Drug Development and IND Process

GC 690

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Important Laws and Regulations

- Laws
  - Federal Food, Drug, and Cosmetic Act
  - Public Health Service Act--Part F Licensing of Biological Products and Clinical Laboratories
- Regulations
  - IND regulations (both drugs and biologics) 21 CFR 312
  - NDA (drugs) regulations--21 CFR 314
  - BLA (biologics)--21 CFR 601
  - Protection of human subjects and informed consent regulations--21 CFR 50
  - IRB regulations--21 CFR 56

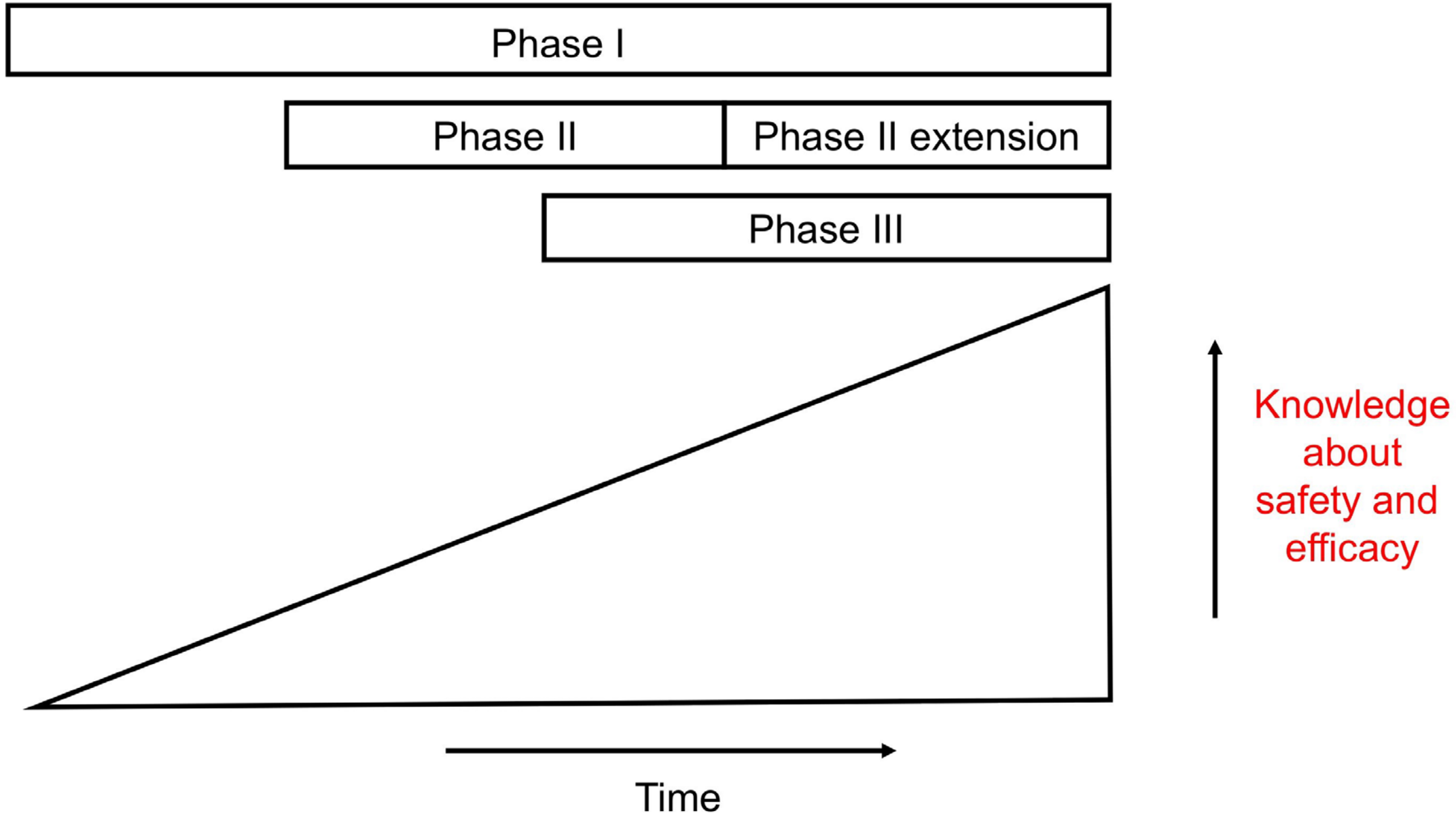
History of US Food and Drug Law/Regulation

