Introduction to FDA Drug and Biologic Review Process

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iSBTc Global Regulatory Summit
October 29, 2008

Outline

- **Regulatory background**
  - US Laws and FDA Regulations
  - History of Regulation
- **Review and Approval process**
- **Clinical Trial Review Process**

Basis for Regulation

- Statutes: **THE LAW (Act) --- passed by Congress and signed by the President**
  - USC (United States Code)

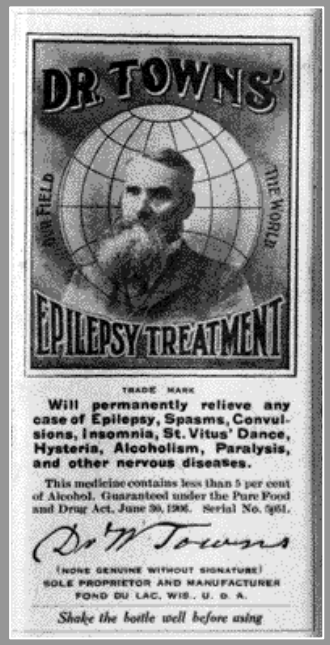
- Regulations: **Detail interpretation of the law --- written by the Agency and approved by the Executive Branch**
  - CFR (Code of Federal Regulations)

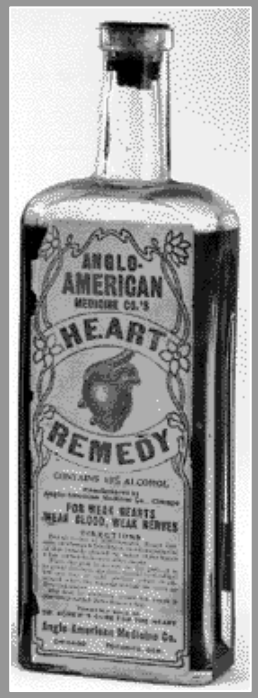
- Guidance: **Issued by individual agencies to reflect current thinking, not binding**.

Legal Requirement for Approval

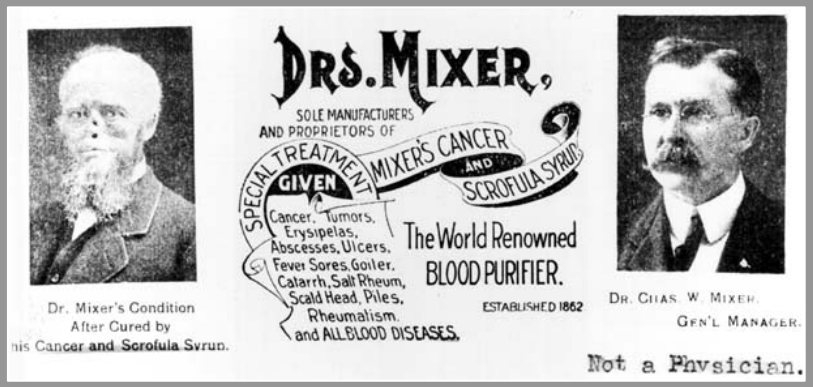
- Accurate and adequate label
  - Food and Drug Act (1906)
- Safety
  - Food, Drug and Cosmetic Act (FDC Act) (1938)
- Effectiveness
  - FDC Act amended 1968

