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# Overview of Medical Product Development and Regulation in the United States

**September 15, 2023**

# Speakers for Today's Session

Richard Graham
Senior Vice President
Head of R&D
Theravance Biopharma

Heidi Marchand, Pharm.D.
Head, Global Regulatory
Policy and Intelligence
Gilead Sciences

Terrell Baptiste
US Regulatory Policy &
Intelligence-Oncology, Lead
Gilead Sciences Inc.

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# Disclaimer

The views and opinions expressed are solely those of the speakers and do not represent those of our current or previous employers

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# Learning Objectives

- To understand the current regulatory system and structure relevant to drug development in the United States
- To understand the Investigational New Drug (IND) application process
- To comprehend the drug development process from preclinical testing through approval in the United States
- Identify the types of products that require FDA approval through a New Drug Application (NDA) or Biologics License Application (BLA) and learn about the associated approval pathways

**Clinical pharmacology strategies, orphan drug designation and pediatric plans are of relevance but not covered in this presentation

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# Important Concepts: Blue Text in Scope for this Presentation

## Clinical Investigation

- United States: Investigational New Drug (Application)
- European Union: Clinical Trial Authorization/Clinical Trial Exemption

## Marketing Approval in the United States

- New Drug Application (NDA)
- Biologic License Application (BLA)

## Marketing Approval in the European Union

- Marketing Authorization Application (MAA)

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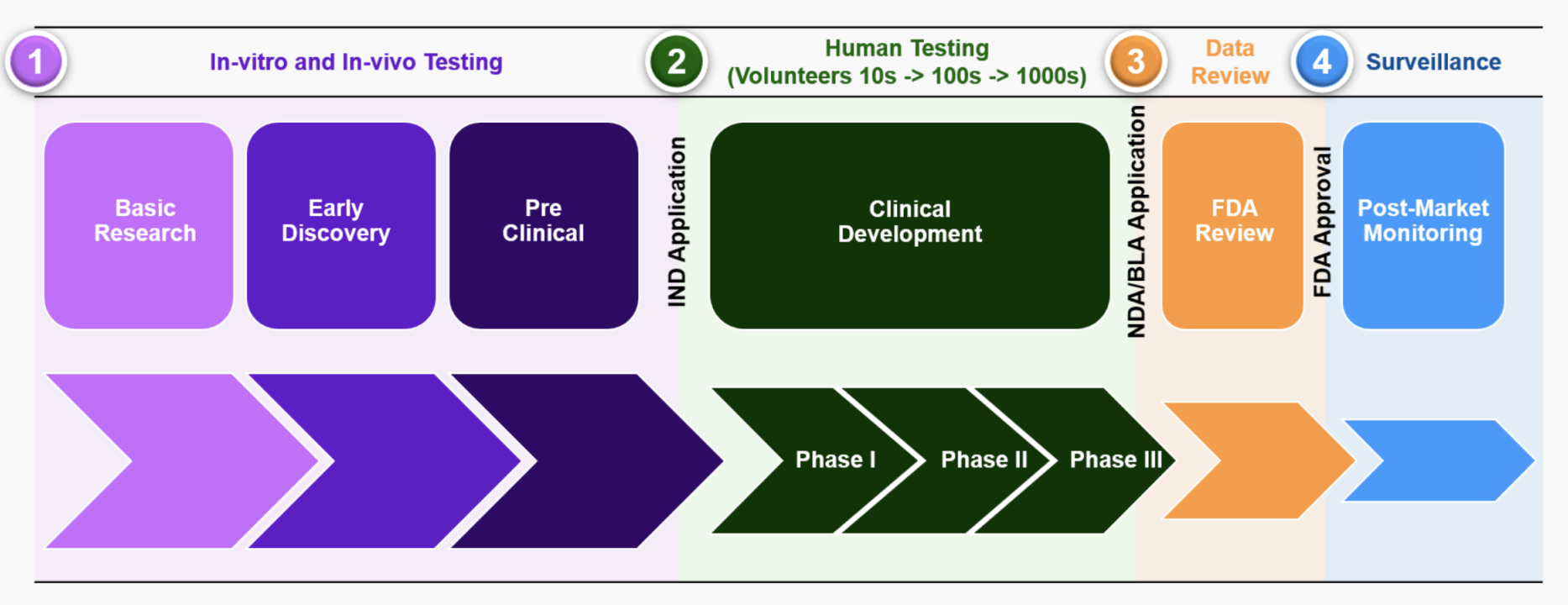
# Brief Overview of the Drug Development and Approval Process




Source: NorthEast BioLab: "Drug Discovery and Development Process", https://www.nebiolab.com/drug-discovery-and-development-process/

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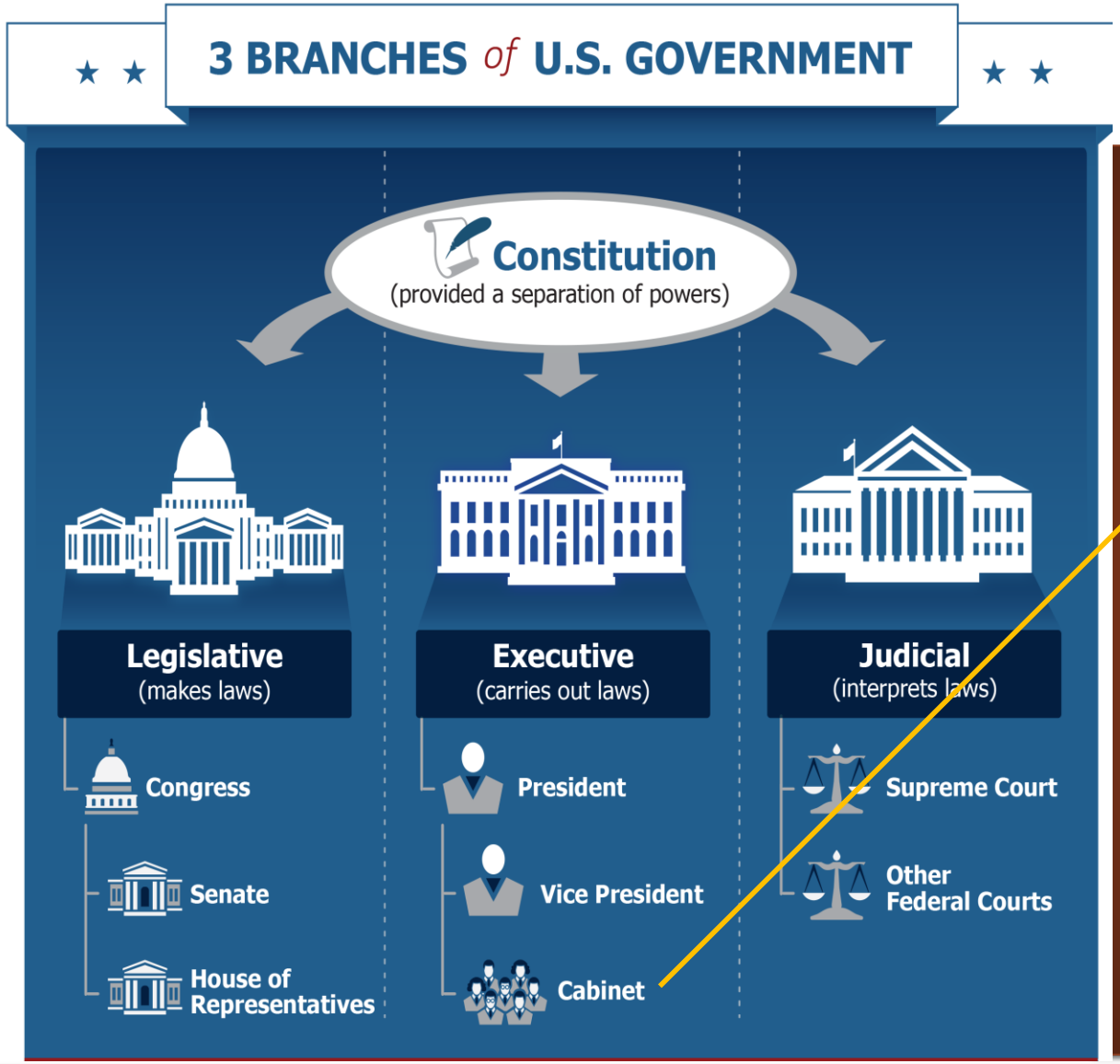
# US Food and Drug Administration Organization and Responsibilities

