

# Drug Development & the FDA

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## Goals & Objectives

- Be able to describe
  - major regulatory events in the drug & biologic, medical device (medical product) and dietary supplement development process
  - concepts of “safety” and “effectiveness”
  - role of hypothesis testing in medical product development

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## Outline

- History of FDA Regulations – really fast; see FDA web site – [www.fda.gov](http://www.fda.gov)
- Drug & biologic, medical device and dietary supplement development process
- Safety & Effectiveness
- International Conference on Harmonisation
  
- Device & Dietary Supplement Development
- Questions any time

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## An History of Disasters -- Drug Emphasis

- Vaccine Act 1813
  - fraudulent smallpox vaccines
- Food & Drugs Act 1906
  - Upton Sinclair, *The Jungle*
  - truthful label (strength & purity)
- Food, Drug & Cosmetic Act 1938
  - “elixir” of sulfanilamide
  - safety, IND, NDA, 60-day review

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## History (2)

- Durham-Humphrey Amendment 1951
  - collateral measures necessary for "safe" use
    - "Caution: Federal law prohibits ..."
    - Rx to OTC switch
- Kefauver-Harris Amendment 1962
  - Thalidomide
  - effectiveness; 180 day NDA review
- Guidelines for Reproductive Studies 1966
  - public pressure

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## History (3)

- Orphan Drug Act 1983
  - rare diseases
  - tax break; patent protection
- ANDA 1984
  - bioequivalence for generic drugs
- Codification of IND Regulations 1987
- Expedited Approval, Serious & Life-Threatening Diseases (AIDS) 1994 ["Subpart E"]
  - Phase 4

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## History (4)

- 1992 Prescription Drug User Fee Act
- 1994 Dietary Supplement Health And Education Act
- 1997 Food And Drug Administration Modernization Act
- 2002-3 Pediatric Labeling – legislation / rulemaking / legal challenges

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## Drug/Biologic History Summary

- truthful label (strength & purity)
- safety under conditions of intended use
- effectiveness under conditions of intended use
- adequate directions for use ... for almost everyone

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## Other "Interesting" Web Sites

- PhRMA – [www.phrma.org](http://www.phrma.org)
- Public Citizen – [www.citizen.org](http://www.citizen.org)

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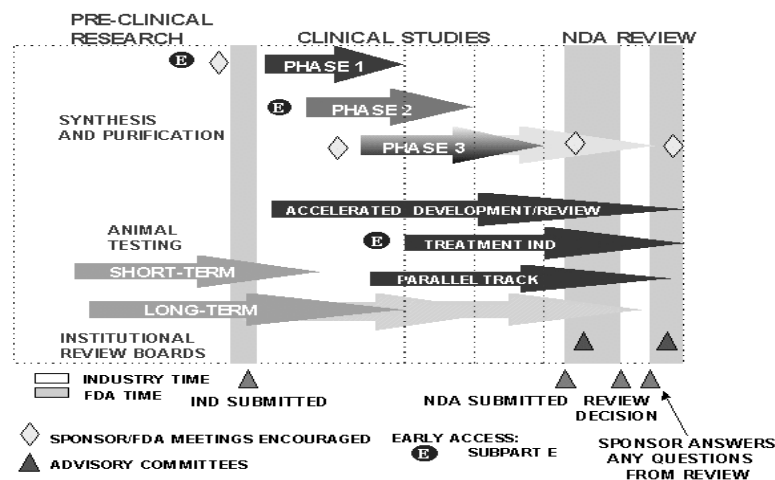
## What is worse?

- regulators mistakenly ...
  - approve a dangerous or ineffective drug
  - fail to approve a beneficial drug

Olson MK. Pharmaceutical Policy Change and the Safety of New Drugs.  
*J Law Econ* 2002;45:615

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## Phases of Drug Development



<http://www.fda.gov/cder/handbook/>

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## Drug Development Phases

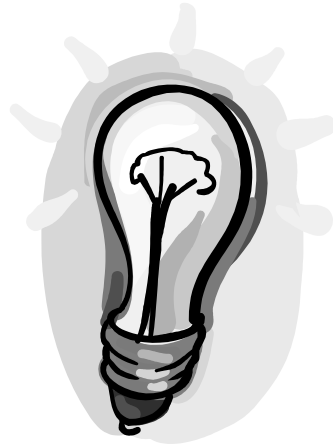
- idea
- "preclinical"
- Investigational New Drug Application (IND)
  - Phase 1
  - Phase 2
  - Phase 3
- New Drug Application (NDA or BLA)
  - Phase 4