History of US Drug and Biologic Regulations

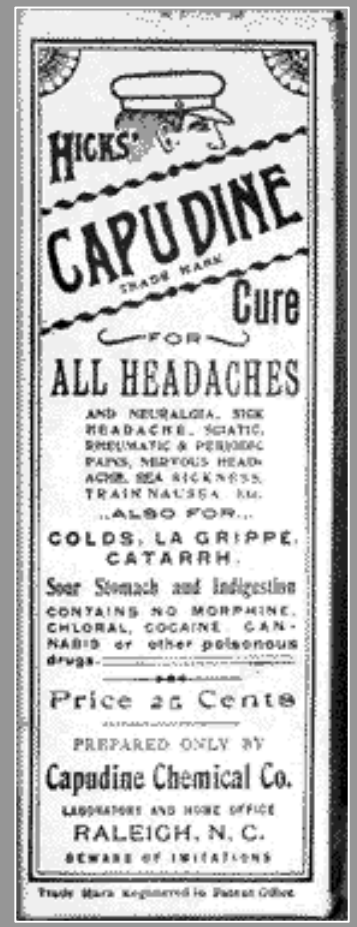

DR TOWNS'
THE WORLD
EPILEPSY TREATMENT
TRADE MARK
Will permanently relieve any case of Epilepsy, Spasms, Convulsions, Insomnia, St. Vitus' Dance, Hysteria, Alcoholism, Paralysis, and other nervous diseases.
This medicine contains less than 5 per cent of Alcohol. Guaranteed under the Pure Food and Drug Act, June 30, 1906. Serial No. 5951.
Dr W Towns
(NONE GENUINE WITHOUT SIGNATURE)
SOLE PROPRIETOR AND MANUFACTURER
FOND DU LAC, WIS., U. S. A.
Shake the bottle well before using


ANGLO-AMERICAN
MEDICINE CO.'S
HEART
REMEDY
CONTAINS 18% ALCOHOL
FOR WEAK HEARTS
THIN BLOOD, WEAK NERVES
DIRECTIONS
Anglo-American Medicine Co.


KINTHO
BEAUTY CREAM
STILLMAN'S
FRECKLE
CREAM
FRECKLE OINTMENT
FATOFF
OBESITY
CREAM
EXCELSIOR
SKIN FOOD
EMPRESS EUGENIE
SUPREME
Complexion Cream


Dr. Mixer's Condition
After Cured by
his Cancer and Scrofula Syrup.
DRS. MIXER,
SOLE MANUFACTURERS
AND PROPRIETORS OF
SPECIAL TREATMENT
GIVEN
MIXER'S CANCER
AND
SCROFULA SYRUP
Cancer, Tumors, Erysipelas, Abscesses, Ulcers, Fever Sores, Goiter, Catarrh, Salt Rheum, Scald Head, Piles, Rheumatism, and ALL BLOOD DISEASES.
The World Renowned
BLOOD PURIFIER.
ESTABLISHED 1862
DR. CHAS. W. MIXER,
GEN'L MANAGER.
Not a Physician.


MACK MAHON
THE
RATTLE SNAKE
OIL KING'S
LINIMENT FOR
RHEUMATISM
AND
CATARRH


HICKS'
CAPUDINE
TRADE MARK
Cure
FOR
ALL HEADACHES
AND NEURALGIA, SICK HEADACHE, SCIATIC, RHEUMATIC & PERIODIC PAINS, NERVOUS HEADACHE, SEA SICKNESS, TRAIN NAUSEA &c.
ALSO FOR
COLDS, LA GRIPPE, CATARRH.
Sour Stomach and Indigestion
CONTAINS NO MORPHINE, CHLORAL, COCAINE, CANNABIS or other poisonous drugs.
Price 25 Cents
PREPARED ONLY BY
Capudine Chemical Co.
LABORATORY AND HOME OFFICE
RALEIGH, N. C.
BEWARE OF IMITATIONS
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Biologics Control Act

1901 13 children in St. Louis died of tetanus after receiving diphtheria antitoxin from a horse named Jim.

9 children die of tetanus from contaminated smallpox vaccine

1902 Biologics Control Act authorizes Hygienic Laboratory to issue regulations to ensure purity and safety of serums, vaccines, and similar products

1944 PHS Act incorporates provisions for biologics regulation. Outlines licensing requirements that are independent from pre-marketing requirements for drugs.

1973 Blood, blood products, and allergenics included in the PHS Act

Food and Drug Act

1905 Samuel Hopkins Adams published “The Great American Fraud,” a commentary on the patent medicine industry exposing cure-all claims for worthless and dangerous patent medicines.

Upton Sinclair publishes “The Jungle” with shocking disclosures of insanitary conditions in meat-packing plants.

1906 Food and Drug Act prohibits interstate commerce in misbranded and adulterated foods, drinks, and drugs.

Food, Drug, and Cosmetic Act

1937 **Sulfanilamide elixir containing diethylene glycol killed 107 people**

1938 Food, Drug, and Cosmetic Act required new drugs to be shown safe before marketing **— starting a new system of drug regulation. It also authorized factory inspections and other provisions.**

Kefauver-Harris Amendments

1962 Thalidomide, a new sleeping pill, was found to have caused birth defects in thousands of babies born in western Europe. Over two million pills distributed in the United States for investigational studies.

