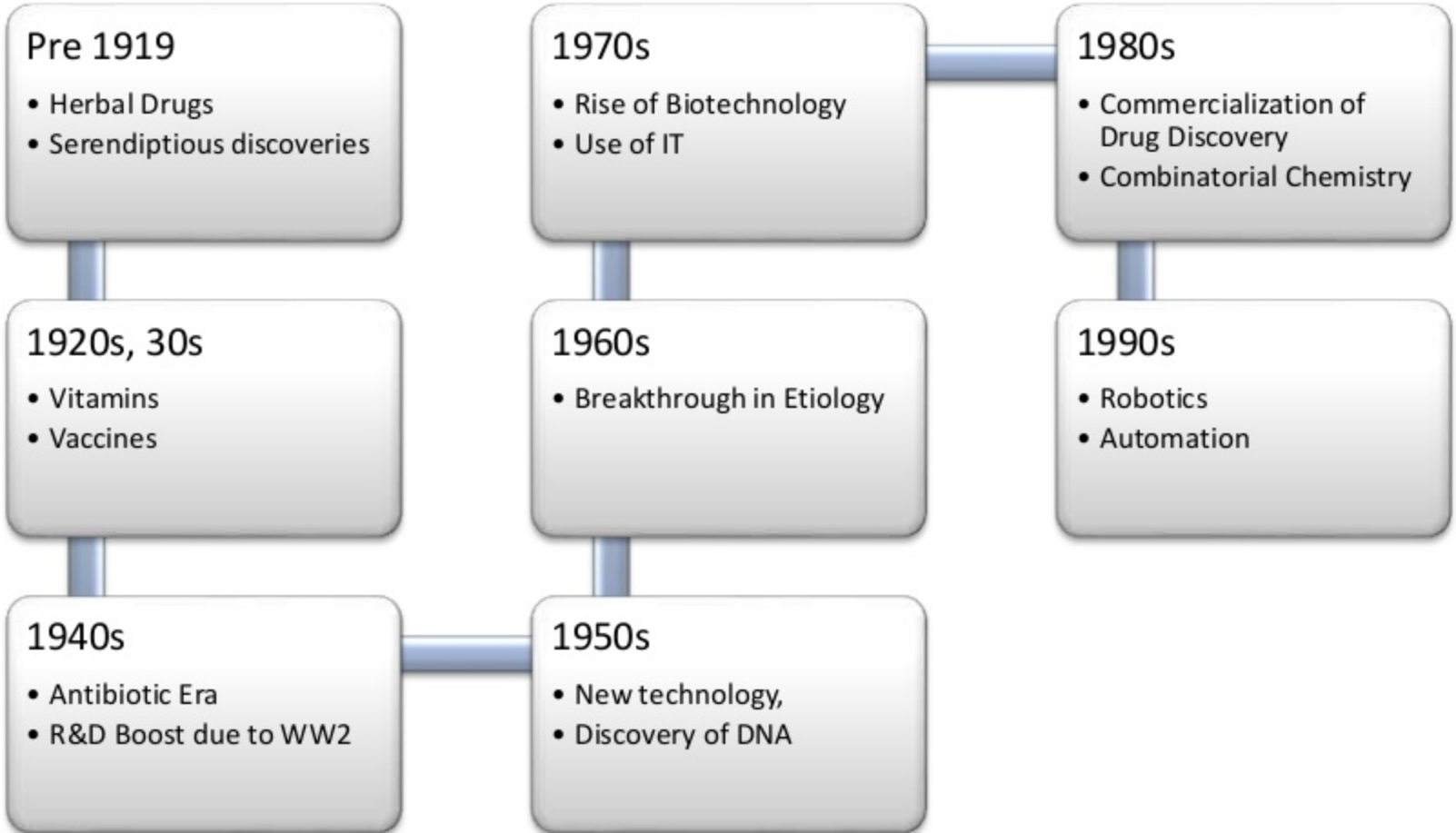

DRUG DISCOVERY
&
DEVELOPMENT

Introduction

- In the past most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery.
- But now we know diseases are controlled at molecular and physiological level.
- Also shape of an molecule at atomic level is well understood.
- Information of Human Genome

History of Drug Discovery :