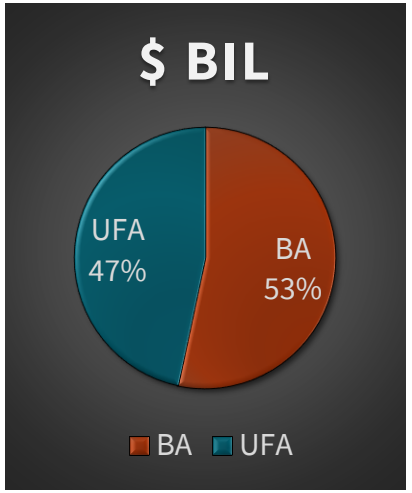
**Heidi Marchand, Pharm.D.**

Head, Global Regulatory Policy and Intelligence
Gilead Sciences

# Food and Drug Administration Organizational Structure




## Health *and* Human Services



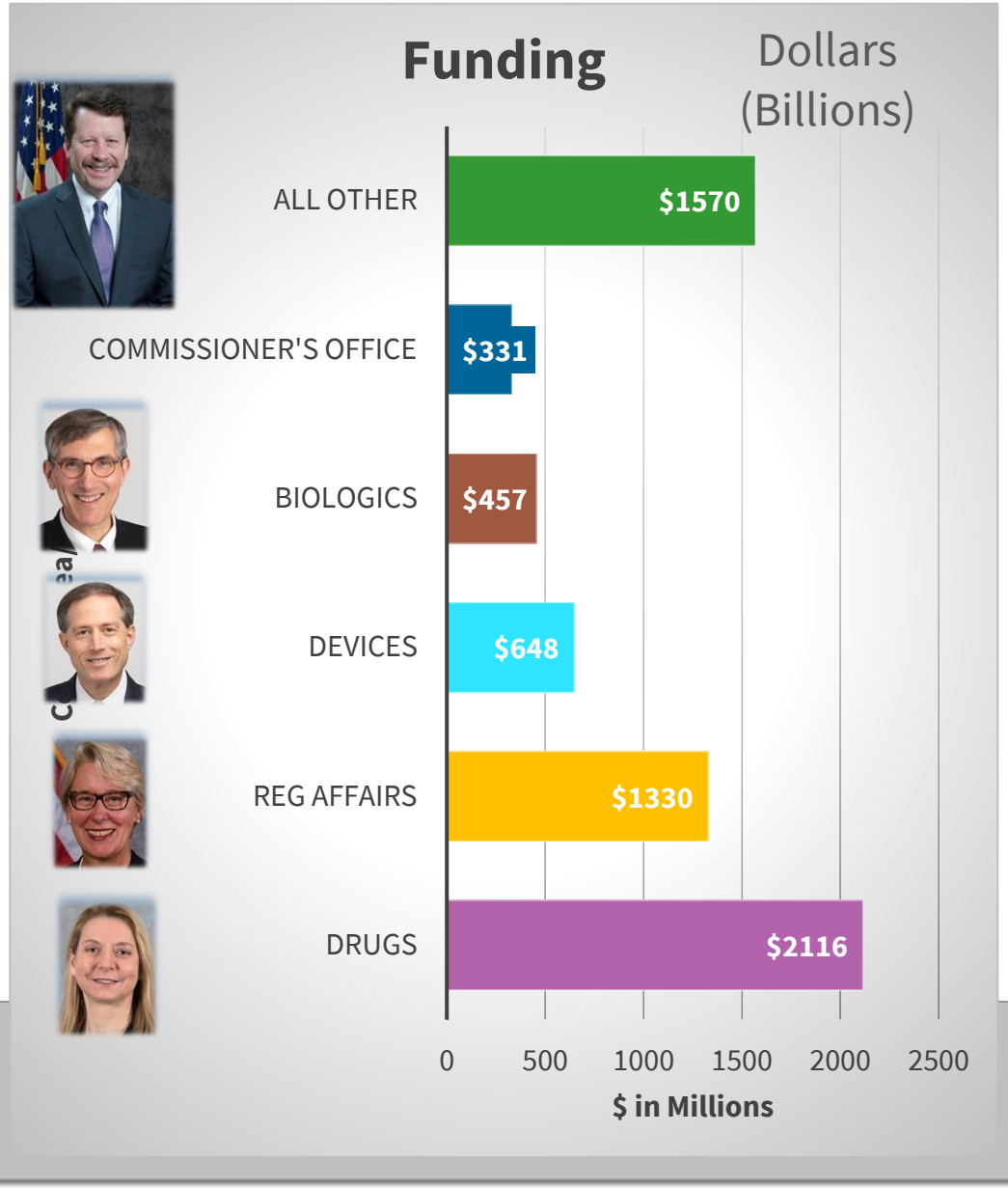

**$6.2B Total FDA**

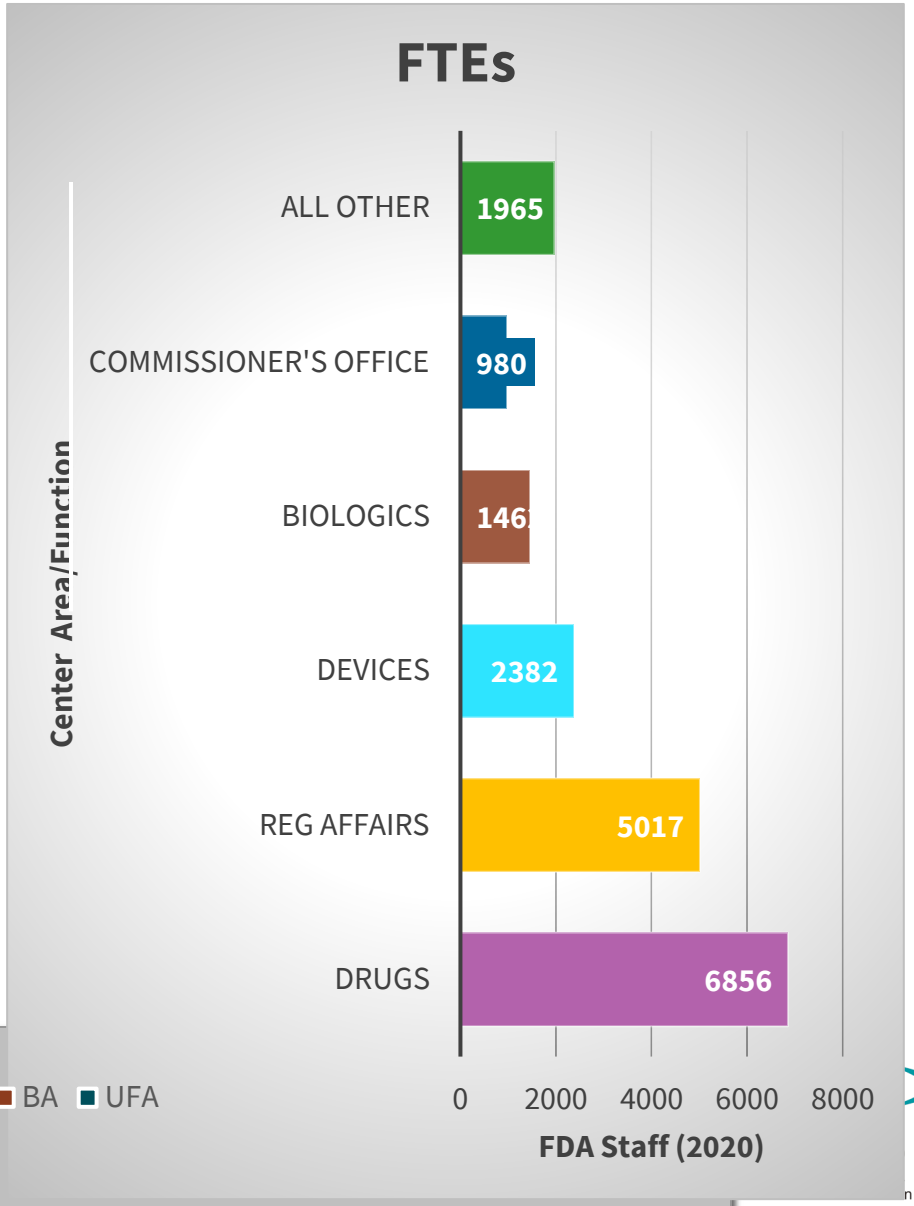
$3.3B- BA

$2.8B-UFAs

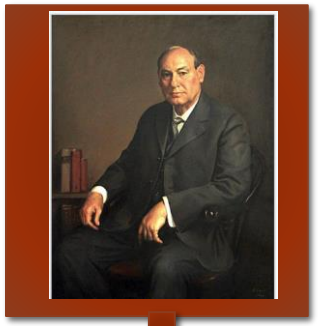
FY 2022 Budget Authorized

User Fee Authorized



# FDA Evolution of Regulatory Oversight and Role



**1883**
**Dr. Harvey Wiley**, founding physician who advocated for safe food and **pure** drugs

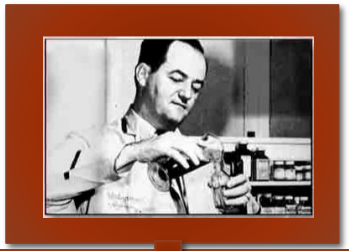

**1906**
President Theodore Roosevelt signs
**The Pure Food and Drug Act**


**1937**
**Elixir of Sulfanilamide**



**1938**
**Federal Food Drug and Cosmetic Act**


**1944 Public Health Service Act**



**1951 Prescription Medication Non-Prescription**

**1962**
**Thalidomide**
Safe and Effective

**1970**
**Patient Package Insert**


**1983**
**Orphan Drug Act**

**1984**
**Generic Drugs**


**1992**
**Prescription Drug User Fee Act**

**2020**
**COVID Pandemic**

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# Food and Drug Administration Organization

Mark Raza
Chief Counsel

Commissioner

Andi L Fristedt
Policy, Leg, Int'l

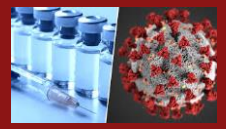
Erica Jefferson
External Affairs

Namandjé Bumpus
Chief Scientist

## Center Leadership

Patrizia Cavazzoni
Drugs

Peter Marks
Biologics



Jeff Shuren
Devices

Carol Cave, Acting
Regulatory Affairs


Food
Toxicology
Tobacco
Veterinary

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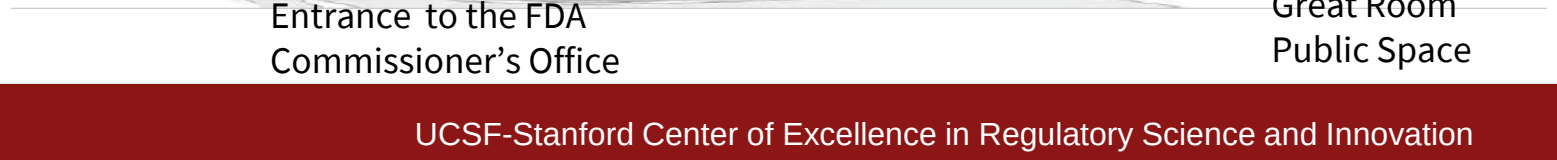
# FDA's White Oak Campus
# New Hampshire Avenue, Silver Spring, MD