BLA – Biologics License Application

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## Idea

- objective: synthesis, isolation of active compound
- modes of discovery
  - "combinatorial" chemistry, Affymax
  - "traditional sources" -- Shaman Pharmaceuticals
  - human genome project
  - targeted discovery
  - dumb luck



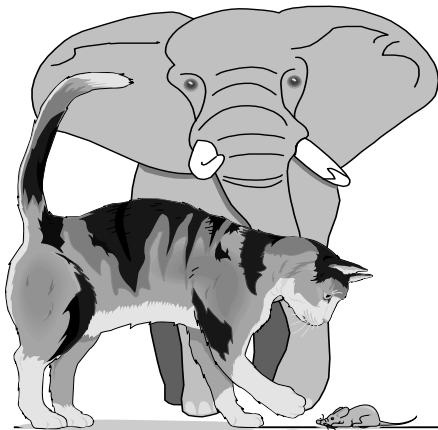
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## Idea (2)

- types of studies
  - purification
  - identification of impurities
  - computer simulations
  - validation, validation, validation
- time: years
- survival: 500,000 → 5,000

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## Pre-Clinical Development



- objective: pharmacology & toxicology in animals
- types of studies
  - acute toxicity
  - sub-acute toxicity (< 3 months)
  - chronic toxicity (6-18 months)
  - reproductive, teratology, mutagenicity

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## Pre-Clinical (2)

- $LD_{50}$  → Tissue culture methods
- ADME
  - Absorption, Distribution, Metabolism, Excretion
- study size: hundreds of animals
- time: 6.5 years
- survival: of 5000 pre-clinical → 5 INDs

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## Phase 1

- objective: safety, dose ranging, pk/pd in "normals"
- types of studies
  - first exposure in humans
  - single dose tolerability
  - multiple dose tolerability
  - dose-ranging based on animal doses

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## Phase 1 (2)

- study size: 20-80
- time: 2-3 years
- survival
  - 80% proceed to Phase 2
  - 5 → 4

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## Phase 1 Failures

- pre-clinical animal models  $\neq$  behavior in humans
- inadequate preclinical data
- change in drug formulation between time of pre-clinical and clinical testing
- pk/pd relationships
- poorly designed clinical studies
- drug too toxic in humans

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## Phase 2 Clinical Studies

- objectives: testing an hypothesis of no difference; safety
- types of studies: small controlled trials in patients
- dose ranging
- study size: 100-300
- time: months - 2 years
- survival: 2 go on to Phase 3

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## Phase 3 Clinical Studies

- objective: testing an hypothesis of no difference; safety
- targeted patients
- “well controlled” studies
  - placebo-controlled
  - double blinded
  - multi-centered (bias)
- size: 100’s - 1000’s
- time: 1-4 years
- survival: 1

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## Phase 2 & 3 Failures

- infrequent adverse reactions observed; but
  - ...
- drug-drug interactions
- drug-disease interactions in ill patients
- genetic
- effectiveness insufficient (20%)
- economic (24%)

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## Application Types

- **New Drug Application (NDA)** (Center for Drug Evaluation and Research - CDER)
  - manufacturing facility approval included in application review
  - includes some “well characterized biologicals”
- **Biologics License Application (BLA)** (Center for Biologics - CBER)
- **510(k) | Premarket Approval (PMA)** (Center for Devices and Radiological Health - CDRH)
- Office of Combination Products

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## NDA | BLA

- FDA has 180 days for review
  - FDA judges both benefit (efficacy) and risks (safety)
  - one specific indication is approved
- Average drug approval story
  - 1: 350,000 approved
  - cost ~ \$500 million
  - time ~ 15 years

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## Phase 4

- post marketing surveillance
  - negotiation
  - accelerated approval for therapies for serious and life-threatening diseases (Subpart E)
  - targeted studies for cause
  - other stages of diseases, other sub-populations, drug-drug interactions, "off-label" uses
- Prescription Drug User Fee Act (PDUFA3)  
"mandates"

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## Safety & Efficacy

- ***Under conditions of intended use***
  - limitations of "well controlled" studies
  - relevance of clinical trial information to alternate ("off label") uses
- "promotion" of off label uses
- domestic (dis)incentives to conduct studies of alternate uses
- PDUFA

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## International Conference on Harmonisation

- US, European Union & Japan
  - efficacy (human clinical trials)
  - safety (animal pharmacology / toxicology)
  - quality (manufacturing)
  - regulatory communication

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## Review & Questions

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