and development
2. Clinical research and development
3. After the compound is on the market, a possible “post-marketing” Phase ³

Clinical Trials

Investigational New Drug (IND) Application and Safety

File IND with the FDA before clinical testing can begin; ensure safety for clinical trial volunteers through an Institutional Review Board.

Before any clinical trial can begin, the researchers must file an Investigational New Drug (IND) application with the FDA. The application includes the results of the preclinical work, the candidate drug’s chemical structure and how it is thought to work in the body, a listing of any side effects and manufacturing information. The IND

also provides a detailed clinical trial plan that outlines how, where and by whom the studies will be performed.

In addition to the IND application, all clinical trials must be reviewed and approved by the Institutional Review Board (IRB) at the institutions where the trials will take place. Statisticians and others are constantly monitoring the data as it becomes available. The FDA or the sponsor company can stop the trial at any time if problems arise. Finally, the company sponsoring the research must provide comprehensive regular reports to the FDA and the IRB on the progress of clinical trials.

Phase 1 Clinical Trial: In Phase 1 trials the candidate drug is tested in people for the first time. These studies are usually conducted with about 20 to 100 healthy volunteers. The main goal of a Phase 1 trial is to discover if the drug is safe in humans. Researchers look at the pharmacokinetics of a drug: How is it absorbed? How is it metabolized and eliminated from the body? They also study the drug’s Pharmacodynamic: Does it cause side effects? Does it produce desired effects? These closely monitored trials are designed to help researchers determine what the safe dosing range is and if it should move on to further development.

Phase 2 Clinical Trial: In Phase 2 trials researchers evaluate the candidate drug’s effectiveness in about 100 to 500 patients with the disease or condition under study, & examine the possible short-term side effects & risks associated with the drug. They also strive to answer these questions: Is the drug working by the expected mechanism? Does it improve the condition in question? Researchers also analyze optimal dose strength and

schedules for using the drug. If the drug continues to show promise, they prepare for the much larger Phase 3 trials.

Phase 3 Clinical Trial

In Phase 3 trials researchers study the drug candidate in a larger number (about 1,000-5,000) of patients to generate statistically significant data about safety, efficacy and the overall benefit-risk relationship of the drug. This phase of research is keys in determining whether the drug is safe and effective. It also provides the basis for labeling instructions to help ensure proper use of the drug. During the Phase 3 trial , researchers are also conducting many other critical studies, including plans for full scale production and preparation of the complex application required for FDA approval.

PHASE 0, 2A AND 2B TRIALS

Phase 0 Trial: The FDA has recently endorsed “micro dosing” or the “phase 0 trial,” which allows researchers to test a small drug dose in fewer human volunteers to quickly weed out drug candidates that are metabolically or biologically ineffective.

Phase 2a and 2b Trials: Sometimes combined with a phase 1 trial, a phase 2a trial is aimed not only at understanding the safety of a potential drug, but also getting an early read on efficacy and dosage in a small group of patients. The resulting phase 2b trial would be designed to build on these results in a larger group of patients for the sake of designing a rigorous and focused phase 3 trials.⁴

5,000 to 10,000 Compounds Yield 1 New Drug to Market																	
Step	Number of Compounds	Years															
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Discovery – identifying & screening	5,000—10,000																
Preclinical Testing - in laboratory and animal studies	250																
Phase I - Safety and dosage evaluated on 20-100 healthy human volunteers	5																
Phase II - Efficacy and side effects tested on 100-500 patient volunteers	1																
Phase III - Effectiveness and reactions to long-term use tested on 1,000 to 5,000 patient volunteers	1																
FDA Review and Approval	1																

New Drug Application (NDA) and Approval

Once all three phases of the clinical trials are complete, the sponsoring company analyzes all of the data. Submit application for approval to FDA. The NDA includes all of the information from the previous years of work, as well as the proposals for manufacturing and labeling of the new medicine.

FDA experts review all the information included in the NDA to determine if it demonstrates that the medicine is safe and effective enough to be approved. Following rigorous review, the FDA can either 1) approve the medicine, 2) send the company an “approvable” letter requesting more information or studies before approval can be given, or 3) deny approval.

Review of an NDA may include an evaluation by an advisory committee, an independent panel of FDA-appointed experts who consider data presented by company representatives and FDA reviewers. Committees then vote on whether the FDA should approve an application, and under what conditions.

NDA Forms and Electronic Submissions:

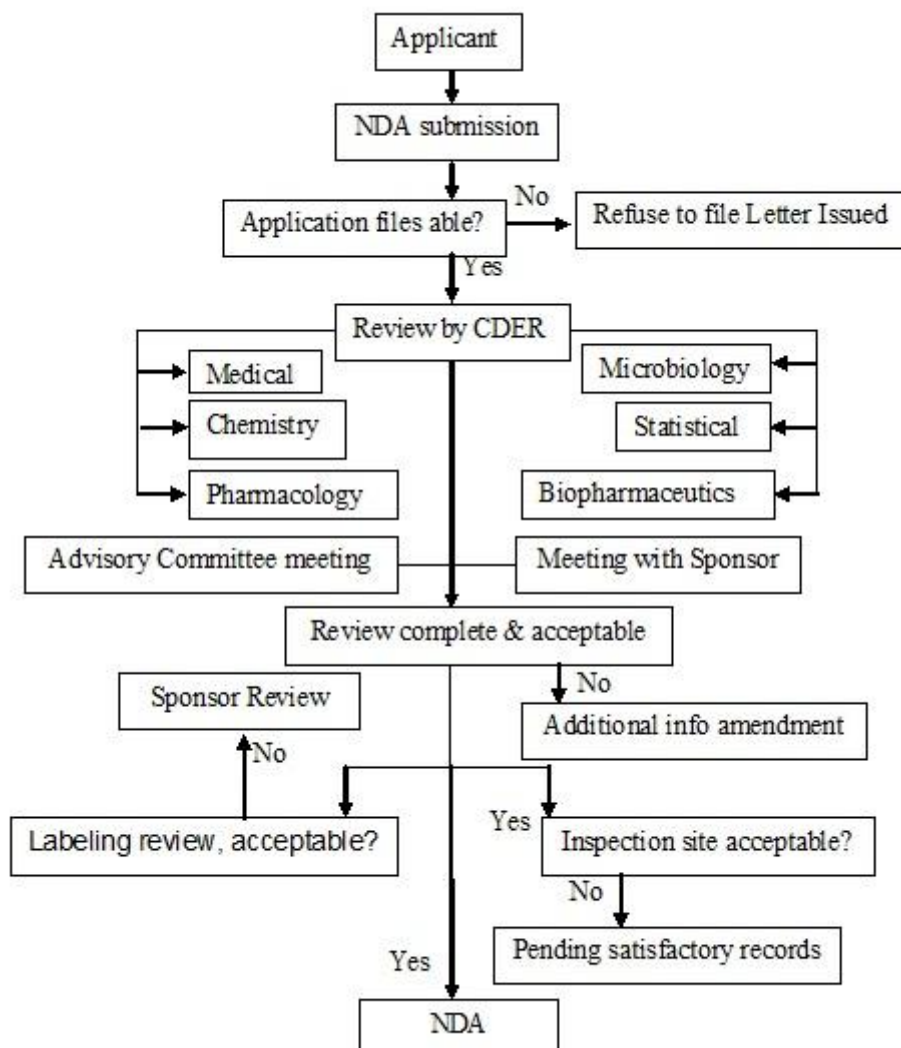
- Form FDA-356h. Application to Market a New Drug, Biologic, or An Antibiotic Drug For Human Use
- Form FDA-3397. User Fee Cover Sheet
- Form FDA-3331. New Drug Application Field Report.⁵

Review Time Frames (21 CFR 314.100):

This time frame includes:

- Within 180 days of receipt of an application, the FDA will review and issue an approval, approvable, or not approvable letter. This 180-day period is called the “review-clock”
- During the review period an applicant may withdraw an application (21 CFR 314-65) and later resubmit it.
- The time period may be extended by mutual agreement between the FDA and the applicant or as the result of submission of a major amendment (21 CFR 314.60)⁶

Review Process of NDA:⁷



BENEFIT VS. RISK: After close to a decade of testing, the company files a New Drug Application (NDA) with the FDA. Reported in the NDA are all the data gathered from all studies of the potential new drug, including the preclinical as well as clinical findings. In particular, it uses the information in the NDA to try to address three major concerns:

- 1) Because no drug has zero risk, the FDA must determine whether the benefits of the drug outweigh the risk, i.e., is the drug effective for its proposed use, and has an acceptable balance between benefits and risks been achieved?
- 2) Based on its assessment of risk and benefit, the FDA must decide what information the package inserts should contain to guide physicians in the use of the new drug.
- 3) Finally, the FDA must assess whether the methods used to manufacture the drug and ensure its quality are adequate to preserve the drug's identity, strength and purity.

Post Approval Activities

Manufacturing: Going from small-scale to large-scale manufacturing is a major undertaking. In many cases, companies must build a new manufacturing facility or reconstruct an old one because the manufacturing process is different from drug to drug. Each facility must meet strict FDA guidelines for Good Manufacturing Practices (GMP).

Ongoing Studies and Phase 4 Trials: Research on a new medicine continues even after approval. As a much

larger number of patients begin to use the drug, companies must continue to monitor it carefully and submit periodic reports, including cases of adverse events, to the FDA. In addition, the FDA sometimes requires a company to conduct additional studies on an approved drug in "Phase 4" studies.

Approval: Once FDA approves the NDA, the new medicine becomes available for physicians to prescribe. The company must continue to submit periodic reports to FDA, including any cases of adverse reactions and appropriate quality-control records. For some medicines, FDA requires additional studies (Phase IV) to evaluate long-term effects.

*Discovering & developing safe and effective new medicines is a long, difficult and expensive process. The research-based pharmaceutical industry will invest \$12.6 billion in research and development this year, and that investment has been doubling every five years.*⁸

Conclusion: The discovery and development of new medicines is a long, complicated process. Each success is built on many, many prior failures. Advances in understanding human biology and disease are opening up exciting new possibilities for breakthrough medicines. At the same time, researchers face great challenges in understanding and applying these advances to the treatment of disease. These possibilities will grow as our scientific knowledge expands and becomes increasingly complex. Research-based pharmaceutical companies are committed to advancing science and bringing new medicines to patients.

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