Building 62
Engineering and Physics/Devices

Building 22
Center for Drugs
Review Divisions




Entrance to the FDA
Commissioner's Office

Buildings 71
Center for Biologics

Buildings 32 & 31
Office of the Commissioner
Center for Drugs Leadership


Great Room
Public Space

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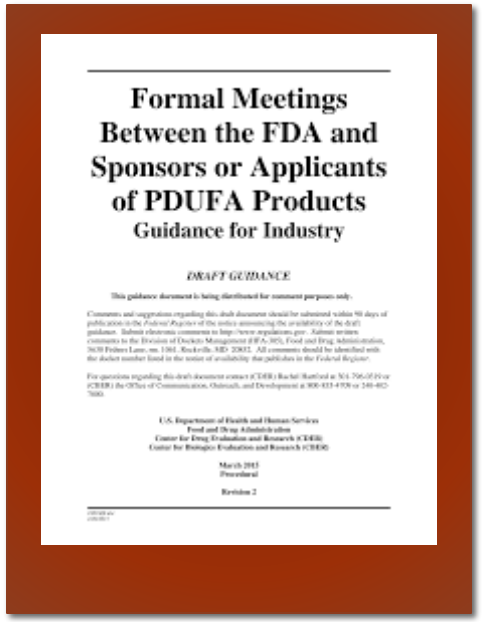
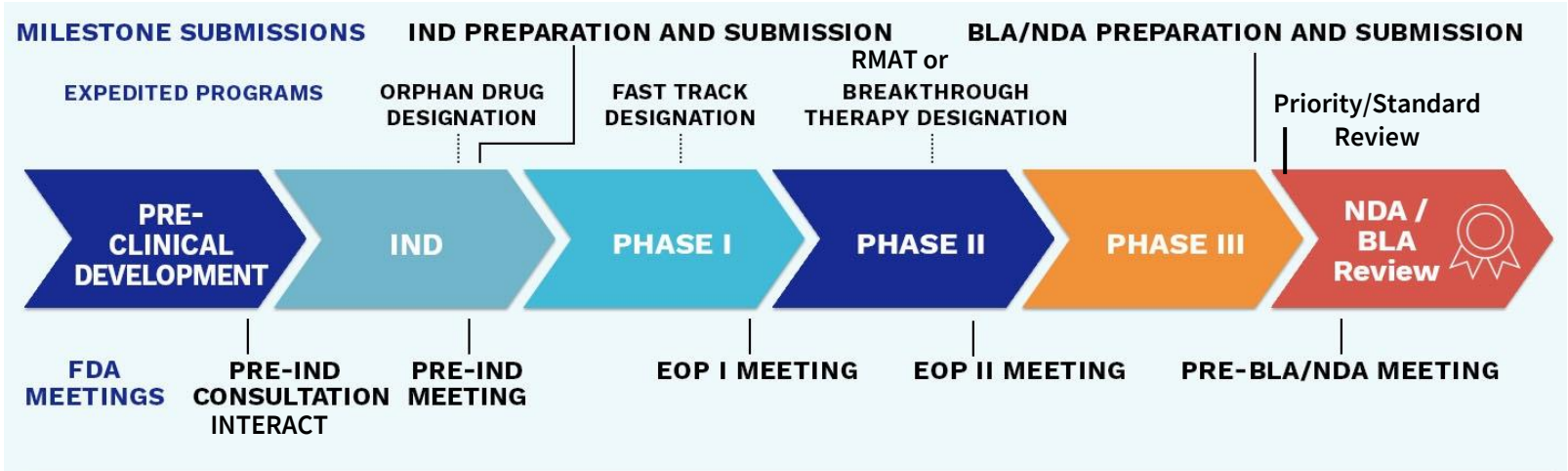
# Opportunities to Interact with the FDA during a product's development


Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products
Guidance for Industry

DRAFT GUIDANCE




**CY 2020**
**meetings** scheduled (PDUFA and BsUFA) 3571
**published guidances** 31
**INDs Received** 1253 (**commercial**) 929 (**research**)= 2182
**INDs w/ Activity** 8100 (**commercial**) 4835 (**research**)= 12935

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# FDA Development and Approval Process for New Drugs

- Before a drug can be tested in people, the drug company performs laboratory and animal tests to discover how the drug works and if it is likely to be safe in humans
- Next a series of tests in people determine whether the drug is safe when used to treat a disease and if it provide a meaningful health benefit
- The company sends evidence from these tests to FDA to prove the drug is safe and effective for its intended use and a team of FDA physicians, statisticians, chemists, pharmacologists, and other scientists review the data
- If this independent and unbiased review established that the health benefits outweigh the known risks of the drug, the drug may be approved for sale in the United States

Reference "FDA Drug Approval Process:" https://www.fda.gov/media/88742/download

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# Small Molecule and Therapeutic Protein Regulatory Pathways

- Therapeutic proteins (large molecules) and small molecules are generally guided by a similar regulatory framework with some differences in application content

- Regulatory guidelines that are specific to LM or SM are based on inherent characteristics of these molecules (i.e., proteins vs chemicals)
  - Investigation New Drug (IND) application is required to administer either LM or SM to humans
  - Biologic License Application (BLA) is required for regulatory review and approval of biologics
  - New Drug Application (NDA) is required for regulatory review and approval of small molecules

- IND, BLA, and NDA content differs for biologics and small molecules
  - SMs drugs are more prone to side-effects due to both on-target and off-target causes
  - Assessing both on and off-target effects (tox) and ADME (DMPK/Clin Pharm) requires additional specific testing and strategies from preclinical through regulatory approval
  - LMs may lead to production of anti-therapeutic antibodies which can increase drug clearance

Other complexities may include combination products and drug/device combinations

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# Section Break (Zoom Poll #1)

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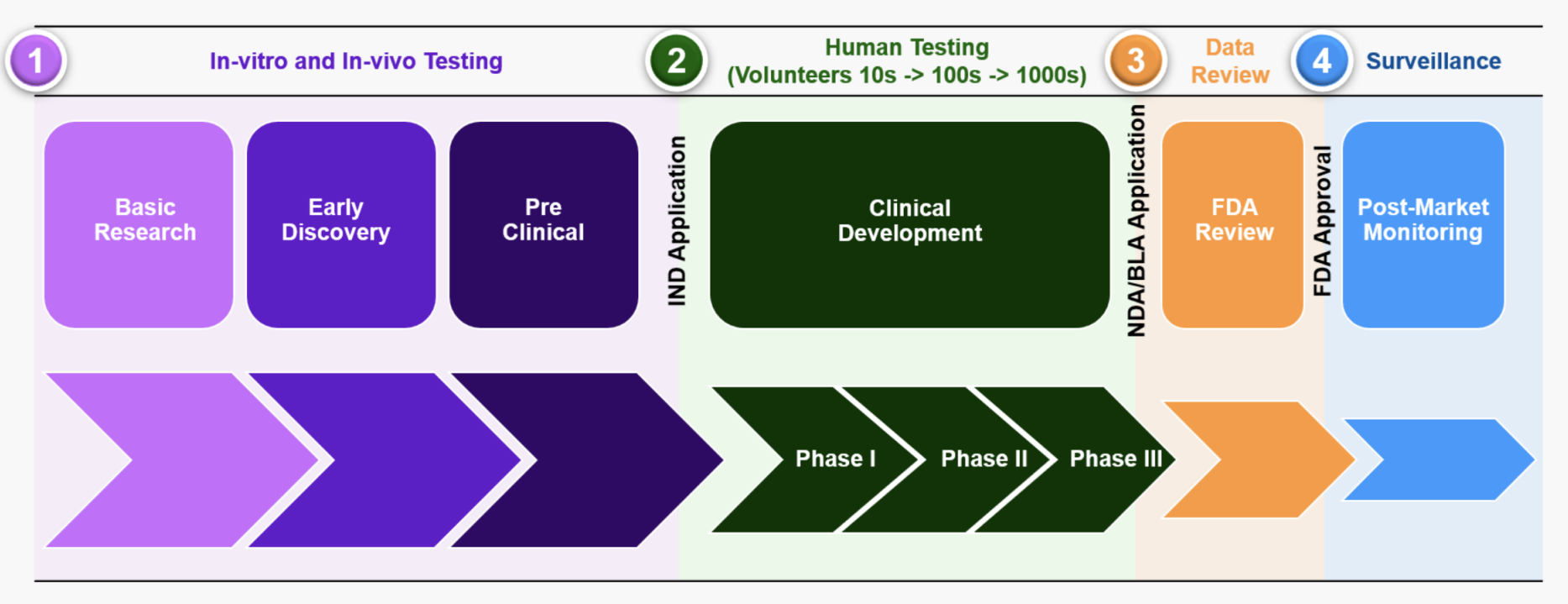
# Section 1: Pre-clinical Testing and IND Application




Source: NorthEast BioLab: "Drug Discovery and Development Process", https://www.nebiolab.com/drug-discovery-and-development-process/

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# Investigational New Drug Application (IND)

- An IND application is a request for authorization from the FDA to administer an investigational drug or biological product to humans

- The IND application must contain information in three broad areas:
  - Animal Pharmacology and Toxicology Studies
  - Manufacturing Information
  - Clinical Protocols and Investigator Information

- Once submitted the sponsor must wait 30 calendar days before initiating any clinical trial
  - FDA will review the IND for safety to assure that research subjects will not be subjected to unreasonable risk
  - FDA may provide the sponsor with notification that it's safe to proceed with the planned study

Source: FDA.gov: "Investigational New Drug (IND) Application", https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application

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# There are Three IND Types

- Investigator-Sponsor IND (Typical)
  - Submitted by sponsor or physician who both initiates and conducts an investigation
  - Physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population
- Emergency Use IND
  - Also called compassionate use or single-patient INDs, are filed for emergency use of an unapproved drug when the clinical situation does not allow sufficient time to submit an IND
- Treatment IND
  - Submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted, and the FDA review takes place

https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application

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# Pre-IND Meetings with the FDA

- Purpose
  - Early interactions with FDA staff can help to prevent clinical hold issues from arising
  - Fosters early communication between sponsors and new drug review divisions to provide guidance on the data necessary to assist in preparing the IND submission

- Potential reasons to request
  - To discuss the scope and design of the Phase 1 trial
  - Novel indication
  - Lack of current relevant guidance documents
  - Unique molecular entity and/or unique studies
  - New sponsors with limited experience
  - Problematic pharmacology/toxicology results

Reference: Guidance for Industry : “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products”