1962 Kefauver-Harris Drug Amendments passed to ensure drug **efficacy** and greater drug safety. It required drug manufacturers to prove the **effectiveness** of their products before marketing them, gave FDA control over drug advertising, and allowed FDA to regulate investigational studies.

A new biologic, drug, or device may not be entered into interstate commerce unless:

- **It is approved by the FDA as safe and effective**

  (biological license application [BLA], new drug application [NDA], pre-market approval [PMA], or other marketing approval)

OR …

- **An IND (Investigational New Drug Application) is in effect**

  (exempting the study from the premarketing approval requirements that are otherwise applicable)

Laws affecting FDA

- More than 20 Statutes affecting FDA
- Two main Laws concerning human drugs and biologicals
  - Food, Drug, and Cosmetic Act (FD&C Act), United States Code (U.S.C.) Title 21, Chapter 9 (enacted in 1938)
  - Public Health Service Act (enacted in 1944), United States Code (U.S.C.) Title 42, Chapter 6A Part F - Licensing of Biological Products and Clinical Laboratories

Food, Drug, and Cosmetic Act (FD&C Act)

- Enacted in 1938 and amended in 1968
  - foods are pure and wholesome, safe to eat, and produced under sanitary conditions
  - drugs and medical devices are **safe and effective** for their intended uses. This includes drugs used in medicated feeds for animals.
  - cosmetics are safe and properly labeled.
  - packaging and **labeling** of these products is truthful and informative.
- Amended 20 times (latest: August, 2004)

Major amendments for FD&C Act

- Orphan Drug Act (Jan. 4, 1983)
- Prescription Drug User Fee Act (PDUFA) of 1992
- Safe Medical Devices Act of 1990
- Food and Drug Administration Modernization Act (FDAMA) of 1997
- Medical Device User Fee and Modernization Act

Public Health Service Act

- United States Code (U.S.C.) Title 42, Chapter 6A Part F - Licensing of Biological Products and Clinical Laboratories
  - The Secretary shall approve a biologics license application on the basis of a demonstration that the **biological product** that is the subject of the application is **safe, pure, and potent**

Public Health Service Act

• "Biological product" defined in this section, the term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Regulations on Drug Approval

- 21 CFR 314.126
  - –Determination of **substantial evidence** to support the claims of **effectiveness** for new drugs.
  - –Primary basis: **Adequate and well-controlled investigations**

- 21 CFR 314.126
  - –Acceptable safety

- 21 CFR 201
  - –Product label
    - Defines an appropriate patient population
    - Provides adequate information to enable safe and effective use

Two Types of Approvals

- Regular (Full) Approval or
- Accelerated Approval

Regular (full) Approval

- Direct clinical benefits
  - Prolongation of overall survival (live longer)
  - Improvement of symptoms (live better)
  - Favorable effect on established surrogate
  - Composite endpoints