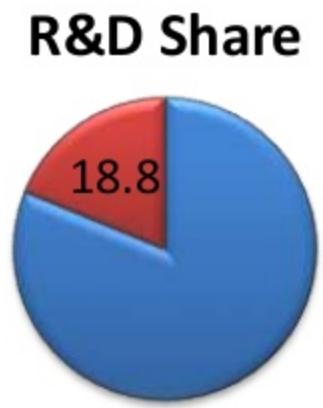


Registration:

- The Ministry of health & Family Welfare and the Ministry of Chemicals & Fertilizers have major role in regulation of IPM.
- NDA must be submitted to DCGI
- Phase III study reported to CDL, Kolkata
- Package inserted approved by DCI
- Marketing approval from FDA

Market Scenerio:

- ~$800 M spent to bring a new drug to market.
- $127 Billion spent on Pharma R&D in 2010
- Share of CROs in research operations is 27%
- World CRO market is 16.3 B (Indian share $500 M)



Top CROs (By Revenue)

Contract Research Organizations	Revenue
Quintiles	$2.5 Billion
Pharmaceutical Product Development	$1.8 Billion
Covance	$1.4 Billion
Charles River Laboratories	$1.2 Billion
Parexel	$930 Million
Icon	$887 Million
Kendle	$590 Million
Pharmanet	$470 Million
PRA International	$410 Million
4G Pharmacovigilance	$391 Million

Top CROs (India)

Contract Research Organizations	Location
Actimus Biosciences	Hyderabad
Advinus Therapeutics	Bangalore
Aurigene Discovery technologies	Bangalore
Chembiotek	Kolkata
GVK Biosciences	Hyderabad
Jubilant Organosys	Bangalore
Ranbaxy Life Sciences	Mumbai
Reliance Life Sciences	Mumbai
Suven Life Sciences	Hyderabad
Syngene	Bangalore

Most valuable R&D Projects

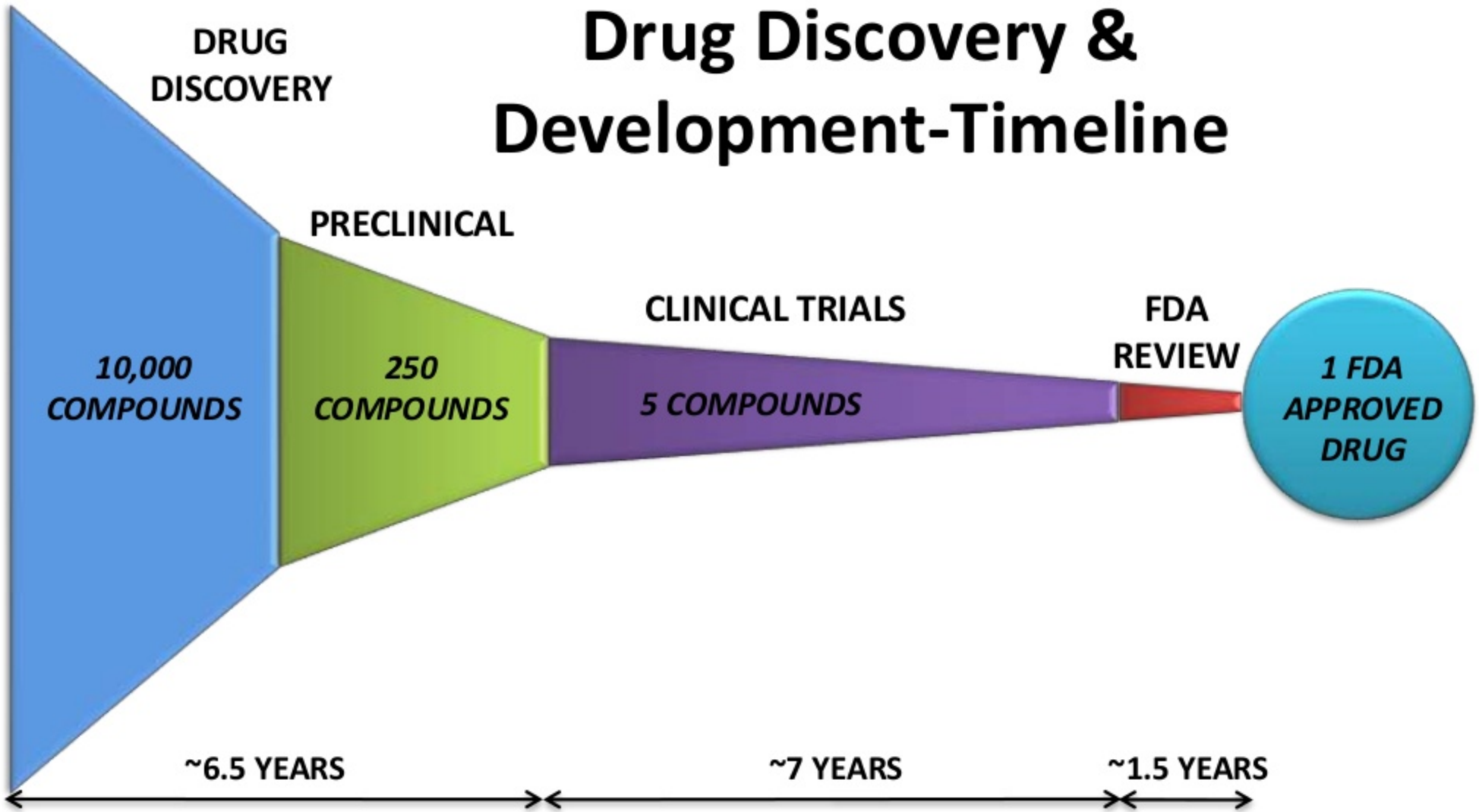
Rank	Product	Company	Phase	Pharmacological class	Today's NPV($mn)
1	Degludec	Novo Nordisk	Phase III	Insulin	5,807
2	Tofacitinib	Pfizer	Phase III	JAK-3 inhibitor	4,953
3	BG-12	Biogen Idec	Phase III	Fumarate	4,666
4	Incivek	J & J	Phase IV	Hep C protease inhibitor	4,332
5	Relovair	Theravance	Phase III	Corticosteroid	4,241
6	DR Cysteamine	Undisclosed	Phase III	Lysosomal transport modulator	4,155
7	AMR 101	Undisclosed	Phase III	Omega-3 fatty acid	4,052
8	Eliquis	Bristol Myers Squibb	Phase IV	Factor Xa inhibitor	3,836
9	Eliquis	Pfizer	Phase IV	Factor Xa inhibitor	3,592
10	Bexssero	Novartis	Phase IV	Meningococcal B vaccine	3,250