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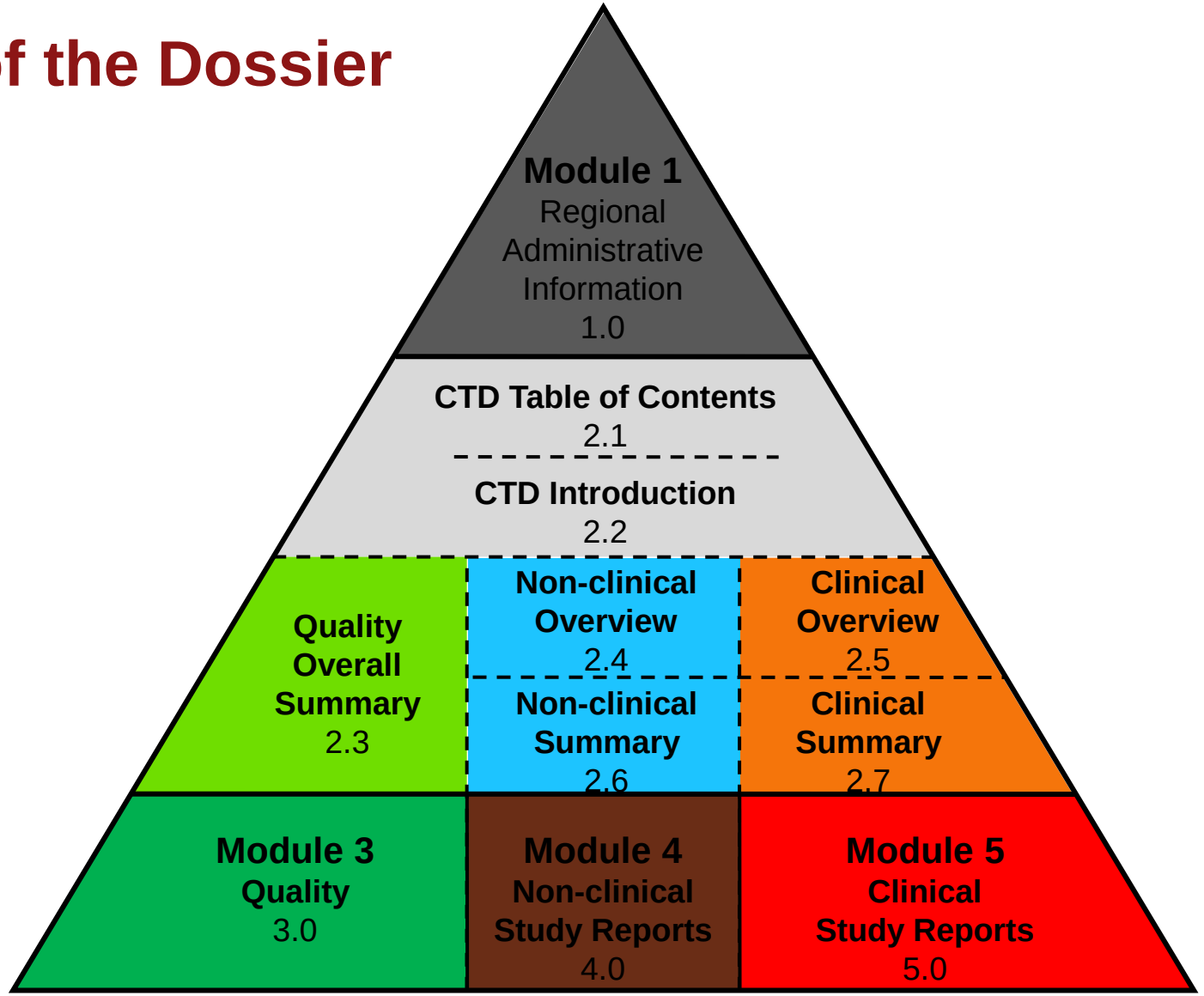
# Overview of the Dossier

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# Regulatory Requirements for an IND

- Chemistry, Manufacturing, and Control (CMC): potency, stability, sterility
  - Composition/controls used for manufacturing the drug substance and product
  - Ensure consistent production and supply consistent batches of the drug

- Animal Pharmacology, Pharmacokinetic and Toxicology Studies
  - Do pre-clinical studies support proposed clinical trial (starting dose, dose escalation)?

- Previous Human Experience With the Investigational Drug
  - Detailed information on previous marketing in US or other countries relevant to safety
  - If marketed outside of US, a list of countries in which the drug has been withdrawn

- Clinical Protocols and Investigator Information
  - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks; including safety and efficacy evaluation, stopping rules, analysis plan
  - Information on the qualification of clinical investigators
  - Commitments to obtain informed consent from research subjects and to obtain review of the study by an institutional review board

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# Chemical Manufacture and Control Requirements for an IND

- Analytical Method
- Degradation Products
- Specifications
- In-process controls
- Methods Validation
- Process Validation
- Drug product and drug substance characterization
- Container / Closure System
- Characterization
- Stability

Amount of information to be submitted depends upon the scope of the proposed clinical investigation (e.g., if short term clinical tests are proposed, stability data may be limited to the same duration)

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# Pharmacology and Drug Disposition Sections of an IND

- Pharmacologic effects and mechanism(s) of action of the drug
- Absorption
- Distribution
- Metabolism
- Excretion

A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known

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# Animal Toxicology and Human Starting Dose for Phase 1

- Regulations and relevant guidance documents
- Nonclinical toxicology requirements
- Selection of the Maximum Recommended Starting Dose (MRSD)

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# Toxicology Studies to Support NMEs are Regulated

- Health authorities worldwide provide regulatory guidance for conducting nonclinical toxicology studies
  - US FDA/EMA Good Laboratory Practices (GLP)
    - US FDA 21 CFR 58
    - Each GLP tox report has a Quality Assurance Statement
  - International Conference on Harmonisation (ICH), members include US, EU, Japan

- Oncology guidance is ICH S9
  - “Nonclinical Evaluation for Anticancer Pharmaceuticals”

- Non-oncology guidance is ICH M3
  - Also applies to adjuvant oncology settings

- Safety Pharmacology ICH S7A/B
  - Effects on cardiovascular, central nervous, and respiratory systems
  - In vitro hERG (QTc prolongation)

- Other: Phototox, genetox, immunotox, carcinogenicity…

# Relevant Guidance Documents

**ICH S1C:** Dose Selection for Carcinogenicity Studies of Pharmaceuticals

**ICH S2 (R1):** Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use

**ICH S3B:** Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies

**ICH S3A:** Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies

**ICH S4A:** Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing)

**ICH S5 (R2):** Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility

**ICH S6:** Preclinical Safety Evaluation Of Biotechnology-Derived Pharmaceuticals

**ICH S7a:** Safety Pharmacology Studies For Human Pharmaceuticals

**ICH S7b:** The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation By Human Pharmaceuticals

**ICH S9:** Nonclinical Evaluation for Anticancer Pharmaceuticals

**ICH E14:** The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic drugs

High Risk IMPs, March 2007: Guideline on requirements for first-in-man clinical trials for potential high-risk Medicinal Products

**ICH M3 (R2):** Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

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# The ICH Guidelines: Studies Needed Prior to Human Exposure

- Genotoxicity (small molecules)
  - A deleterious action on a cell's genetic material affecting its integrity
  - Genotoxic substances are those with affinity to interact with DNA, rendering them potentially mutagenic or carcinogenic
- Safety Pharmacology
  - In vitro and in vivo studies to evaluate the impact on the CVS, CNS, and respiratory systems
- Absorption, Distribution, Metabolism, and Excretion
  - Classical biotransformation studies for large molecules are not required
- Tissue Cross-Reactivity (large molecules)
  - Assure that the experimental antibody does not bind to epitopes other then the target site and this could lead to treatment-related toxicity in human subjects
- Immunogenicity (large molecules)
  - Assessed in repeat-dose toxicity studies for total and neutralizing Abs against the product
- Local Tolerance
  - Evaluation by the intended therapeutic route as part of general toxicity studies
- Single Dose Toxicity Studies
  - Relationship of dose to systemic and/or local toxicity, select doses for repeat-dose studies

General tox studies are project dependent, with duration of dosing to match Phase 1 design and duration

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# The ICH Guidelines: Repeated Dose Toxicology Studies

| Maximum Duration of Clinical Trial | Minimum Duration of Repeat Dose Toxicity Studies to support Clinical Trials | |
|---|---|---|
| | **Rodents** | **Non-rodents** |
| Up to 2 weeks | 2 weeks | 2 weeks |
| Between 2 weeks and 6 months | Same as clinical trial | Same as clinical trial |
| > 6 months | 6 months | 9 months* |

*6 months may be justified in certain circumstances e.g., intermittent treatment or life-threatening diseases such as cancer or when immunogenicity or tolerance problems confound conduct of longer-term studies. In EU, studies of 6 mo duration in non-rodents is acceptable. However, a global package would require 9 mo study.
Clinical trials of longer duration than 6 mo can be initiated providing the data are available from a 3 mo rodent and a 3 mo non-rodent study, and complete data from the chronic rodent and non-rodent study are available before 3 mo of dosing is exceeded in the clinical trial (ICH M3)
Biopharmaceuticals which produce immunosuppression may require longer duration studies to determine potential for emergence of virally related tumors Ref: ICH M3, July 2008

# Key Considerations for the Nonclinical Safety Program

- Characterize the safety and potential risks to humans
  - Is there specific organ toxicity?
  - Is effect reversible?
  - Is effect associated with a biomarker?
  - Is the safety margin acceptable?
- Starting Dose in humans
  - Consider NOAEL (typical) or HNSTD (oncology)
- Guide Clinicians
  - What should be monitored in clinical practice?
  - Clinical biomarker?
- Support Clinical Dosing Duration
  - In general, equal to dosing duration in clinic
  - Support for studies in special populations (e.g., WOCBP)
- Generate Data for Package Insert (drug label)

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# Safety Assessment IND Enabling Program

- General Toxicity
  - Single dose PK/tolerability study in rodent and non-rodent
  - Pilot repeat dose studies in two species
  - Repeat dose studies with recovery in rodent and non-rodent (to match Phase I)

- Genetic Toxicology Battery
  - Ames assay
  - In vitro chromosomal aberrations or in vitro (or in vivo rat) micronucleus study

- Safety Pharmacology (assess CV, CNS, or respiratory changes)
  - hERG (in vitro)
  - Non-rodent CV safety pharmacology study (telemetry for ECG, QT, hemodynamics)
  - Respiratory safety pharmacology study in rodents (pulmonary function)
  - Modified Irwin study (neurobehavioral study) or include in repeat dose tox study

- Reproductive/developmental tox studies conducted later in development
  - Typically prior to Phase 2 (i.e., before exposing further HV or patients)

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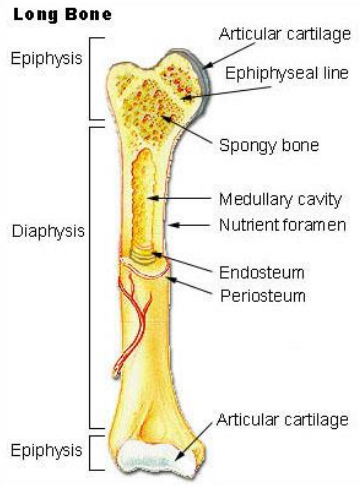
# Repeated Dose Toxicology Study

- Conducted for Large and Small Molecules

- Objective is to characterize toxicity of molecule
  - Apoptosis/proliferation - bone marrow, gut, lymphoid
  - Metabolic effects - pancreas, liver, thyroid, body wt, food con.
  - Degeneration/atrophy - bone, gonads, CNS
  - Necrosis - target organ vs. general
  - Vascular system effects
  - Inflammation




