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DRUG DISCOVERY CHALLENGES

Shaik Abdul Saleem*, Dr. J. N. Suresh Kumar and Shaik Munwar

Assistant professor, Department of Pharmacology, Narasaraopeta institute of pharmaceutical sciences, Kotappakonda Road, Yallamanda post, Narasaraopeta, Guntur District, Andhra Pradesh-522601.

***Corresponding Author: Shaik Abdul Saleem**
Assistant professor, Department of Pharmacology, Narasaraopeta institute of pharmaceutical sciences, Kotappakonda Road, Yallamanda post, Narasaraopeta, Guntur District, Andhra Pradesh-522601. **Mail ID**: pharmacy14443@gmail.com

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ABSTRACT

Low productivity, rising R&D costs, dissipating proprietary products and dwindling pipelines are driving the pharmaceutical industry to unprecedented challenges and scrutiny. In this presentation we reflect on the current status of the pharmaceutical industry and reasons for continued low productivity. An emerging 'symbiotic model of innovation', that addresses underlying issues in drug failure and attempts to narrow gaps in current drug discovery processes, is discussed to boost productivity. The model emphasizes partnerships in innovation to deliver quality products in a cost-effective system. We are also discussing diverse options to build a balanced research portfolio with higher potential for persistent delivery of drug molecules.

KEYWORDS: Drug, IND, NDA and Clinical Trails.

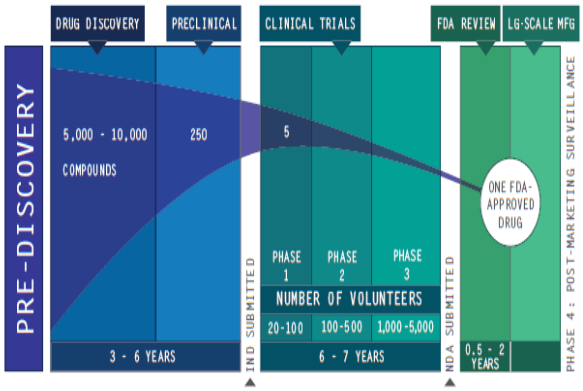
- The task of discovering and developing safe and effective drugs is gaining a lot of importance these days.
- It is becoming an increasingly challenging undertaking.
- Facts of Drug discovery and development:

1. Time 10-15 years
2. Cost $800 million-$1 billion
3. Drugs tested 5000-10,000
4. Subjects tested 1000-5000
5. Drugs approved 1
6. Modern drug discovery is the product of cooperation.
7. Both public and private organizations play unique roles in translating basic research into medicine.
8. Major bio pharmaceutical companies are the primary source of R&D funding for new medicines.
9. Smaller companies conduct basic research, drug discovery, preclinical experiments and, in some cases, clinical trials.
10. The National Institutes of Health (NIH) provides leadership and funding stimulates basic research and early stage development of technologies.

- Number of people involved is similar to a small telephone directory.
  100-2000 people from various fields of science
- Success requires

1. Immense resources
2. The best scientific minds,
3. Highly sophisticated technology
4. Complex project management.

- It also takes persistence and, sometimes lucks.



- The production of a new drug involves following steps:

1. Discovery
2. Preclinical Testing
3. Clinical Trials
4. NDA and Approval
5. Manufacture
6. Post-Marketing Surveillance
7. The challenge of finding a new drug is an incredible thing.
8. The discovery process includes all early research to identify a new drug candidate and testing it in the lab.

9. The process takes approximately 3-6 years. By the end, researchers hope to have a Promising candidate drug to test in people.