- 1906 Pure Food and Drug Act
  - Prohibited interstate commerce of misbranded and adulterated food and drugs
  - Unsanitary conditions in meat-packing plants, poisonous preservatives, food dyes, dangerous patent medicines
- 1938 Federal Food, Drug, and Cosmetic Act
  - Must provide scientific evidence of safety
  - Sulfanilimide overdoses
- 1962 Kefauver-Harris Drug Amendments
  - IND regs
  - Required proof of safety AND efficacy
  - Thalidomide

Regulatory Functions in Drug Development

- Approval process is step-wise
  - Clinical candidate compound
  - Investigational New Drug (IND) Application
  - Pre-NDA clinical development (Phases I-III)
  - New Drug Application (NDA)
  - Post-marketing clinical studies (Phase IV)

Regulatory Functions in Drug Development



Regulatory Functions in Drug Development

- Approval process is step-wise
  - Investigational New Drug Application (IND)
    - Must convince the FDA that
      - the drug has reasonable chance of being effective
      - toxicologic data support use in humans
      - physical chemical properties are well-described
      - process is reproducible and results in reasonable pure preparation
    - Once approved, clinical testing in the US may begin

Regulatory Functions in Drug Development

- When is an IND required?
  - All unapproved drugs
  - Vitamins, supplements with drug claims
  - Botanicals with drug claims
- What should be included in an IND?
  - Brief regulatory context
  - CMC, pharm-tox, clinical data to support proposed clinical trial
- What documents are relevant?
  - IND regulations: 21 CFR 312
  - Guidance: Content and Format of INDs…
  - In clearance: Sponsor-investigator guidance

Regulatory Functions in Drug Development

- New IND Requirements : Chemistry/Manufacturing Data
  - Sufficient to assure identification, quality, and strength of the drug
  - Impurities, sterility
  - Product consistency
  - Stability of clinical trial formulation

Regulatory Functions in Drug Development

- New IND Requirements: Pharmacology/Toxicology Data
  - Acute toxicity data from studies conducted in 2 species. Generally,
    - Life-threatening toxicity in rodents
    - Study in non-rodents (dog)
  - Histopathology in at least 1 species (usually 2)
  - Results sufficient to determine the starting dose for clinical trials

Regulatory Functions in Drug Development

- IND Review
  - 30-day review clock
    - Primary goal is safety review
    - May proceed on day 30 unless FDA imposes a Clinical Hold

- **WHEN IS IND NOT NEEDED**

- **A. Exemption Category 1** [21 CFR 312.2(b)(1)] – **All criteria for this category must apply**

- ___ The drug product is lawfully marketed in the United States.

- ___ It is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

- ___ It is not intended to support a significant change in the advertising for the product;

- ___ It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

- ___ It is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and

- ___ It is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7].

B In Vitro Diagnostic Biological Product [21 CFR 312.2(b)(2)]

___ The study is a clinical investigation involving a (a) blood grouping serum; (b) reagent red blood cells; and/or (c) anti-human globulin and the product is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and it is shipped in compliance with Sec. 312.160.

C. In Vitro and Animal Testing [21 CFR 312.2(b)(3)] ___ A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with Sec. 312.160. **D. Use of Placebo** [21 CFR 312.2(b)(5)]

___ A clinical investigation involving use of a placebo is exempt from IND requirements if the investigation does not otherwise require submission of an IND.

- When the investigator or TJU holds the IND/IDE, the investigator/TJU becomes the "**sponsor**" of the research and assumes responsibility to ensure that all FDA regulatory criteria for sponsors are met. Please provide your plan for meeting FDA regulatory criteria for sponsors.

For example:

- Investigator who holds an IND or IDE will assign some or all responsibilities to meet FDA sponsor requirements to a contract research organization (CRO).