- Identify potential safety liabilities to inform the clinical safety plan and to determine the starting dose

- Typical to conduct initial repeated dose studies as pilots
  - First look at toxicity
  - Use data to select doses for definitive (GLP) studies

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# Repeated Dose Toxicology Study

- First Definitive (GLP) Toxicology Studies for IND
  - Designed to support Phase 1
  - Generally 4 weeks in duration for small molecules to support 4 weeks of clinical dosing
  - Duration for large molecules is generally 8 to 12 weeks
- Subchronic Study - Approximately 13 weeks duration
  - Continue to characterize toxicity
  - Supports longer-term clinical trials up to 3 months duration
  - May also be conducted to bridge to chronic study
- Chronic Study - 6 to 9 months duration (6 months for LMs)
  - Dose selection focused on long term tolerability
- Carcinogenicity - up to 2 years
  - Alternative models may be considered (transgenic mouse)
  - Driven by indication and intended clinical use (i.e., lifetime)

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# Interspecies Scaling for Human Starting Dose Selection

For non-oncology (Healthy Volunteer Study)—MRSD determination

- Avoid toxicity but choose doses that allow reasonably rapid attainment of the trial objectives (tolerability, PD or PK profile)
- Consider all relevant preclinical data
  - Pharmacologically active dose
  - Full toxicologic profile
  - ADME
- Special considerations for oncology, see ICH S9

References:
FDA.gov: "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" July 2005
EMA.Europa.eu: "ICH Topic S9 "Nonclinical Evaluation for Anticancer Pharmaceuticals" December 2008

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# Selection of MRSD for Drugs Administered to Cancer Patients

Setting the Start Dose for First Administration in Humans

Rodent (rat) $STD_{10}$ = 3 mg/kg (18 mg/$m^2$)

↓

*Is 1/10 Rat $STD_{10}$ (1.8 mg/ $m^2$) severely toxic to non-rodents?*

No, the dog HNSTD = 0.3 mg/kg (6 mg/ $m^2$)

↓

*Is the rodent an inappropriate species?*

No

↓

Start Dose = 1/10 Rat $STD_{10}$ = 0.3 mg/kg (rat)

0.3 mg/kg (rat) ´ 0.16 [a] (conversion factor) = 0.05 mg/kg (human)

↓

Therefore,

MRSD = 0.05 mg/kg (human) ´ 60 kg patient weight = 3 mg/day starting dose

**HNSTD = highest non-severely toxic dose; MRSD = maximum recommended starting dose; $STD_{10}$ = severely toxic dose to 10%.**

[a] Rat conversion factor of 6 divided human conversion factor of 37.

Reference:

EMA.Europa.eu: "ICH Topic S9 "Nonclinical Evaluation for Anticancer Pharmaceuticals" December 2008

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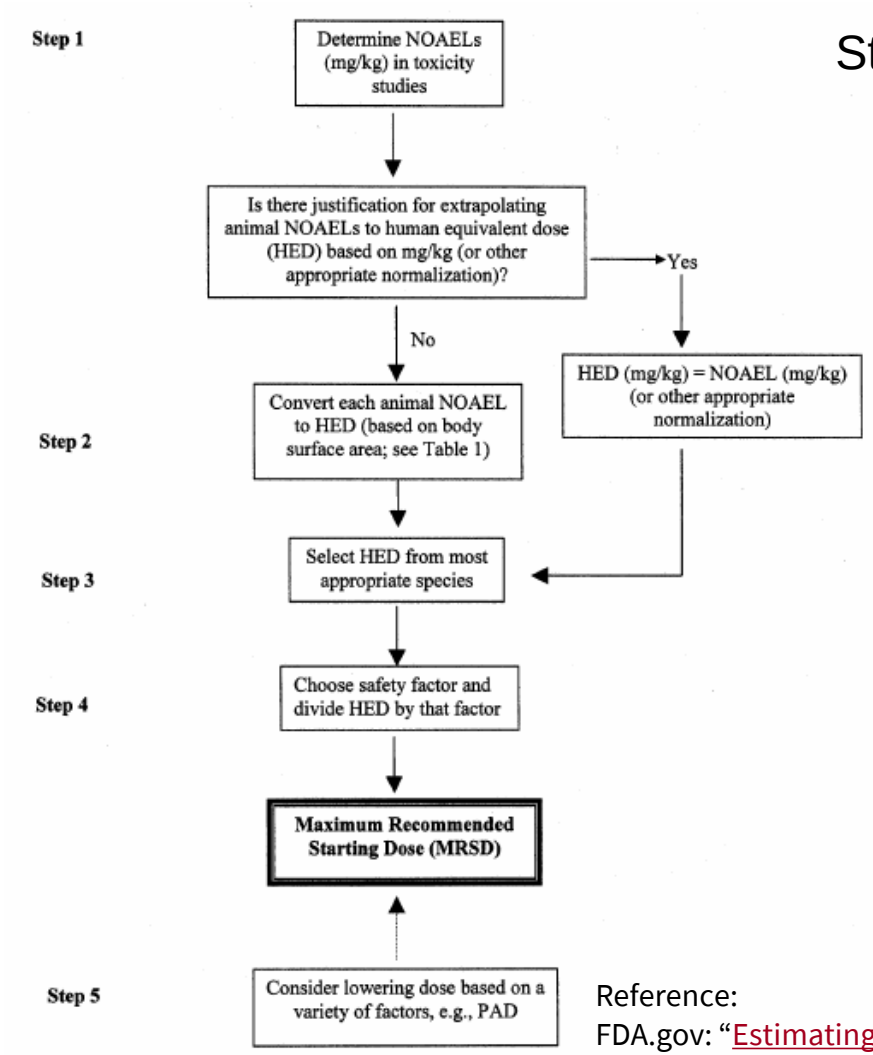
# Selection of MRSD for Drugs Administered to Healthy Subjects




Step 1: No Observed Adverse Effect Level (NOAEL) Determination

Step 2: Human Equivalent Dose (HED) Calculation

Step 3: Most Appropriate Species Selection

Step 4: Application of Safety Factor

Reference:
FDA.gov: "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" July 2005

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# Interspecies Scaling; Maximum Recommended Starting Dose

- Step 1: No Observed Adverse Effect Level (NOAEL) Determination
  - The highest dose level that does not produce a significant increase in adverse effects in comparison to the control group
  - Three types of findings used to determine NOAEL
    - Overt toxicity (clinical signs, macro- and microscopic lesions)
    - Surrogate markers of toxicity (e.g., serum liver enzyme levels)
    - Exaggerated pharmacodynamic effects (e.g., initiation of biochemical cascade)

- Step 2: Human Equivalent Dose (HED) Calculation
  - Conversion based on BSA
  - Conversion based on BW
  - Other exceptions (e.g., alternative routes of administration, administration to anatomical compartments, proteins administered IV, larger than 100,000 Da)

As a general rule, an AE observed in nonclinical toxicology studies used to define a NOAEL for the purpose of dose selection should be based on an effect that would be unacceptable if produced by the initial dose in a trial conducted in healthy volunteers

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# Interspecies Scaling; Maximum Recommended Starting Dose

- Step 3: Most Appropriate Species Selection
  - HEDs calculated from all toxicology species relevant to the proposed human trial
  - In the absence of data on species relevance, the default position is to use the most sensitive species
  - Possible factors to influence the species selection
    - Species differences in ADME
    - Class experience indicating a particular animal is more tox relevant to human
    - Factors unique to biologic products (e.g., expression of relevant receptors or epitopes)

- Step 4: Application of Safety Factor; default factor is 10
  - Provides a margin of safety for protection of human subjects
    - Uncertainties due to enhanced sensitivity to pharmacologic activity in humans
    - Difficulties in detecting certain toxicities in animals (e.g., headache, myalgias, mental disturbances)
    - Differences in receptor densities or affinities
    - Unexpected toxicities
    - Interspecies differences in ADME

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# Regulatory Decision Making at the IND Stage

- Allow study to proceed
- Impose full clinical hold
- Impose partial clinical hold
  - Limit on dose escalation
  - Exclude some indications or ages
- Exemptions (to reduce burden on researchers)
  - Trial results will not be used for approval of new indication or for labeling changes and
  - Trial is not intended to change advertising and
  - Trial does not involve a route or dose or population that significantly increases risk

The regulatory goals of an IND review are to protect safety and rights of human subjects and to ensure scientific quality of the clinical investigation to permit evaluation of drug's safety and activity

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# Potential Reasons for Clinical Hold

- Subjects at unreasonable risk for injury
  - Dose not supported by non-clinical studies
  - No safety stopping rules
- IND does not contain sufficient information to assess the risks of the trial
- IB misleading or incomplete
- Unqualified investigator

Lifting of Clinical Hold: (1) sponsor corrects deficiencies, (2) sponsor submits FDA “Complete Response” to ALL hold issues with appropriate justification to proceed, (3) FDA responds within 30 days of receipt of the “Complete Response”

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# Special Case of Exploratory IND: Microdose Study

- Clinical study where sub-pharmacological doses are administered to primarily assess the PK of a molecule
  - Total dose < 1/100 of the dose calculated to yield a pharmacological effect up to a maximum total dose of 100 µg
- Can be used to ascertain human PK in a Phase 0 setting before a molecule enters full development
  - Single dose study, IV/oral, healthy volunteers (N=4 to 6)
- Useful tool for projects where human PK can be the driver for decision making and there is low confidence in preclinical PK predictions
- Minimal data package required compared to a regular FIH study
  - Only about 10g of 'GMP-like' compound
  - single dose rat tox package "+"
  - eIND or CTA

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Reference: A pharmacokinetic evaluation of four novel H1 antagonists and one reference compound diphenhydramine after an oral and intravenous microdose to human subjects (HVs). Madan et al., 2008 BJCP

