# The Drug Development Process and Design of Clinical Trials

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# Clinical Trial Design Guidance

- Clinical Trial: a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions. (NIH, PHS398 instructions)
- OHSU Mission Code 54: A study of a drug (device, or diagnostic) where it "…is administered or dispensed to, or used involving, one or more human subjects" and is a "prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical...interventions (drugs,...devices, or new ways of using known drugs...or devices)."
- Phases of Clinical Trials
  - For NIH studies: SF424 and PHS398 instructions
  - For drug development: Code of Federal Regulations (CFR): Title 21, Part 312, Section 21 (21CFR312.21)

# Regulatory Definitions

- *IND*: Investigational New Drug Application
- *IDE*: Investigational Device Exemption
- *NDA*: New Drug Application
- *PMA*: Premarket Approval
- *BLA*: Biologic License Application

# When is an IND/IDE Required?

- The product is investigational (has not been cleared for marketing by the FDA) or;
- The investigation of the product (even if cleared for marketing) poses a significantly increased risk or decreased acceptability of risk
  - Different dose or schedule
  - Different route of administration
  - Different patient population

(21CFR312.2)

# Approval Process Summary

| Timeframe | Investigational Product Type | | |
|---|---|---|---|
| | Drug | Biologic | Device (Class III) |
| Start of Development[1] | IND | IND | IDE |
| End of Development[2] | NDA | BLA | PMA |