- Discovery involves following:

1. Prediscovery- Understanding the disease
2. Target Identification- Choose a molecule to target with a drug
3. Target Validation- Test the target and Confirm its role in disease
4. Drug Discovery- Find a promising lead compound that could become a drug
5. Early Safety tests- Perform initial tests on Leads
6. Lead Optimization- Alter the structure of lead compounds to improve properties

- 5000-10,000 molecules are selected and tested.
- Drug Discovery (*Finding a lead compound*) can be made in any of the following methods:

1. From nature
2. Ethnopharmacognosy
3. High-throughput screening
4. Biotechnology

- **Scientists test Absorption, Distribution, Metabolism, Excretion and Toxicological (ADME / Tox) properties, or "pharmacokinetics," of each lead.**
- Successful drugs must be:

1. Absorbed into the bloodstream,
2. Distributed to the proper site of action in the body,
3. Metabolized efficiently and effectively,
4. Successfully excreted from the body and
5. Demonstrated to be not toxic.
6. With more optimized compounds in hand, researchers turn their attention to testing them extensively to determine if they should move on to testing in humans.
7. Scientists carry out *in vitro and in vivo tests.*
8. They try to understand a drug's *Kinetics, Toxicity and Carcinogenicity.*
9. The U.S. Food and Drug Administration (FDA) requires extremely thorough testing before the candidate drug can be studied in humans.

- Around 250 drugs are tested in Pre-clinical phase of which at least 5 molecules are selected as *'Candidate drugs'*.
- After selection of Candidate drugs, Sponsors file an IND (*Investigational New Drug*) Application to FDA.
- The application includes

1. The results of the preclinical work,
2. The candidate drug's chemical structure and
3. How it is thought to work in the body,
4. A listing of any side effects and
5. 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.
- This process includes the development of appropriate informed consent, which will be required of all clinical trial participants.
- The FDA or the sponsor company can stop the trial at any time if problems arise.
- The company sponsoring the research must provide comprehensive regular reports to the FDA and the IRB on the progress of clinical trials.
- This phase is the longest one in drug development ranging from 2-10 years.
- A suitable clinical trial design is developed. These include:

1. Placebo controlled trials
2. Randomized trials
3. Double blinded studies

- Clinical trials comprise of three phases-
- Phase 1
- Phase 2
- Phase 3

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.
- Usually last 6 months to 1 year (30% of drugs fail Phase 1 testing)
- Used to determine

1. Pharmacokinetic data
2. Pharmacodynamic data
3. Max. tolerated dose
4. Adverse reactions profile

Phase 2 trials

- In Phase 2 trials researchers evaluate the candidate drug's effectiveness in about 100 to 500 patients with the disease or condition under study
- Usually last Few weeks - 2 years (37% of drugs fail Phase 2 testing)
- Used to know

1. Preliminary evidence of efficacy
2. Pharmacodynamic effects in patients
3. Optimal dosage ranges and dosing schedule

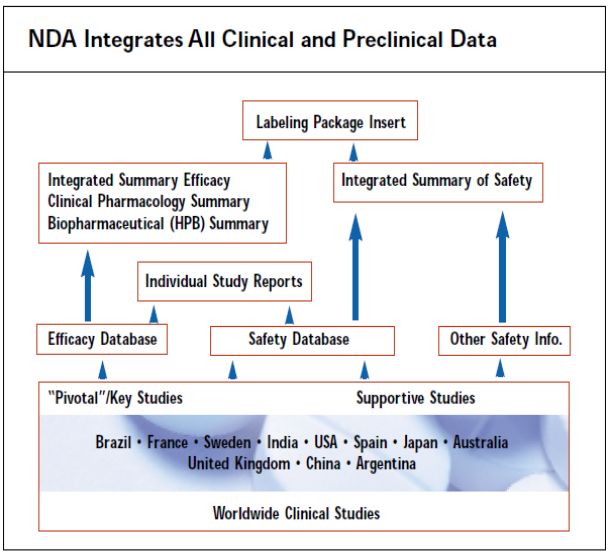
- Phase 2 trials are followed by a meeting with FDA to Obtain agreement on Phase 3 adequate and well controlled study design and analysis plan

Phase 3 trials

- In Phase 3 trials researchers study the drug candidate in a larger number (about 1,000-5,000) of patients.
- Usually last 3 years (6% fail Phase 3 testing)