# Section Break (Zoom Poll #2)

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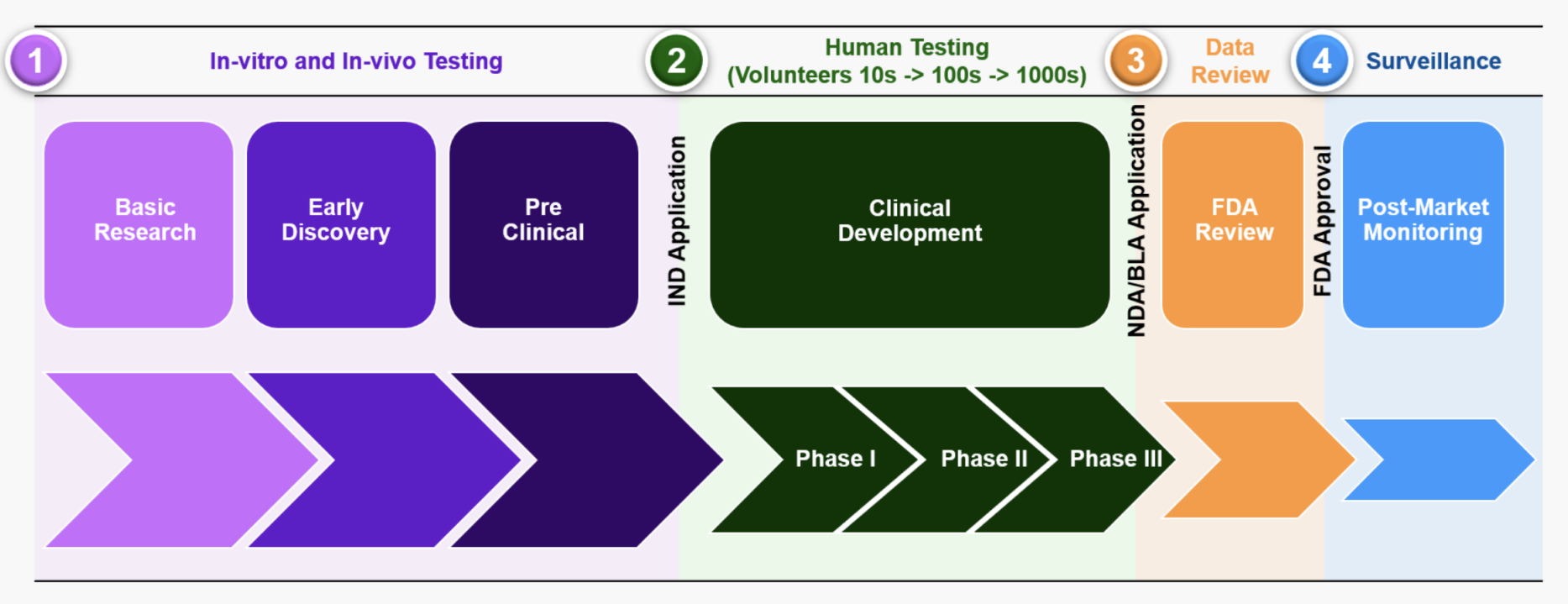
# Section 2: Human Testing and Clinical Development




Source: NorthEast BioLab: "Drug Discovery and Development Process", https://www.nebiolab.com/drug-discovery-and-development-process/

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# Considerations for First Time in Human Trials

- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s)
- Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society
- A trial should be initiated and continued only if the anticipated benefits justify the risks
- The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society

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# Institutional Review Board and Independent Ethics Committee

- An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects
- Special attention should be paid to trials that may include vulnerable subjects
- The IRB/IEC should
  - Review a proposed clinical trial within a reasonable time
  - Consider investigator qualifications
  - Conduct continuing review, at least once per year
  - Ensure protocol addresses relevant ethical concerns and meets applicable regulatory requirements
  - Review amount and method of payment to subjects to assure no undue influence

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# Investigator's Brochure

- Intended to provide the investigator with insights necessary for the management of study conduct and study subjects throughout a clinical trial

- May include key aspects and safety measures of a clinical trial protocol
  - Dose (of the study drug)
  - Frequency of dosing
  - Methods of administration
  - Safety monitoring procedures

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# Typical Goals of a Phase 1 Study; Safety and Dosage
## (20 to 100 HV or people with disease/condition)

- Drug metabolism and pharmacological actions
- Side effects as they relate to dose
- Immunogenicity (Large Molecules)
- Determination of dose limiting toxicity and maximum tolerated dose
- Drug activity
- Pharmacodynamic biomarkers to predict response

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Reference:. Key Concepts of Clinical Trials: A Narrative Review. Umscheid et al., Postgrad Med. 2011 Sep; 123(5): 194–204

# Phase 2 Trials; “Therapeutic Exploratory Trials”
## (up to several hundred people with disease/condition)

- Duration of several months to 2 years
- Answer questions essential to phase 3 planning
- Optimization of dosage (amount and frequency), route, and endpoints
- Preliminary assessment of efficacy
- Limited statistical power to establish efficacy
- Provides data for end of phase 2 meeting with FDA

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Reference:. Key Concepts of Clinical Trials: A Narrative Review. Umscheid et al., Postgrad Med. 2011 Sep; 123(5): 194–204

# Phase 3 Trials; "Therapeutic Confirmatory or Pivotal Trial"
## (300 to 3,000 people with disease/condition)

- Duration of 1 to 4 years
- May compare intervention with standard of care or placebo
- Many different design types (equivalency, noninferiority, etc)
- Typically balanced in treatment allocation to eliminate biases
- May include stratification to balance arms on prespecified characteristics
- Generally blinded to minimize assessment bias of subjective outcomes

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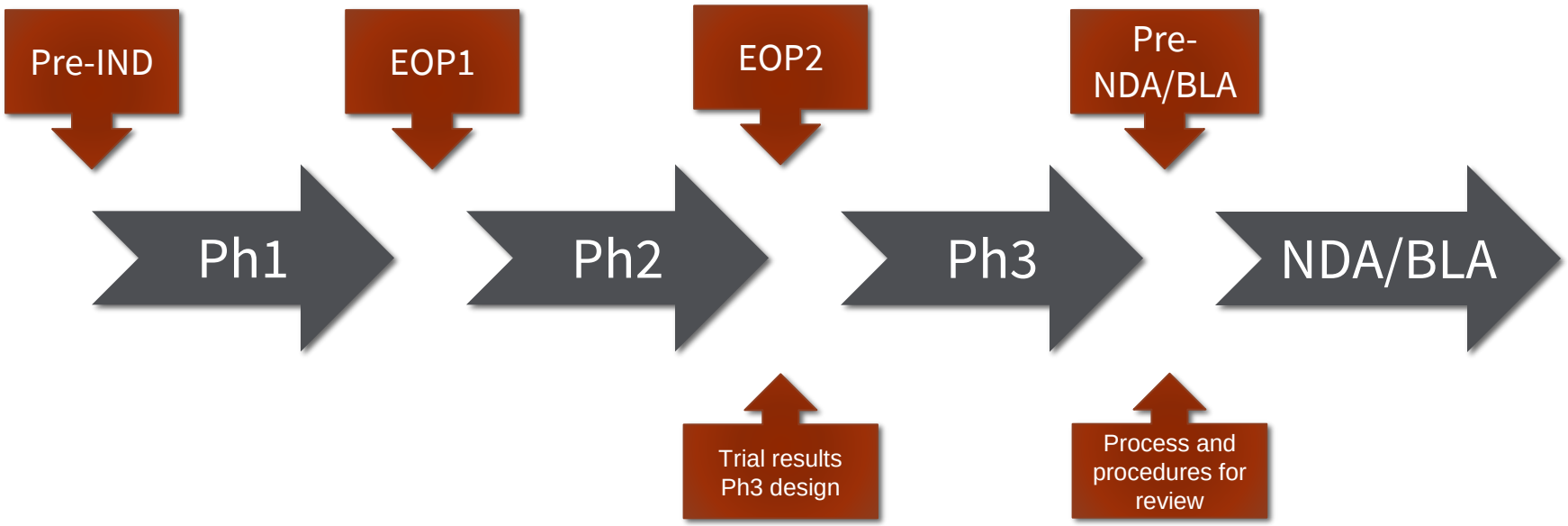
Reference:. Key Concepts of Clinical Trials: A Narrative Review. Umscheid et al., Postgrad Med. 2011 Sep; 123(5): 194–204

# Formal Meetings Between FDA and Sponsors or Applicants




- Consultation on data format
- Consultation on electronic submission

Source: FDA.gov: "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products"

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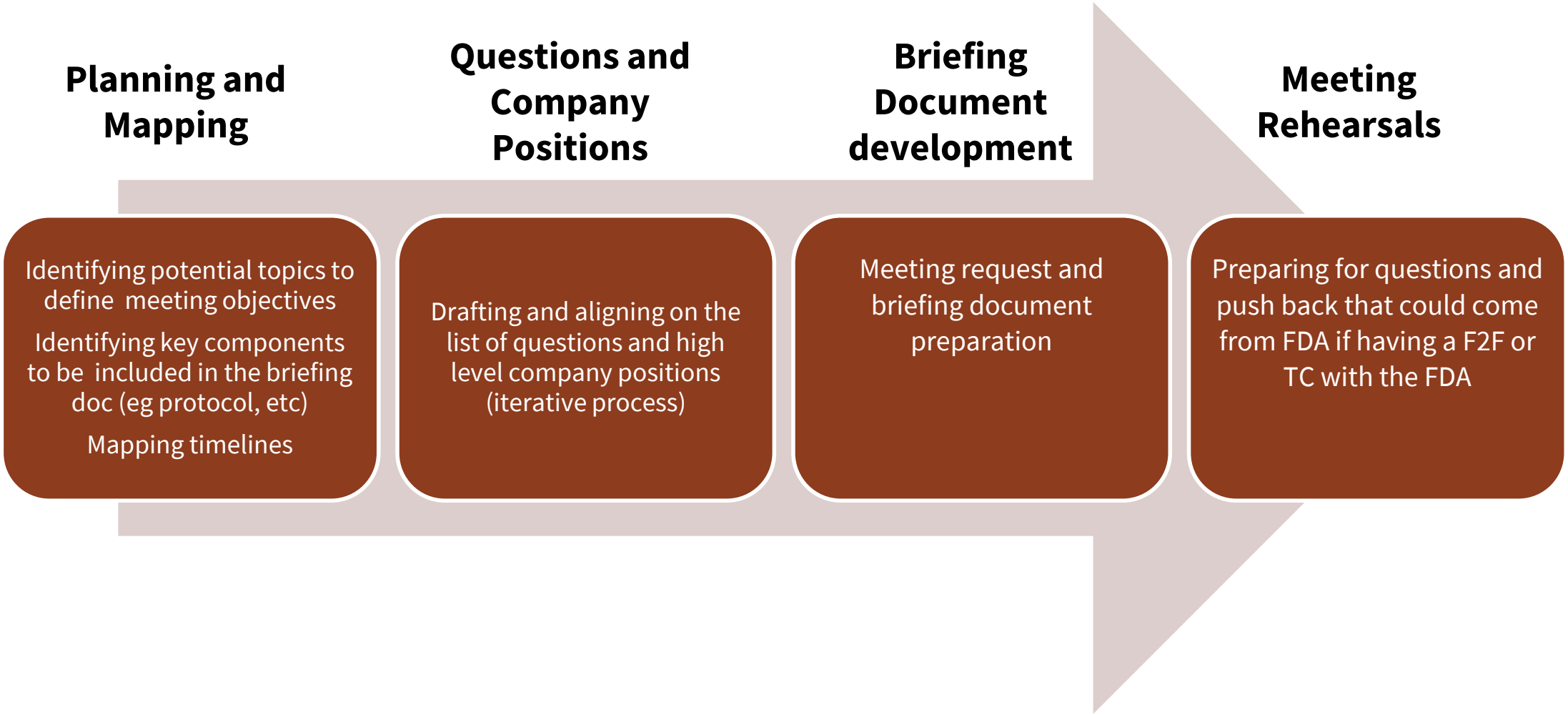
# Preparing for FDA Meetings

