Drug Development: Why Does it Cost so Much?

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Drug Development

• Process by which new chemical entities (or biologics) move from discovery to pre-clinical evaluation to regulatory approval for safe and effective use in man for the cure, mitigation or prevention of disease

• Requires: genome science, chemical synthesis, animal pharmacology and toxicology, drug formulation, analytical chemistry, clinical pharmacology, medicine, statistics and epidemiology
Drug Development

• Goal: develop a plan that has clear objectives, is dynamic, and evolves over time

• Outcomes:
  – Approved drug
  – Termination of development with the least investment
Drug Development Process / Life Cycle Activities

**DISCOVERY**
- Discovery effort (planning and execution)

**DEVELOPMENT**
- Development and Global Registration (planning and execution)

**PRODUCT**
- Product Life Cycle Management (planning and execution)
  - Approval
  - First Launch
  - End of Patent

- Identify Drug Candidate
- Start Phase I
- Start Phase II
- Start Phase III
- Regulatory Submission
Drug Development Challenge

Bridging the Gap

Proof of concept & relevance

Early stage Gap Funding

The Valley of Death

Federally or state funded basic research New Ideas

Commercial Development
Drug Discovery Methods

- **Mechanism** based – identify target (e.g., receptor) → create knock-out, do high throughput screening → identify effective compounds → optimize

- **Function** based – screen compounds for ability to normalize function in cells and tissues from humans with disease or transgenic animals with human disease mutation

- **Physiology** based – use organ or animal models; large number of possible mechanisms; effective but slow
Drug Development Scenario: 

ASTHMA

• Is a new therapy needed? Are currently available therapies effective and safe?
• What type of new therapy should be pursued? Need to know pathophysiology, cell and molecular biology, genetics, environmental factors, etc.
  – anti-inflammatory, airway wall remodeling
• What are the best targets in that category?
  – leukotrienes, NO, proteases, cytokines
Drug Development Scenario: **ASTHMA**

- **What approach to take?** Traditional drug screens, clone receptor, antisense oligonucleotides, etc.
  - Soluble IL-4 receptors, anti-CD4 and anti-IgE antibodies

- **What pre-clinical and clinical testing is needed?**
  - *In vitro* testing, animal models
  - Human studies

- **What are the regulatory hurdles?**
  - IND
  - NDA
Therapeutic Advances from Drug Discovery

- Hypertension - ACE and All inhibitors
- Type 2 Diabetes Mellitus - new oral hypoglycemics
- Hypercholesterolemia - statins
- Peptic Ulcer Disease/GERD - PPIs
- Asthma - leukotriene modifiers, anti-IgE antibody
- Arthritis/Pain - COX-2 inhibitors
- Transplantation - immunosuppressants (cyclosporin, tacrolimus)
- Cancer – molecularly targeted treatments
Therapeutic Advances

• Modify disease - inflammatory diseases (e.g., ulcerative colitis, RA, psoriasis)
  – prevent progression
  – reverse changes

• Prevent disease - cancer, infections, CAD

• Infectious diseases - HIV, hepatitis C
Unmet Medical Needs

• Modify disease - emphysema
  – reverse changes
• Prevent disease - type 1 diabetes
• Infectious diseases
  – Antibiotic resistance
  – Some viral diseases (e.g., Ebola)
• Acute Respiratory Distress Syndrome (ARDS)
Drug Development

• Identify disease and target population
  – No therapy for severe disease
  – Therapies available but not ideal and large patient population

• Screen and identify lead compound through pre-clinical testing (lab and animal studies) - assess safety and biological activity (2 years)

• File Investigational New Drug (IND) application
Types of Studies

• Phase 0*
• Phase 1
• Phase 2 (2a and 2b)
• Phase 3 (3a and 3b)
• File NDA
• Phase 4
• Specialized studies
Phase 0 (Exploratory)

- Subtherapeutic doses ("microdose") of a new drug are given to a small group of patients (<15) for up to a week to determine pharmacokinetic and pharmacodynamic properties, and biodistribution (by imaging)
- Can be initiated with less or different pre-clinical support than a traditional phase 1 study
- Caveats:
  - Drug must have wide therapeutic index or target "serious diseases"
  - Target must be known
  - Validated biomarker must exist
  - No therapeutic benefit to participants
Phase 1 Studies

• First studies in humans after obtaining IND
• Single-dose followed by short-term multiple dose studies – follow-up for days to weeks
• Determine initial safety profile, maximally tolerated dose (MTD), and pharmacokinetic profile including ADME (absorption, distribution, metabolism, excretion)
• Usually 20-100 healthy volunteers
• For studies of “toxic” therapies (e.g., Oncology, AIDS studies) “volunteers” have the disease
• Duration ~1.5 years
Phase 2 Studies

• Determine effectiveness in the condition or disease of interest
• Define appropriate dose (dose-ranging studies)
• Begin to identify side effects/toxicity (over 4-6 weeks)
• Typically 100-300 patient volunteers
• Duration ~2 years
Phase 3 Studies