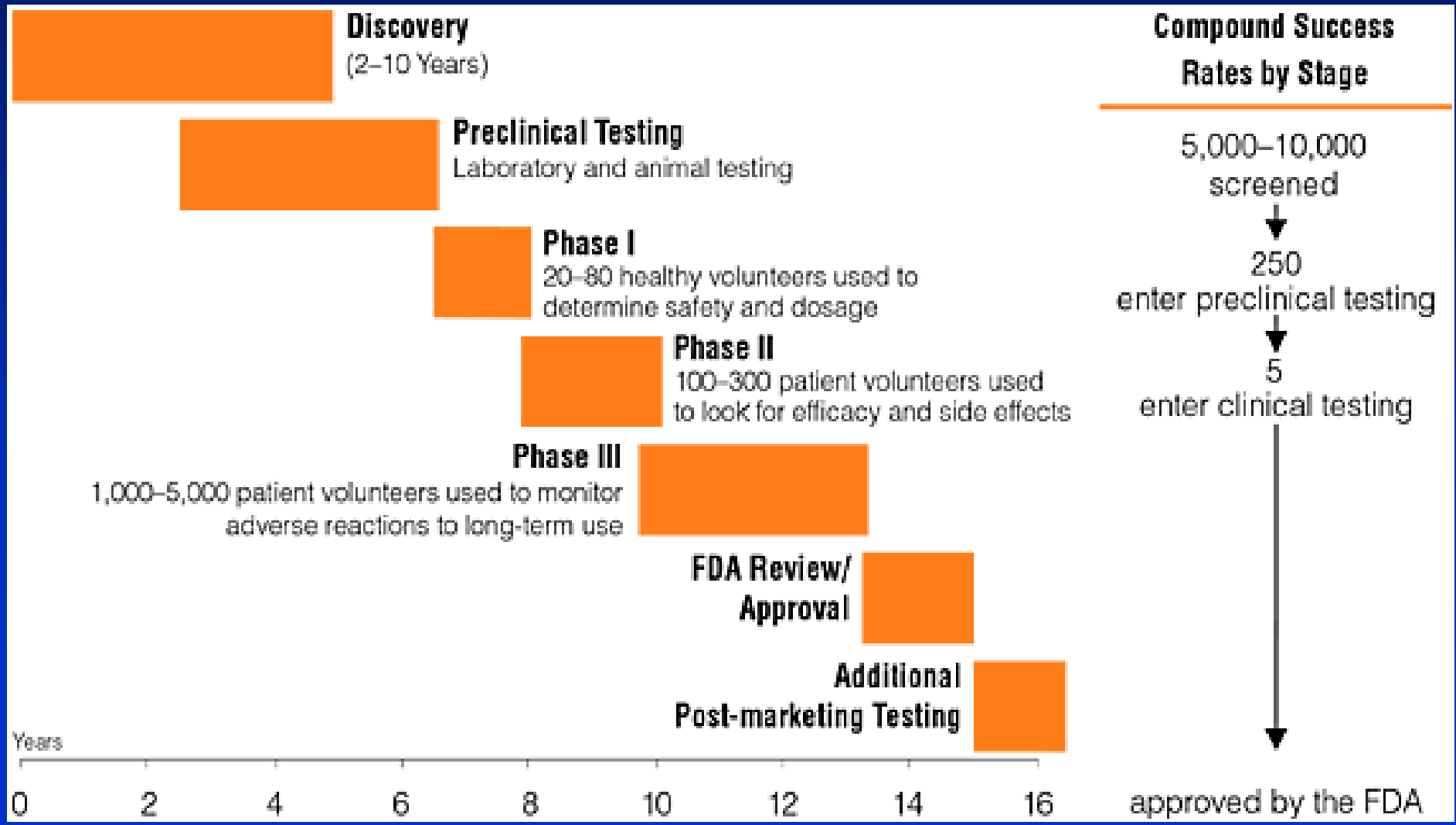
Accelerated Approval

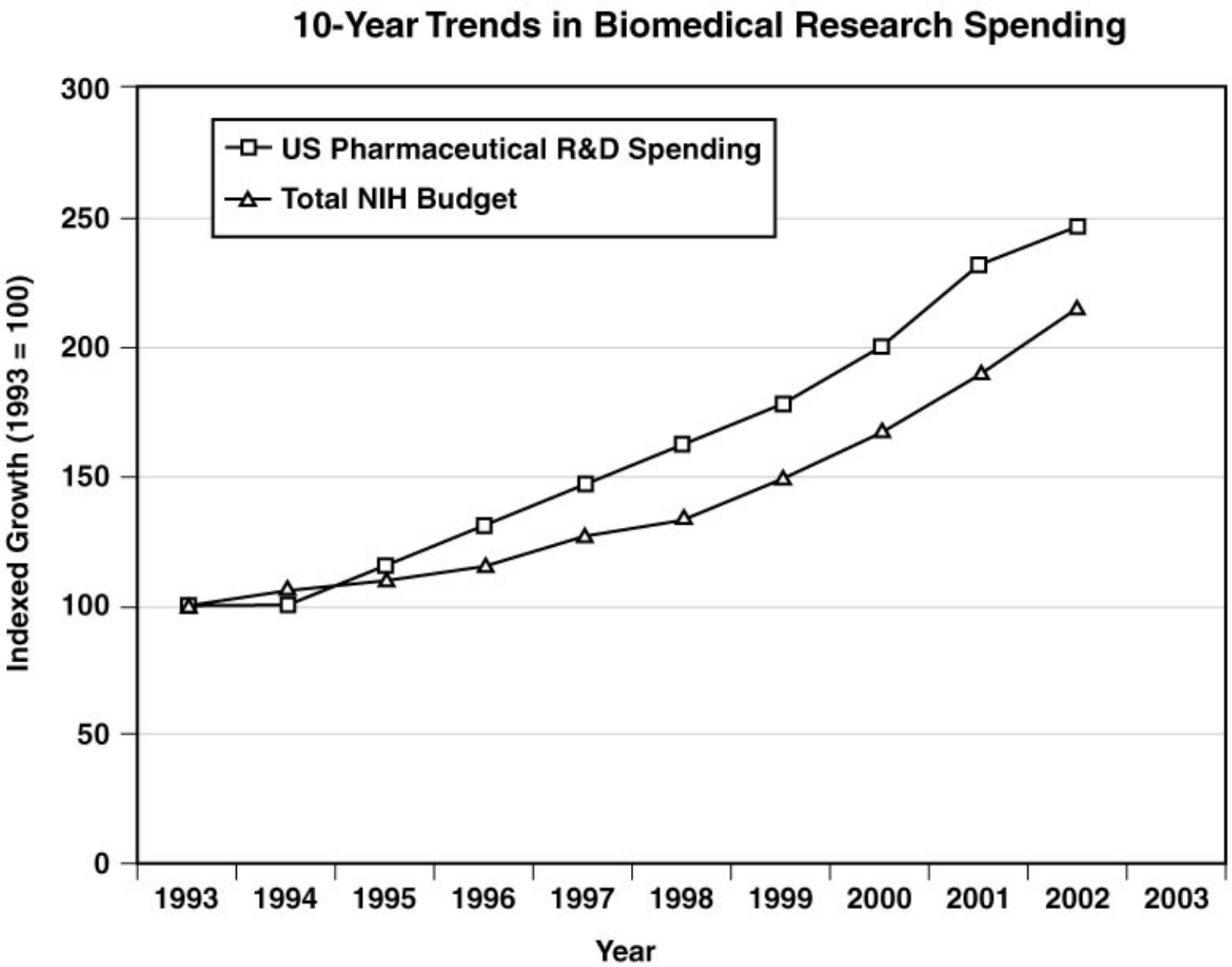
- 21 CFR 314.510 for drugs (subpart H)
- 21 CFR 691.41 for biologics (subpart E)
- The product
  - Treats serious or life-threatening illnesses
  - Provides meaningful therapeutic benefit to patients over existing treatments
  - Is tested in adequate and well-controlled clinical trials
  - Has an effect on a **surrogate endpoint** that is **reasonably likely**, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, **to predict clinical benefit** or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity
  - Fulfils post-marketing commitment to verify and describe its clinical benefit