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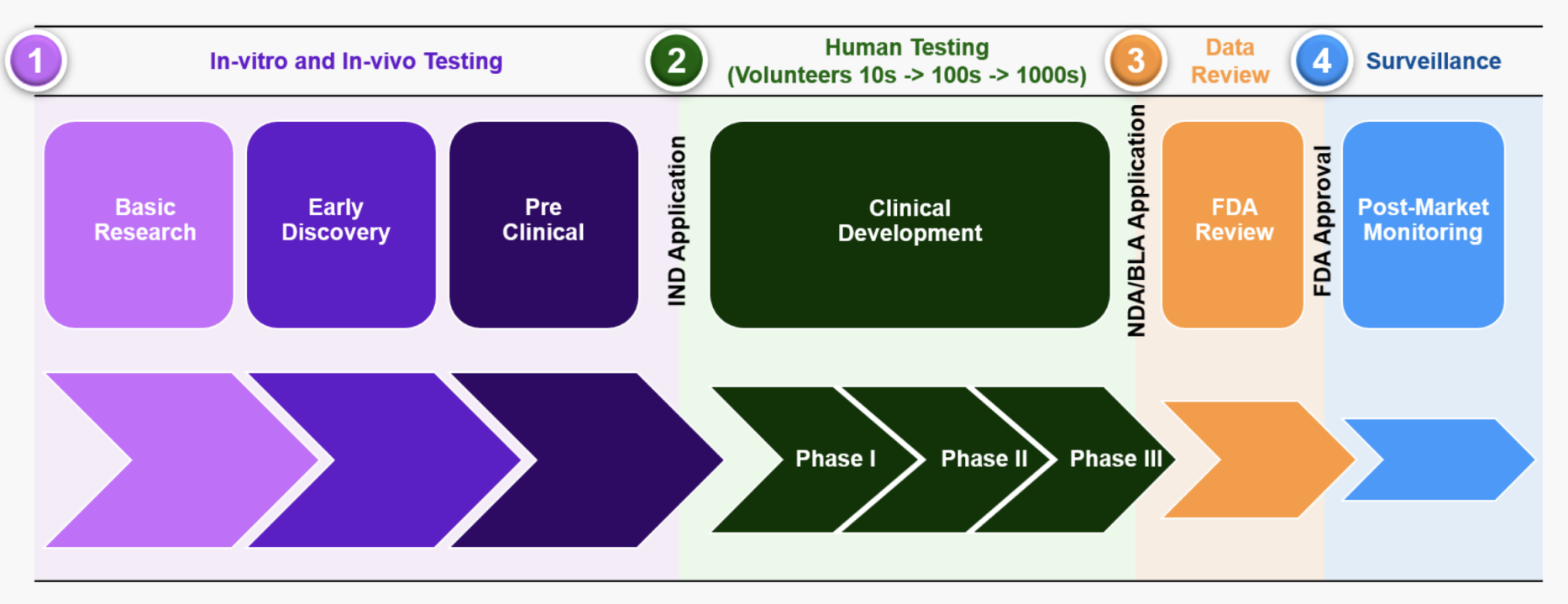
# Section 3: Regulatory Approval Pathways




Source: NorthEast BioLab: "Drug Discovery and Development Process", https://www.nebiolab.com/drug-discovery-and-development-process/

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# FDA Expedited Programs for Serious Conditions Drugs and Biologics

**Terrell Baptiste, MBA**

Global Regulatory Policy and Intelligence, Oncology Lead
Gilead Sciences

# Expedited Programs for Serious Conditions Drugs and Biologics

**Regular Approval (RA):** Direct evidence of clinical benefit (longer or better life) or established surrogate endpoints for clinical benefit

**Priority Review**

FDA's goal is to act on an application within 6 months

**Accelerated Approval**

Allows drugs for serious conditions with unmet medical need to be approved based on a surrogate endpoint

**Fast Track**

Designed to facilitate drug development and expedite the review of drugs to treat serious conditions and fill an unmet medical need

**Breakthrough Therapy**

Designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy

**Background**

Roots of expedited programs to date back to the **HIV/AIDS crisis**;

**Expedited Programs**

1. **Shorten** the timeline for **demonstration efficacy** (through use of surrogate endpoints) and;
2. Reduce the **timeframe of NDA review** by FDA.

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# Expedited Programs for Serious Conditions and HIV Drug Approval

**Does History Repeat itself?**



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# Expedited Programs for Serious Conditions

| | Unmet Medical Need | Surrogate Endpoint | Clinically Significant Endpoint | Serious Disease or Condition | Significant improvement |
|---|---|---|---|---|---|
| Key Definitions | An unmet medical need is a condition whose treatment or diagnosis is not addressed adequately by available therapy; includes an immediate need for a defined population or longer-term need for society[1] | Substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit[2] | (For Breakthrough Therapy) End points based on irreversible morbidity or mortality (IMM), or on symptoms that represent serious consequences of the disease[3] | Disease or condition associated with morbidity that has substantial impact on day-to-day functioning[4] | • Evidence of increased safety and effectiveness in treatment, prevention, or diagnosis of condition (or subpopulation)<br>• Elimination or substantial reduction of a treatment-limiting drug reaction<br>• Documented enhancement of patient compliance impacting serious outcomes[5] |

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# Priority Review

| | |
|---|---|
| **Established** | Prescription Drug User Act (PDUFA) of 1992 |
| **Requirements** | Must address a **serious condition**; and<br>Demonstrate, via scientifically valid information/clinical trial data, possible **significant improvement** in safety or effectiveness over standard of care |
| **Features** | Request is made with NDA/BLA submission **late in development**<br>FDA aims to act on a drug sponsor's marketing application in **six months, compared with ten months** for standard review |
| **Benefits** | • **Directs overall attention** and **resources** to the evaluation of applications **as compared** to **standard** applications<br>• Time |

## FDA's priority review vouchers (PRV)

Spur development of treatments for diseases with less commercial appeal

- Tropical Disease
- Rare Pediatric Disease
- Material Threat Medical Countermeasure

**Market for PRVs**

Reference: FDA.gov: "Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review"

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# Fast Track Designation

| | |
|---|---|
| **Established** | Section 506(b) of the FD&C Act, as added by section 112 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and amended by section 901 of the Food and Drug Administration Safety and Innovation Act of 2012 |
| **Requirements** | Intended, for the **treatment of a serious or life-threatening disease** or condition, and **could address unmet medical need** or is **qualified infectious disease product**<br>FTD can be requested **as early as the IND; fast track designations must only have the potential to address an unmet medical need** |
| **Features** | • FDA response time for FTD is within **60 calendar days** of receipt of the request<br>• Actions to expedite development and review<br>• Rolling review |
| **Benefits** | • Development program can be accelerated through increased interactions with the FDA<br>• Product could be eligible for priority review at NDA/BLA submission<br>• FDA may consider reviewing portions of the marketing application before the application is complete (known as "rolling review") |

Recent analysis found that the development time from IND application to FDA approval was, on average, a year shorter for FTD products than for products without this designation

Reference: FDA.gov: "Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review"

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# Breakthrough Therapy Designation

| | |
|---|---|
| **Established** | 2001; Section 506(a) of the FD&C Act, as added by section 902 of FDASIA |
| **Requirements** | Drug is intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate **substantial improvement** over existing therapies on 1 or more **clinically significant endpoints**, observed early in clinical development. |
| **Features** | • Can be requested at the time the IND is opened<br>• Can also be requested anytime thereafter, although ideally no later than the End-of Phase 2 meeting<br>• FDA response time for BTD is within 60 calendar days of receipt of the request |
| **Benefits** | • Same as Fast Track Benefits<br>• Intensive guidance on an efficient drug development program, beginning as early as Phase 1<br>• FDA organizational commitment involving senior managers, and a cross-disciplinary project lead from FDA |

A recent analysis of 2012-2016 drug approvals found that the development time from IND application to FDA approval was, on average, over 3 years (!) shorter for BTD products than for products without this designation (Hwang, 2017).