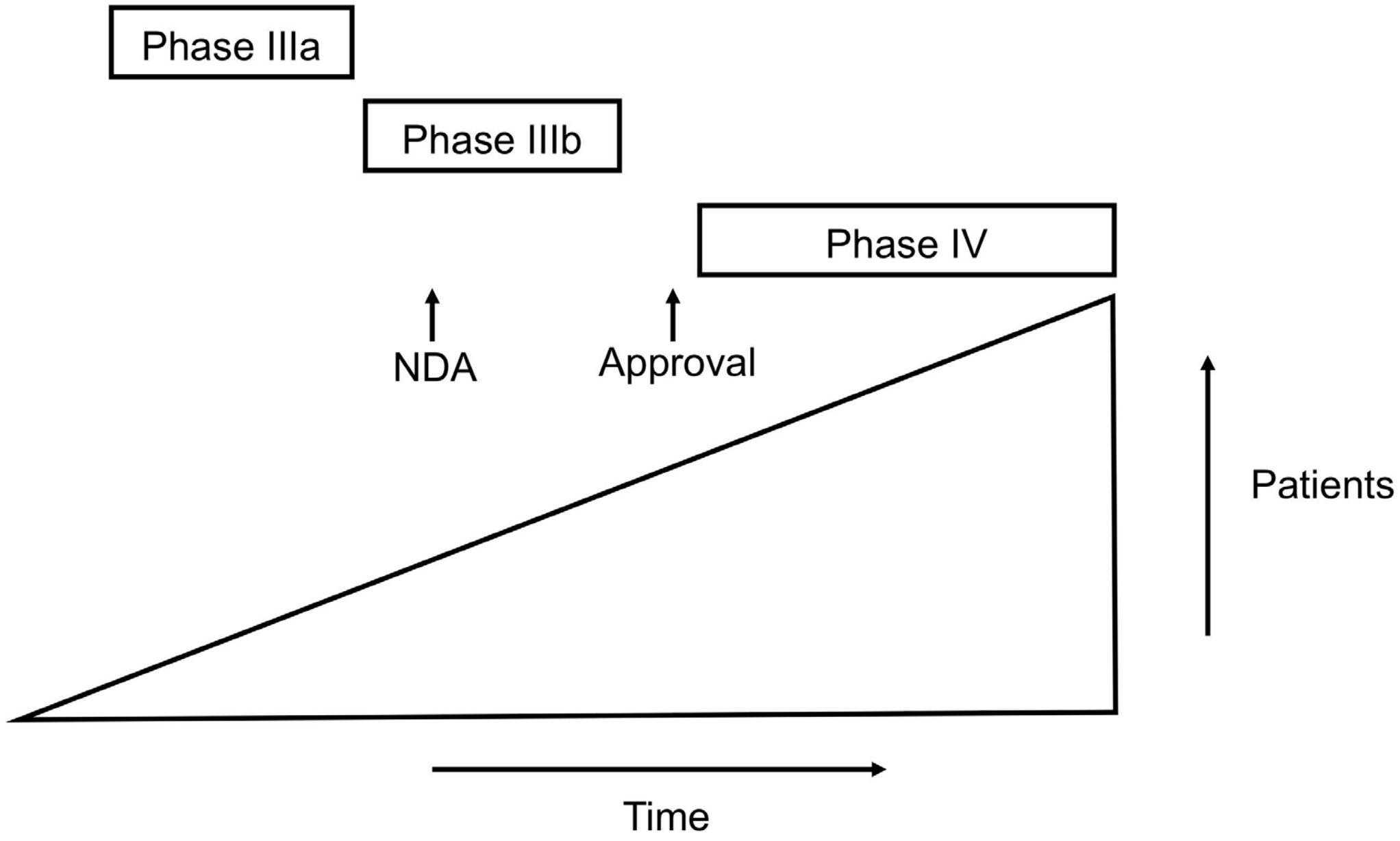
- Investigator will undergo an audit by a CRO to ensure that procedures are in place so that all FDA regulatory requirements of sponsors will be met.

- Investigator will assign responsibility of compliance with some FDA regulatory requirements to a CRO and investigator will obtain an audit from a CRO to ensure that procedures are in place so that all other FDA regulatory requirements of sponsors will be met.

Regulatory Functions in Drug Development

- Approval process is step-wise
  - New Drug Application (NDA)
    - Food, Drug and Cosmetic Act
      - Does not require sponsor to know every medically important event caused by the drug
      - Does not require sponsor to know the best and optimal uses and all indications for the drug
      - Principle: Allows product with proven efficacy to reach market in a reasonable time, and additional data will be acquired about the drug after marketing

Regulatory Functions in Drug Development



Exploratory IND Guidance

In January 2006, FDA issued "Exploratory IND Studies" (e.g., for small- and laboratory-scale investigations where often nonclinical testing and data submission exceed what is needed) Guidance:

- Makes recommendations on preclinical and clinical approaches and on chemistry, manufacturing, and controls information to be included in the IND
- Discusses the types of studies that can be performed under an exploratory IND (e.g., proof-of-concept studies)
- Discusses need for good laboratory practices (GLP)
- ***Enables researchers to concentrate resources on promising candidates, not those that ultimately fail, and to target resources appropriately***