[1]Before studied in humans

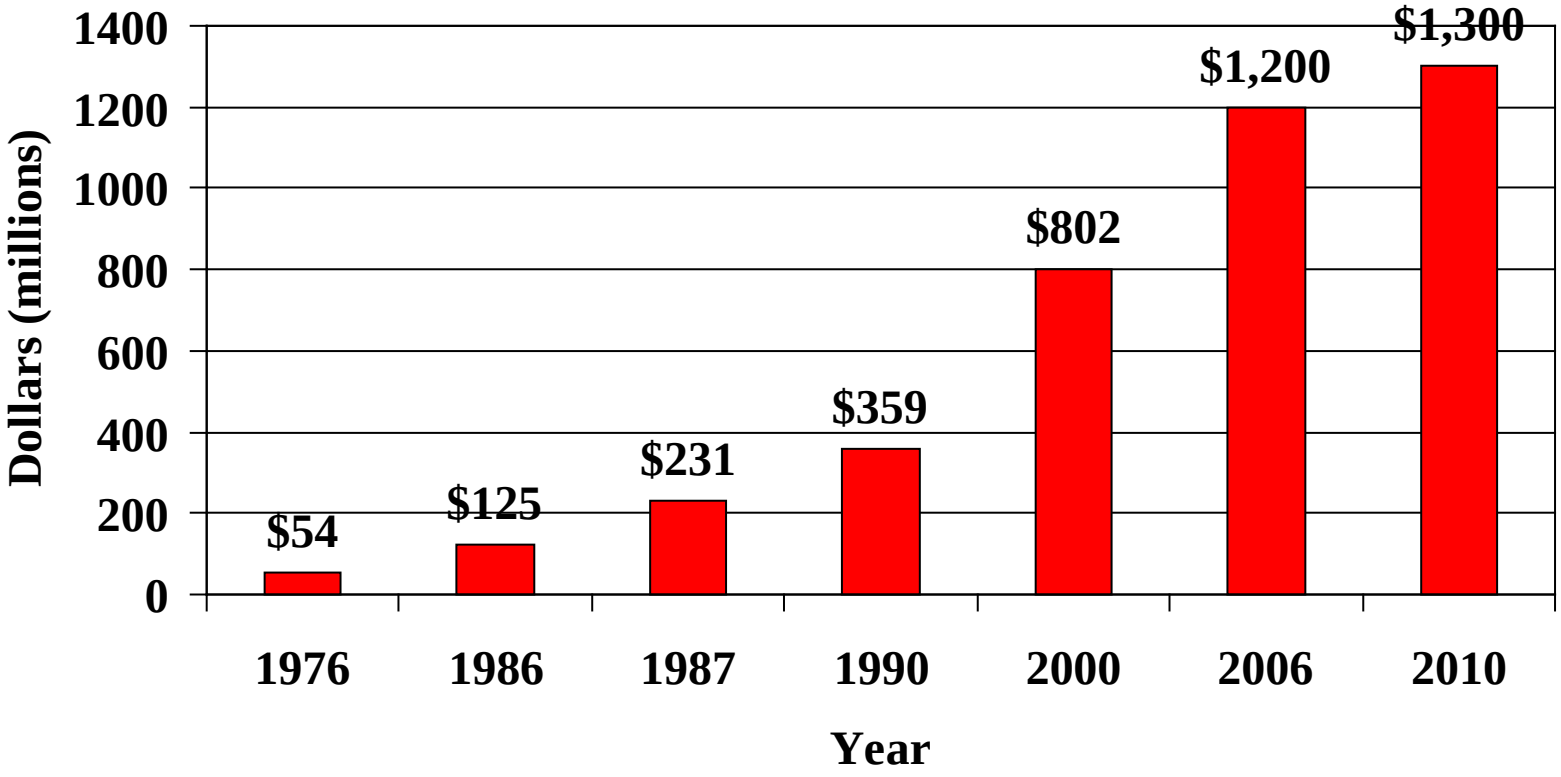
[2]To obtain approval to market

# Drug Development Overview[1]

| Drug Discovery | | | Drug Development | | | | | | Market |
|---|---|---|---|---|---|---|---|---|---|
| | **Early Research /Preclinical Testing** | | **Clinical Trials** | | | | **FDA** | | **Phase IV** |
| | | | **Phase I** | **Phase II** | **Phase III** | | | | |
| **Years** | 6.5 | | 1.5 | 2 | 3.5 | | 1.5 | 15 Total | Additional post-marketing testing required by FDA |
| **Test Population** | Laboratory and animal studies | **File IND at FDA** | 20 to 80 healthy volunteers | 100 to 300 patient volunteers | 1000 to 3000 patient volunteers | **File NDA at FDA** | Review process/ approval | | |
| **Purpose** | Assess Safety and biological activity | | Determine safety and dosage | Evaluate effectiveness look for side effects | Confirm effectiveness, monitor adverse reactions from long-term use | | | | |
| **Success Rate** | 5,000 compounds evaluated | | 5 enter trials | | | | 1 approved | | |

[1]The Drug Development and Approval Process, B. Spilker, PhRMA Publications.

# Cost of Developing a New Drug




*Source: Hansen, 1979; Weggins, 1987, DiMasi, 1991: Office of Technology Assessment, 1993;Tufts Center for Drug Development, 2001, 2006: DiMasi & Grabowski, 2007, 1993;Tufts Center for Drug Development, 2010.*

# Preclinical Testing

- Includes:
  - Basic laboratory testing (test tube and petri dish)
  - Animal testing
- To test:
  - Biological activity
  - Toxicology (carcinogenicity, teratogenicity)
  - Physical chemistry
    - Formulation
    - Interactions
    - Stability

# Phase I

- First studies in humans
- To evaluate:
  - Dose
    - Maximum and minimum
    - Schedule/route/regimen
  - Safety
  - Toxicity
  - Other
    - Pharmacokinetics (PK) : Distribution and excretion of the drug
    - Pharmacodynamics (PD): Interactions with other agents

# Phase I (cont.)

- Subject population:
  - Healthy normal subjects or end-stage patients
  - Men and women
- Sample size:  tens
- Typical study design:
  - Cohort dose escalation or multiple dose administration
  - Single center (prolonged observation)
- Usual study duration:  ~1 year

# Phase II

- To evaluate:
  - Efficacy
  - Target population
  - Safety
  - Dose range
- Utilizes the regimen determined in phase I
- Subject population:
  - Potential target population of patients
  - May be heterogenous indication

# Phase II (cont.)

- Sample size: ~50 - 200 patients
- Typical study design:
  - Controlled (placebo or comparator)
  - Open label or blinded/randomized
  - 2 - 4 study sites
  - Often surrogate endpoints
- Usual study duration: 1 - 2 years

# Phase III

- Also called “Pivotal trial”, primary evidence for FDA submission
- Final manufacturing facillities
- To evaluate:
  - Effectiveness
  - Validity of endpoints
  - Long term safety
- Subject population:
  - Target population of patients
  - Single specific indication/study

# Phase III (cont.)

- Sample size:  hundreds - thousands
- Typical study design:
  - Controlled to standard treatment (placebo if no standard)
  - Randomized, double blinded
  - Multicenter
  - Validated endpoints
- Usual study duration:  Usually >2 years

# Phase IV

- After approval of the drug/device (post-marketing)
- Maybe required as contingency of approval
- To evaluate:
  - Differential effects in segments of the population
    - Age
    - Gender
    - Race
  - Low incidence toxicities/longterm safety
  - New uses/indications
  - New combinations with other drugs
  - New dosages/regimens

# Phase IV (cont.)

- To evaluate (cont.)
  - Marketing issues
    - Comparison with competitor
    - Market priming/testing
    - Market expansion/exposure
  - Drug utilization
    - Cost effectiveness
    - Quality of life
    - Compliance
- May be designed like Phases I-III
- May require an IND if poses an increased risk