IND Application Process: For The New Clinical Investigator

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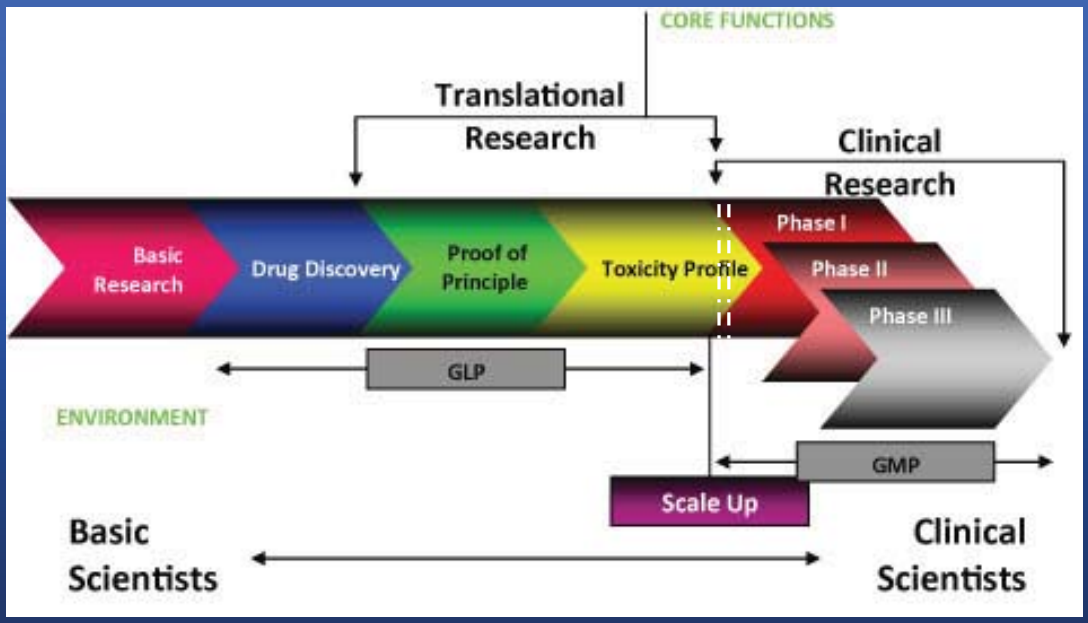
Presentation Outline

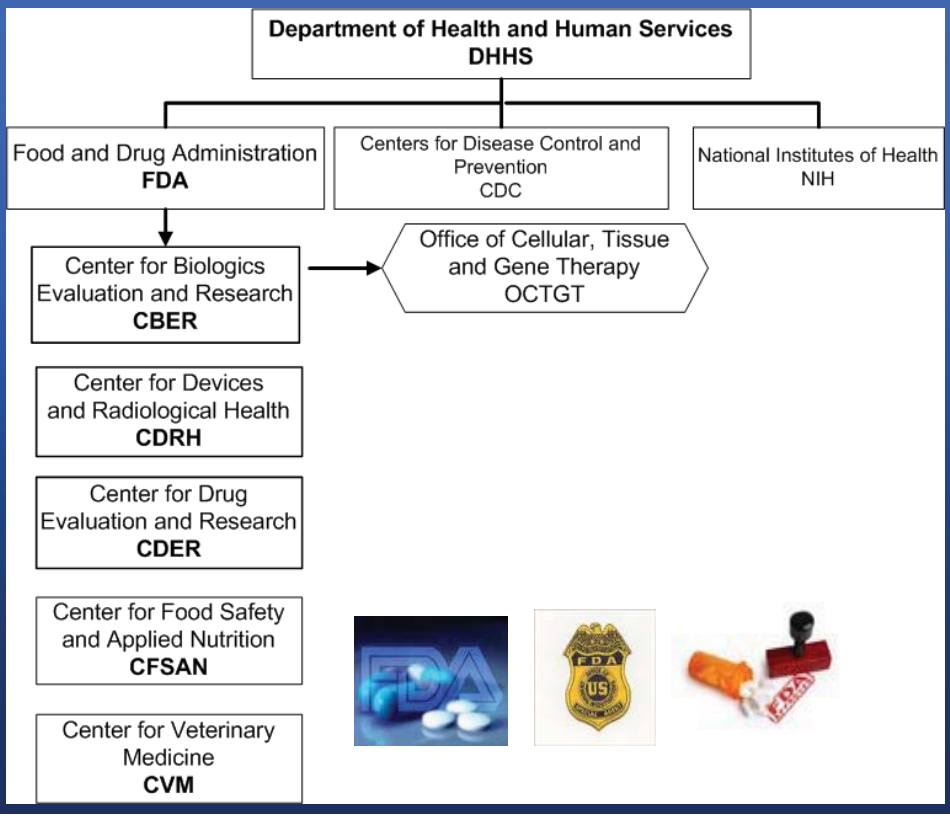
- Journey from basic to clinical research
- Introduction to FDA
- Product Development Timeline
- Clinical Research Roadmap - Cellular Therapy
- FDA communications and submissions