• Confirm effectiveness in larger studies
• Typically need 2 positive, well-designed studies
• Monitor adverse events over a longer period (12-24 weeks)
• 1,000-3,000 patient volunteers
• Duration ~2.5 years
• Need to scale-up manufacturing to ensure adequate supply of drug
Food/Drug/Disease Interaction Studies

- Effect of disease (e.g., liver, kidney, CHF)
- Interactions between new drug and other medications
- Drugs that affect activity of cytochrome P450
  - Coumadin
  - Medications by mouth
- Effect of meals on absorption (if drug taken by mouth)
- Effect of meals on absorption (if drug taken by mouth)
Phases 1 - 3

• Many questions unanswered at end of phase 3 studies
  – longer term toxicity (Vioxx, Avandia)
  – use in special populations
  – role of genetic factors

• Make plans to do these additional studies before completing phase 3 studies
Drug Development

• File New Drug Application (NDA) at end of phase 3 – FDA reviews data
  – 1 year
• Total time to introduction into the market
  – 8-10 years
• Patent protection ~20 years (~8-10 years after approval)
• Cost of developing a new drug $1+ billion
Phase 4/Additional Studies

• Compare to competitors
• New indications
• “Real-world” effectiveness (e.g., in practice setting)
• Effects in special populations (e.g., elderly, children)
• Define mechanisms of disease (often investigator-initiated)
• Pharmacoeconomics
• Pharmacogenetics
• Quality of life
Investigator-Initiated Trials

• Goals
  – Explore different/new uses, doses or patient subsets
  – Explore basic physiologic and pathophysiologic mechanisms

• Specific investigator and manufacturer requirements
  – Investigator IND (reference company file)
  – Reports to FDA and company
  – Company may assist with study design and adverse event reporting, and provide drug
Pharmacoeconomics

• Study of net economic impact of pharmaceutical selection and use on total cost of delivering health care
• Health care utilization (efficiency) vs. efficacy and safety
• “Value” – a benefit for money spent
• Perceptions of Value based on
  – Individual metrics of benefit
  – Perspective – patient, provider, payer, or society
  – Cost, efficacy, quality of life (QOL)
  – Type of therapy – new/unique vs. add-on vs. me too
• Value is a multivariate concept
  – Costs and consequences, plus
  – Economic, clinical, humanistic outcome dimensions
Quality of Life

- Efficacy, safety and cost-effectiveness studies – all viewed as important in decision making
- QOL studies – often viewed as supplemental (key in biologicals)
- QOL studies
  - Disease specific (FACT in cancer, AQLQ in asthma)
  - Generic (SF-36 health survey)
- What role does QOL play in drug trials and formulary decisions?
- Who benefits from QOL data?
- Who should pay for better QOL information?
Pharmacogenetic Studies

• Goals
  – Identify therapy with high likelihood of success and/or reduced toxicity in individual patients
  – Improve individual responses
  – Reduce use of ineffective treatments
  – Reduce cost of drug development – more efficient trials
Pharmacogenetic Studies

• Potential disadvantages
  – Smaller target population with reduced sales
  – Cost of genotyping
  – Additional patient consent
  – Unclear clinical significance
  – Ethics including impact on insurance coverage
Failure Rates of New Chemical Entities

- 10,000-30,000 new substances identified in basic research (increasing with genome screening)
- 10-20 reach chemical synthesis and screening
- 5-10 undergo pre-clinical testing
- 2-5 enter clinical trials
- 1 is approved and marketed
Failure Rates of INDs

• 33% enter phase 2
• 27% enter phase 3
• 20% undergo FDA review
• Not all that undergo review are approved
Why are drugs not approved?

• Inadequate characterization of dose-response profiles (peak response and time-course of response during dosing interval)
• Flaws in study design or drug development plan – inappropriate studies, difficult to interpret studies, studies based on unfounded assumptions
• Inadequate characterization of the benefit-risk profile
• Inadequate proof of improved quality of life or pharmacoeconomic benefit
Successful Clinical Drug Development

• Requires
  – Right Disease
  – Right Drug
Successful Clinical Drug Development: *DISEASE*

- Defined target disease with known natural history
- Defined patient population with the target disease
- Identified patient characteristics potentially responsive to therapeutic interventions
- Defined and quantifiable measures of the disease which:
  - change over a sufficiently short period of time for use in prospective studies
  - sensitive in dose-response fashion to therapy
Successful Clinical Drug Development: 

**DRUG**

- Profile of non-limiting pre-clinical toxicological findings
- Pharmaceutical formulation which gets drug to site of action
- Methods to characterize pharmacokinetic and pharmacodynamic properties of the drug in man
- Defined and measurable non-disease-related effects of the drug
Key Trends in Drug Development

• Consolidation
• Outsourcing
• Internationalization
• Economic pressures for more rapid drug development
• Pediatric studies to extend patent by 6 months
Future Drug Development

• Gene is a drug
• Patient becomes a bioreactor
• Gene therapy is limited to patient, not offspring
• New vector delivery systems - non-immunogenic, last $> 1$ year
Adherence to Treatment

“HAVE SOMEONE FORCE ONE OF THESE DOWN YOUR THROAT EVERY SIX HOURS.”