Clinically Significant Endpoints

- Surrogate endpoint
- Pharmacodynamic biomarker
- Improved safety profile

**FDA working to update**

Reference: FDA.gov: "Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review"
https://camargopharma.com/resources/blog/breakthrough-the-barriers-breakthrough-therapy-designation-for-505b2/

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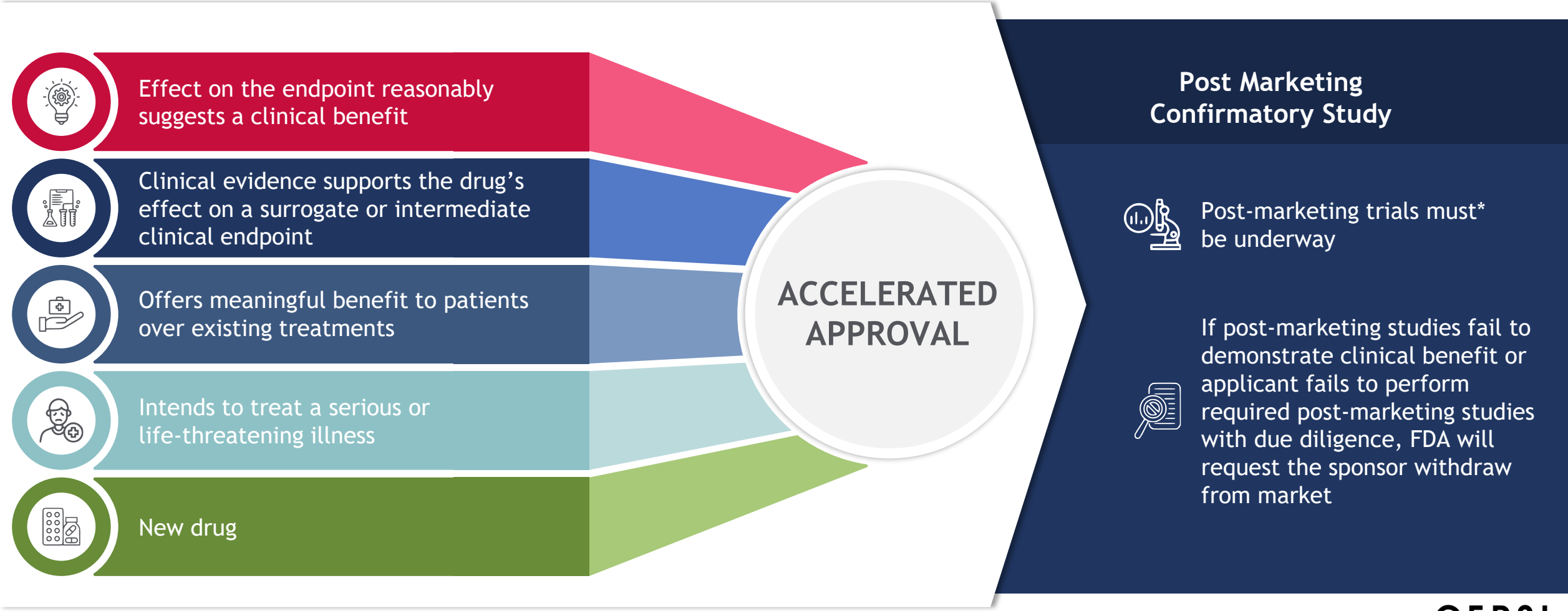
# Accelerated Approval Pathway

| | |
|---|---|
| **Established** | 1992 21 CFR part 314, subpart H 21 CFR part 601, subpart E Section 506(c) of the FD&C Act, as amended by section 901 of FDASIA |
| **Requirements** | Must treat a serious condition AND provide a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint) |
| **Features** | Drug companies are required to conduct studies to confirm the anticipated clinical benefit.<br>If the confirmatory trial shows that the drug provides a clinical benefit, then the FDA grants approval for the drug. |
| **Benefits** | • Potential smaller sample size for clinical trials for approval<br>• Potential early read out and overall shorter clinical trial period (assuming surrogate precedes the clinical benefit endpoint by a significant amount)<br>• Potential early access to therapies for patients with serious illnesses<br>• Potential faster timeline to approval<br>• Potential for reduced development cost |
| **Standards** | "[T]he **evidence available at the time** of approval under this rule **will meet the statutory standard**, in that there must be **evidence** from **adequate and well-controlled studies showing that the drug will have the effect it is represented to have in its labeling.**" > "An [**accelerated**] **approval based on assessment of a different type of data demonstrating** "that the same statutory standard **has been met.**" |

# Accelerated Approval Pathway

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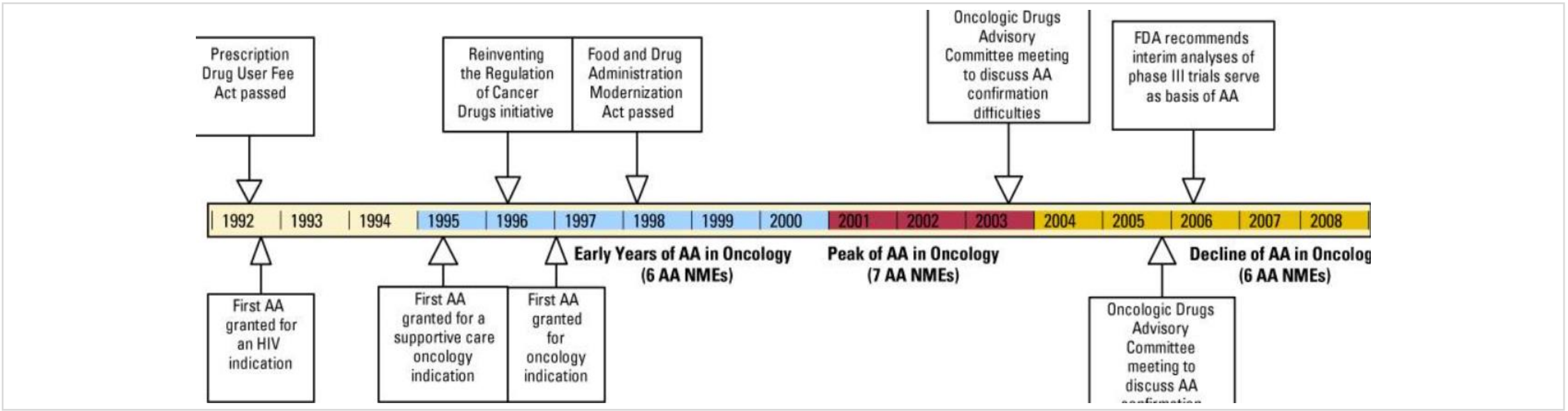
# Accelerated Approval History




- Early AAs were based on an interim analysis of a surrogate endpoint evaluated in Randomized Controlled Trials (RCT)
- Subsequent demonstration of clinical benefit and regular drug approval usually were based on final analysis of a non-surrogate or established endpoints in the same trial

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

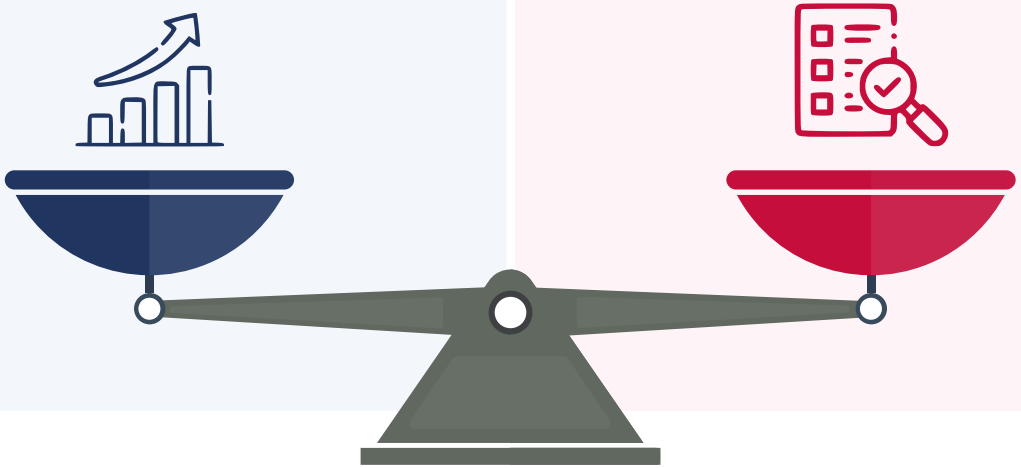
J Clin Oncol. 2009 Sep 10; 27(26): 4398–4405. PMCID: PMC2744277
Published online 2009 Jul 27. doi: 10.1200/JCO.2008.21.1961 PMID: 19636013

**Accelerated Approval of Cancer Drugs: Improved Access to Therapeutic Breakthroughs or Early Release of Unsafe and Ineffective Drugs?**

Elizabeth A. Richey, E. Alison Lyons, Jonathan R. Nebeker, Veena Shankaran, June M. McKoy, Thanh Ha Luu,

# Accelerated approval has successfully allowed for approval of transformative drugs years earlier

**Earlier marketing of promising drugs with increased uncertainty**



**Re-evaluation necessary when results change the risk/benefit**

Beaver, J. A., & Author Affiliations From the Oncology Center of Excellence. (2021). *"Dangling" accelerated approvals in oncology: Nejm.*

The NEW ENGLAND JOURNAL of MEDICINE

"The small percentage of drugs whose clinical benefit is **ultimately not confirmed should be viewed not as a failure of accelerated approval but rather as an expected trade-off** in expediting drug development that benefits patients with severe or life-threatening diseases."

# New Law “Modernizes” Accelerated Approval

Establishment of an FDA intra-agency Accelerated Approval Council

- Senior FDA leadership
- RWE may be used for PMR

Draft and Final guidance re AA

- Early novel trial design discussions
- AA novel endpoints/surrogates
- Statutory “authority” to require PMR
- Expedited withdrawal procedures

12/31/2023

First report 12/31/2023

Draft 6/30/24 8/31/25

FDA

Annualized AA Council report on FDA website

- AA details e.g., PMR etc
- Sponsors progress report required post-approval studies **every six months**

**CDER Guidance Agenda**
**New & Revised Draft Guidance Documents**
**Planned for Publication in Calendar Year 2023[1]**

Civil Monetary Penalties for Failure to Meet Accelerated Post Marketing Requirements (Updates 2011 Guidance)

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# Accelerated Approval Pathway Horizon

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

**STRENGTHENING THE ACCELERATED APPROVAL PATHWAY: AN ANALYSIS OF POTENTIAL POLICY REFORMS AND THEIR IMPACT ON UNCERTAINTY, ACCESS, INNOVATION, AND COSTS**

April 26, 2021

The New York Times

House Committees Demand F.D.A. Records on Alzheimer's Drug Approval

A later analysis by Biogen found that participants receiving the highest dose of aducanumab in one trial experienced a very slight slowing...


**Trust in Data**

Single Arm Studies/ Observational Studies FDA called "single arm studies a collection of case studies." * rare disease and genetically likely excluded

**Interest in Pricing**

**Rob Califf** - Some wisdom to drugs costing less until you have full approval and demonstration of efficacy

**Trials must be underway**

"There is a significant difference between setting an "expectation" about having clinical trials under way at the time of approval vs the statutory "authority" to require it"


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# End of Section (Zoom Poll #3)

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# Overall Summary: Key Points to Consider

- FDA is responsible for protecting and promoting public health through the control of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices, cosmetics, animal foods & feed and veterinary products

- An IND application is a request for authorization from the FDA to administer an investigational drug or biological product to humans

- In vitro and in vivo (animal) experiments are essential prior to administration of a new molecule entity to human subjects and form the basis of an IND

- Medical product development is a long process with high regulatory standards.  FDA has developed approaches to making drugs available as rapidly as possible.

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