- Used for
- Confirmation of efficacy
- Establishment of complete safety profile
- Base of regulatory information (labeling)
- Assessement of risk/benefit
- Phase 3 trials are both the costliest and longest trials.
- Hundreds of sites around the world participate in the study to get a large and diverse group of patients.
- Coordinating all the sites and the data coming from them is a monumental task.
- In addition to these Trials additional special trials should be performed to evaluate drug in:

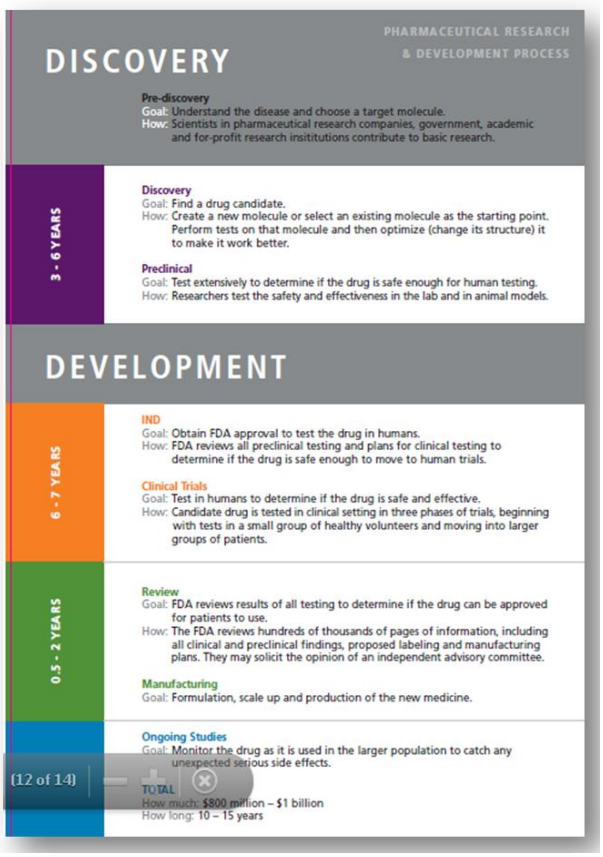
1. Special populations
2. Interactions
3. Special conditions
4. Special toxicities
5. Addiction potential
6. Once all three phases of the clinical trials are complete, the sponsoring company analyzes all of the data. If the findings demonstrate that the experimental medicine is both safe and effective, the company files *a New Drug Application* (NDA) with the FDA requesting approval to market the drug.
7. The NDA includes *an integrated summary of efficacy (ISE) and of safety (ISS).*
8. NDA contains all the pre-clinical and clinical data from previous 7-10 years of study.
9. NDA contains several thousands of pages of reports.



- When evaluating NDAs, regulatory agencies look at:

1. Validity of pivotal studies
2. Replicability of pivotal studies (consistency across studies)
3. Establishment of supportable dosage and dose regimen(s)
4. Clinical relevance of efficacy results
5. Clinical seriousness of safety profile (in context of seriousness of condition being treated)
6. Over all usefulness of drug (Risk/Benefit ratio)
7. Generalizability across populations (demographic groups, concomitant medications, intercurrent diseases, geographic regions, and even cultural groups)

- FDA assures that a drug claimed to be safe and effective for treatment of a specified disease or condition has, in fact, been proven to be so.
- 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.
- The FDA takes about 1 year to review a typical NDA.
- 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.
- 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).
- Research on a new medicine continues even after approval.
- These studies are generally termed as Phase 4 trials
- 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.
- These trials can be set up to evaluate long-term safety or how the new medicine affects a specific subgroup of patients.
- Yearly safety reports must be filed with the applicable regulatory agencies as long as a drug remains on the market.
- If safety concerns arise, the FDA may demand withdrawal of a From the market anytime.



The discovery and development of new medicines is a long, complicated process.

- Research-based pharmaceutical companies are committed to advancing science and bringing new medicines to patients.
- Increased support from Governments and Organizations may help in development of safer and cost effective medicines.

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