Drug/Biological Development

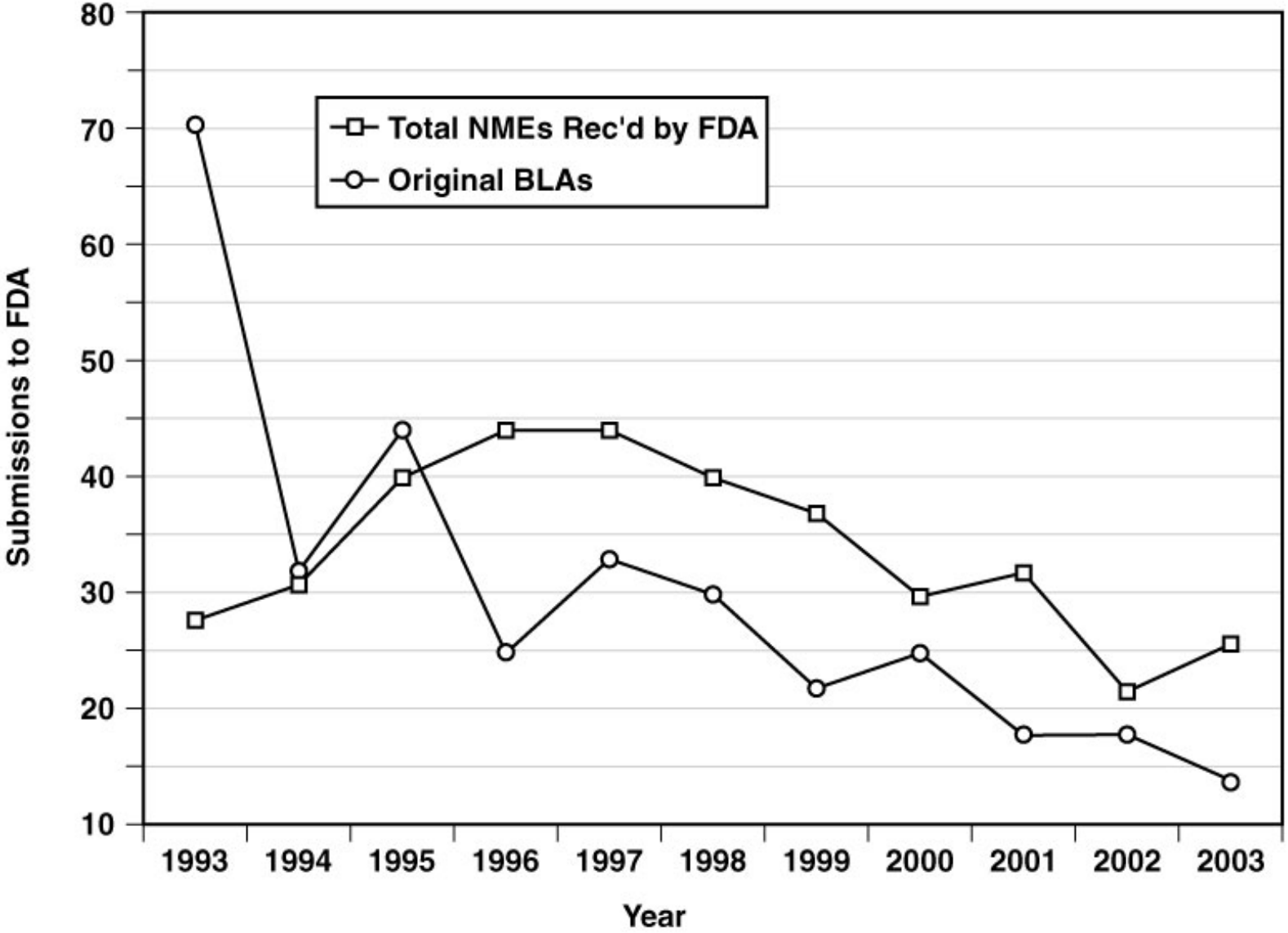
- An orderly process starting from scientific discovery
- Multiple components involving critical decision making
- Time and cost

Traditional Paradigm for Drug Development




10-Year Trends in Biomedical Research Spending
US Pharmaceutical R&D Spending
Total NIH Budget
Indexed Growth (1993 = 100)
300
250
200
150
100
50
0
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
Year

10-Year Trends in Major Drug and Biological Product Submissions to FDA



Review Process

- Starts with the sponsor's application
- NDA: New Drug Application
  - Mainly in the Center for Drugs
- BLA: Biological Licensure Application
  - Mainly in the Center for Biologics and some in Center for Drugs

Review Process

- Team approach
  - Clinical reviewer in collaboration with biostatistician: clinical data to determine the efficacy and safety
  - Other disciplines reviewers:
    - Clinical pharmacologist
    - Toxicologist
    - Chemistry, Manufacturing and Control (CMC) reviewer (chemist or biologist)

Application status

- **Regular: 10 month**
- **Priority: 6 month**
- **Mid-cycle Review Team Meeting**

FDA Advisory Committee Meeting (1)

- Advisors
  - Special Government Employees (SGEs)
  - Pre-screened for Conflict of Interests (COI)
- Meeting agenda and dates announced in advance in Federal Register
- Briefing Package
  - From Sponsor
  - From FDA
  - Made public prior to the meeting

FDA Advisory Committee Meeting (2)

- **Presentations**
  - **Sponsor**
  - **FDA**
  - **Public (need to pre-register)**
- **Committee discussion of questions posed by FDA**
- **Committee Votes if there are voting questions**

FDA Advisory Committee Meeting (3)

- FDA makes its own decision whether to approve a product or not after AC meeting

Public Information after Approval

- For approved drugs and biologics, information (letters, labeling, reviews) is accessible
  - http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
  - http://www.fda.gov/cber/products.htm
- Food and Drug Administration Amendments Act of 2007 (FDAAA) requires internet web posting after approval
  - Immediate publication of summary review, no later than 48 hours
  - Action Package no later than 30 days
    - Review memos
    - Action letters