Top Companies by R&D Expense:

Sr. No.	Company	R & D spend($bn),2010
1	Novartis	7.9
2	Merck & Co	8.1
3	Roche	7.8
4	GlaxoSmithKline	5.7
5	Sanofi	5.8
6	Pfizer	9.1
7	Johnson & Johnson	4.5
8	Eli Lilly	4.7
9	AstraZeneca	4.2
10	Takeda	3.4
11	Bayer	2.3
12	Bristol-Myers Squibb	3.3
13	Boehringer Ingelheim	3.1
14	Amgen	2.8
15	Novo Nordisk	1.7

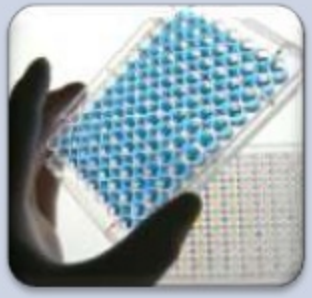
Drug Development Cost Break-up

R&D Function	%
Discovery/Basic Research	
Synthesis & Extraction	10.0
Biological Screening & testing	14.2
Preclinical Testing	
Toxicology & Safety testing	4.5
Pharmaceutical Dosage Formulation	7.3
Clinical Trials	
Phase I, II, III	29.1
Phase IV	11.7
Manufacturing & QC	8.3
IND & NDA	4.1
Bioavailability	1.8
Others	9.0
Total	100.0

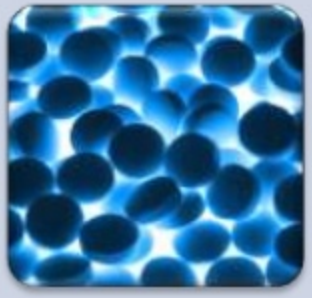

Drug Discovery & Development-Timeline
DRUG DISCOVERY
PRECLINICAL
CLINICAL TRIALS
FDA REVIEW
10,000 COMPOUNDS
250 COMPOUNDS
5 COMPOUNDS
1 FDA APPROVED DRUG
~6.5 YEARS
~7 YEARS
~1.5 YEARS