The IND Process

- **Preclinical testing/investigation**
  - ***In vitro* tests/animal testing**
    - **"reasonably safe" determination (21 C.F.R. § 312.23)**
  - **Pharmacological data**
  - **Toxicity testing**
- **"Good Laboratory Practice" (GLP) (21 C.F.R. Part 58)**
  - **Governs preclinical testing conduct**
    - **Organization, personnel, facilities, study conduct, and records retention**

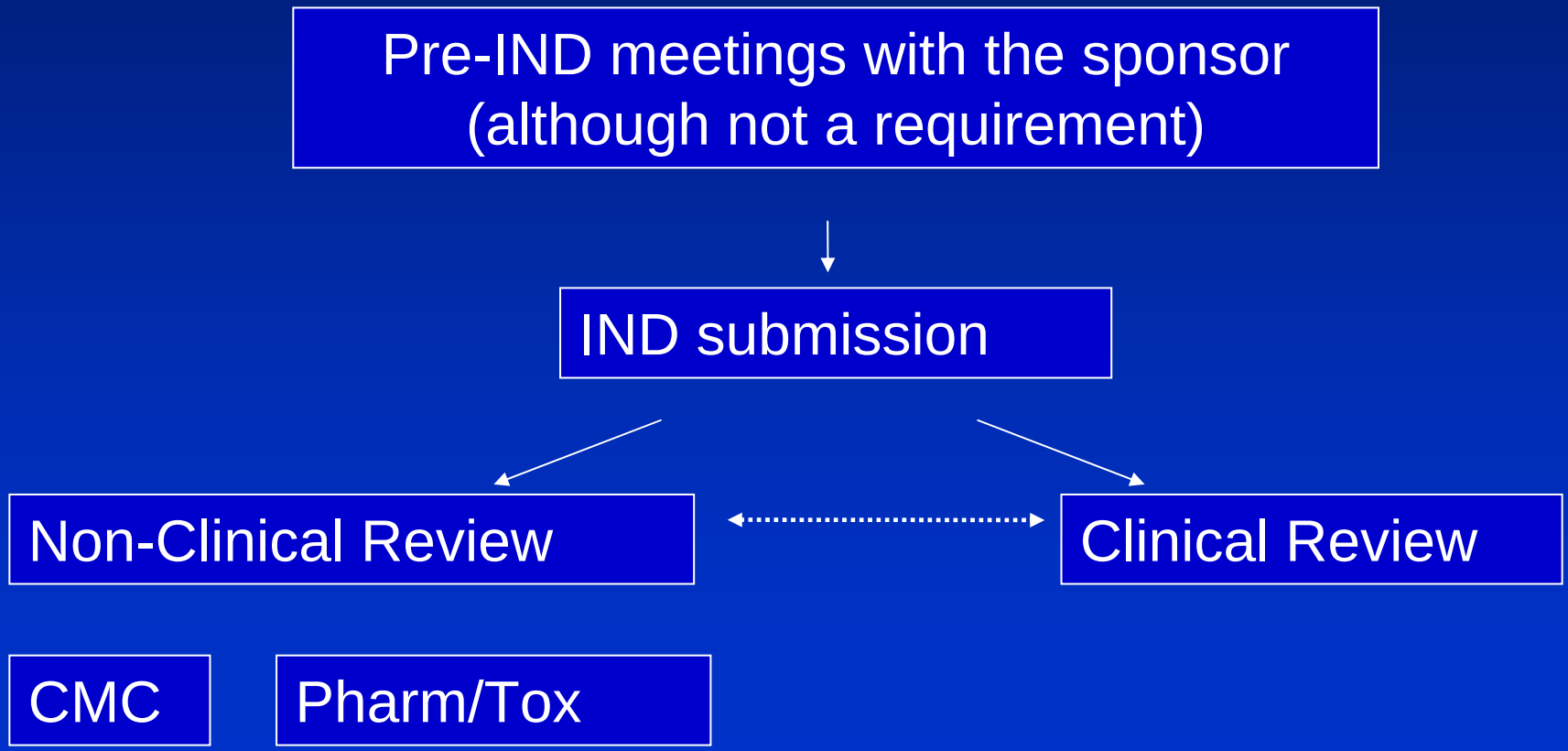
The IND Process

- **Clinical testing/investigation and "Good Clinical Practice" (GCP)**
  - **Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.**
  - **See Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance (April 1996)**
    - **Details GCP principles**