Drug Discovery

- Drugs Discovery methods:
  - Random Screening
  - Molecular Manipulation
  - Molecular Designing
  - Drug Metabolites
  - Serendipity





Target Selection

- Cellular and Genetic Targets
- Genomics
- Proteomics
- Bioinformatics

Lead Discovery

- Synthesis and Isolation
- Combinatorial Chemistry
- Assay development
- High-Throughput Screening

Medicinal Chemistry

- Library Development
- SAR Studies
- In Silico Screening
- Chemical Synthesis

In Vitro Studies

- Drug Affinity and Selectivity
- Cell Disease Models
- MOA
- Lead Candidate Refinement

In Vivo Studies

- Animal models of Disease States
- Behavioural Studies
- Functional Imaging
- Ex-Vivo Studies

Clinical Trials and Therapeutics

Cellular & Genetic Targets

Genomics

Proteomics

Bioinformatics

Target Selection

- Target selection in drug discovery is defined as the decision to focus on finding an agent with a particular biological action that is anticipated to have therapeutic utility — is influenced by a complex balance of scientific, medical and strategic considerations.
- Target identification: to identify molecular targets that are involved in disease progression.
- Target validation: to prove that manipulating the molecular target can provide therapeutic benefit for patients.

Target Selection → Lead Discovery → Medicinal Chemistry → In Vitro Studies → In Vivo Studies → Clinical Trials

Cellular & Genetic Targets

Genomics

Proteomics

Bioinformatics

Target Selection

Biochemical Classes of Drug Targets

- G-protein coupled receptors - 45%
- enzymes - 28%
- hormones and factors - 11%
- ion channels - 5%
- nuclear receptors - 2%

Techniques for Target Identification

Cellular & Genetic Targets

Genomics

Proteomics

Bioinformatics

Cellular & Genetic Targets:

Involves the identification of the function of a potential therapeutic drug target and its role in the disease process.

For small-molecule drugs, this step in the process involves identification of the target receptors or enzymes whereas for some biologic approaches the focus is at the gene or transcription level.

Drugs usually act on either cellular or genetic chemicals in the body, known as targets, which are believed to be associated with disease.

Target Selection → Lead Discovery → Medicinal Chemistry → In Vitro Studies → In Vivo Studies → Clinical Trials

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Cellular & Genetic Targets:

Scientists use a variety of techniques to identify and isolate individual targets to learn more about their functions and how they influence disease.

Compounds are then identified that have various interactions with the drug targets that might be helpful in treatment of a specific disease.

Target Selection → Lead Discovery → Medicinal Chemistry → In Vitro Studies → In Vivo Studies → Clinical Trials

Cellular & Genetic Targets

Genomics

Proteomics

Bioinformatics

Genomics:

The study of genes and their function. Genomics aims to understand the structure of the genome, including the mapping genes and sequencing the DNA.

Seeks to exploit the findings from the sequencing of the human and other genomes to find new drug targets.

Human Genome consists of a sequence of around 3 billion nucleotides (the A C G T bases) which in turn probably encode 35,000 – 50,000 genes.

Target Selection → Lead Discovery → Medicinal Chemistry → In Vitro Studies → In Vivo Studies → Clinical Trials

Cellular & Genetic Targets

Genomics

Proteomics

Bioinformatics

Genomics:

Drew's estimates that the number of genes implicated in disease, both those due to defects in single genes and those arising from combinations of genes, is about 1,000

Based on 5 or 10 linked proteins per gene, he proposes that the number of potential drug targets may lie between 5,000 and 10,000.

Single Nucleotide Polymorphism (SNP) libraries: are used to compare the genomes from both healthy and sick people and to identify where their genomes vary.

Target Selection → Lead Discovery → Medicinal Chemistry → In Vitro Studies → In Vivo Studies → Clinical Trials

Cellular & Genetic Targets

Genomics

Proteomics

Bioinformatics

Proteomics:

It is the study of the proteome, the complete set of proteins produced by a species, using the technologies of large – scale protein separation and identification.

It is becoming increasingly evident that the complexity of biological systems lies at the level of the proteins, and that genomics alone will not suffice to understand these systems.

It is also at the protein level that disease processes become manifest, and at which most (91%) drugs act.

Therefore, the analysis of proteins (including protein-protein, protein-nucleic acid, and protein ligand interactions) will be utmost importance to target discovery.

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