Regulatory Considerations in reviewing 1st in-human use of investigational agents (phase I)

- The product manufacturing and characterization?
- The level of safety assurance needed for beginning clinical trials
- Clinical study design

Review Process for Phase 1 Trials



Review process for phase I trials --- continued

CMC

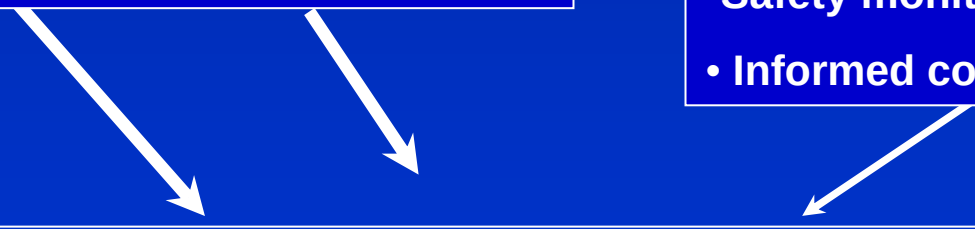
Pharm/Tox

Clinical Review

- Product manufacturing, characterization and testing
- Pre-clinical studies

  Dosing, toxicity, biodistribution, proof of concept, safety monitoring

- **Patient population**
- **dose, schedule and administration**
- **dose escalation**
- **DLT definition and Optimal Maximum Dose determination**
- **Stopping rules**
- **Safety monitoring and evaluation**
- **Informed consent**



Decision (within 30 days) for IND to proceed

Review process for phase II, III trials

CMC

Pharm/Tox

- Product manufacturing, characterization and testing and **Potency**
- Pre-clinical studies

Clinical Review

Proposed clinical trials may proceed

Phase 2 studies

- Begin if Phase 1 studies do not reveal unacceptable toxicity.
- Primarily focus on collection of preliminary data on
  - – whether the drug has effect in a defined patient population
  - –the relationship between dose and effectiveness.
- Continue to evaluate safety and short-term side effects.
- For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment -- usually a placebo or a different drug.

Phase 3 studies

- **Begin if preliminary evidence of effectiveness is shown during phase 2.**
- **Gather more information about safety and effectiveness in a defined population.**
- **May form the primary basis of an efficacy claim**

Some considerations of phase II and phase III studies

- **Protocol design**
  - Patient population
  - Choice of endpoints
  - Choice of control (placebo vs. active control)
  - Evaluation
- **Study conduct and execution**
  - Study sites
  - Investigator's brochure
  - DSMB
  - CRF
- **Protocol design**
  - Data collection and Evaluation
  - Statistical analytic plan
  - Assumption of effect size, power and sample size
- **Implications for labeling.**
  - Currently available therapies for the indication sought
  - possibility of the study to generate data to support the claim

Special protocol assessment

[Section 505(b)(4)(c) of the FDA Modernization Act].

- **Agreement between the sponsor and FDA documented in writing**
  - Protocol design
  - Primary efficacy endpoints
  - Study conduct
  - Data analyses
  - Clearly described labeling statements one could expect if the data are supportive and the product is approved
  - whether the design and planned analysis of a study adequately address objectives in support of a regulatory submission.

- **The sponsor submits protocols with specific questions**
  - Animal carcinogenicity protocols,
  - Final product stability protocols or
  - clinical protocols for phase 3 trials whose data will form the primary basis for an efficacy claim

- **FDA documents in writing within 45 days any agreement or disagreement to the sponsor**

Interactions with FDA

- Early interactions with FDA are critical
- Know your guidance documents
- Consider early in translational research the questions that will be asked at the clinical trial phase
- Phone, face to face; formal or informal: dialogue is encouraged

Interactions with FDA

- Scientific meetings, conferences, workshops
- Pre-Pre-IND
- Pre-IND meetings
- End of Phase 1 meeting
- End of Phase 2 meeting
- Special Protocol Assessment review
- Fast Track program application
- New protocol submission under existing IND

Conclusion

- Drug and biologic development is an orderly process involving multiple components
- Academia, industry and regulatory bodies are integral parts of this process
- Many challenges exist for product characterization as well as testing the safety and effectiveness in humans throughout the life cycle of the product development
- FDA critical path and other initiatives aim to help the development of drugs and biologics
- Frequent and early engagement with FDA are strongly encouraged

Contact Information

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