From Basic to Clinical Research

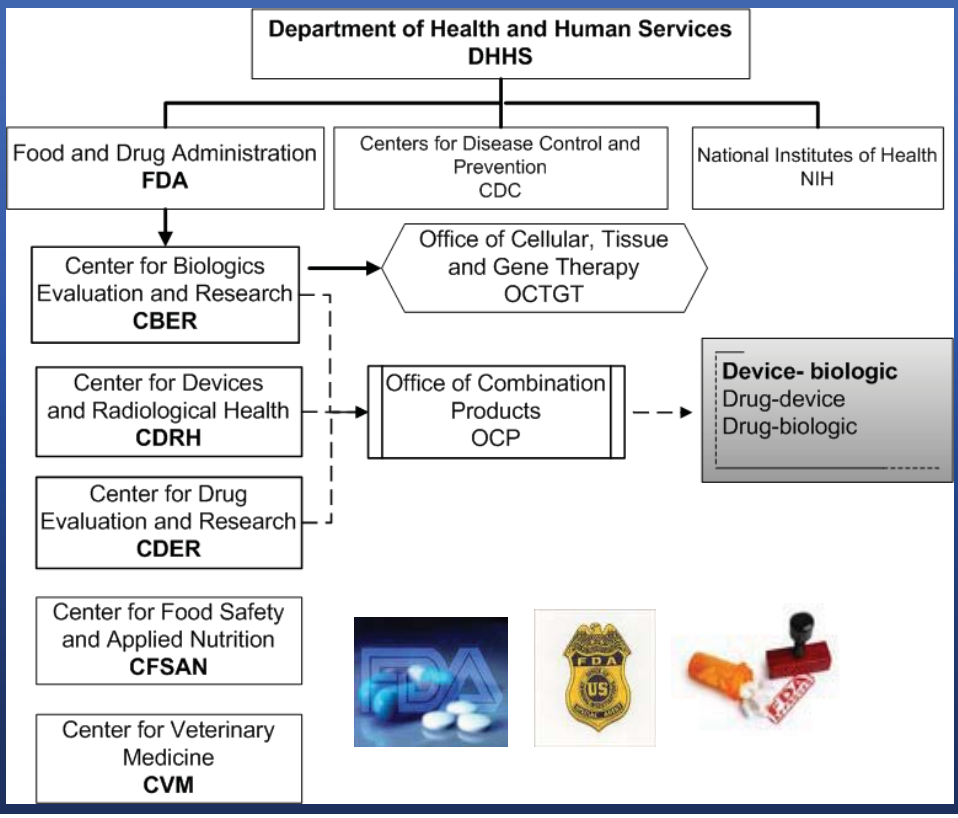


NHLBI, NIH- PACT Manual of Procedures (MOP)

Introduction to FDA



Introduction to FDA



Common FDA Applications

	DRUG	BIOLOGIC	DEVICE
Product Type:			
Investigational Use:	IND	IND	IDE

IND- Investigational New Drug
IDE- Investigational Device Exemption

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Devices

Class I- low risk (e.g., disposable gloves, syringes)

Class II- intermediate risk (e.g., blood glucose tests, infusion pumps)

Class III- greatest risk (e.g., life saving or sustaining implantable devices)

Common FDA applications

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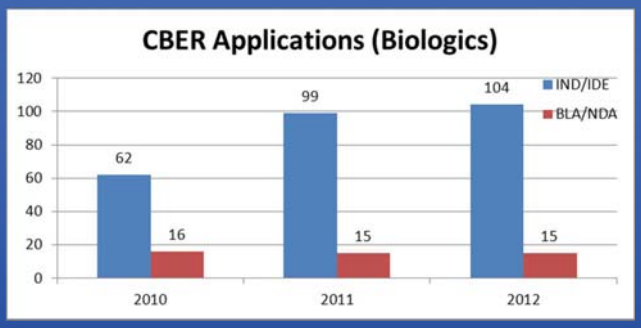
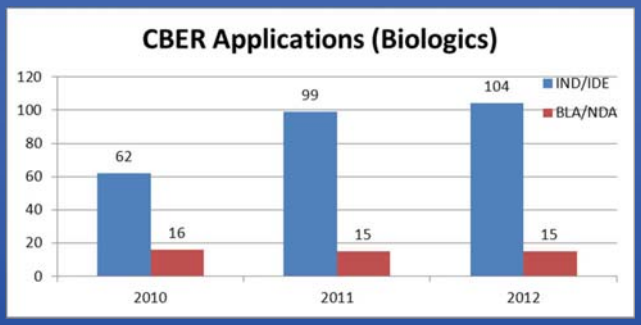
Commercialization:	NDA	BLA	PMA

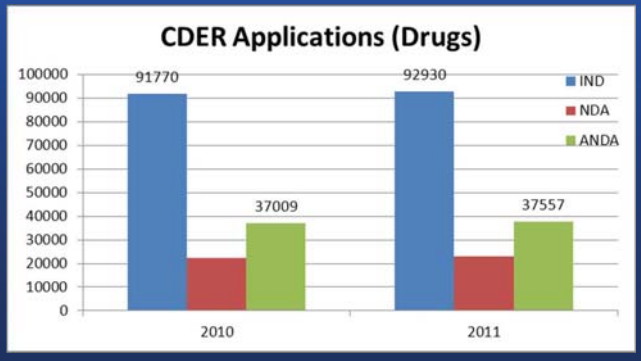
NDA- New Drug Application
BLA- Biologics License Application
PMA- Premarket Approval Application

Applications Reviewed by FDA



Applications Reviewed by FDA



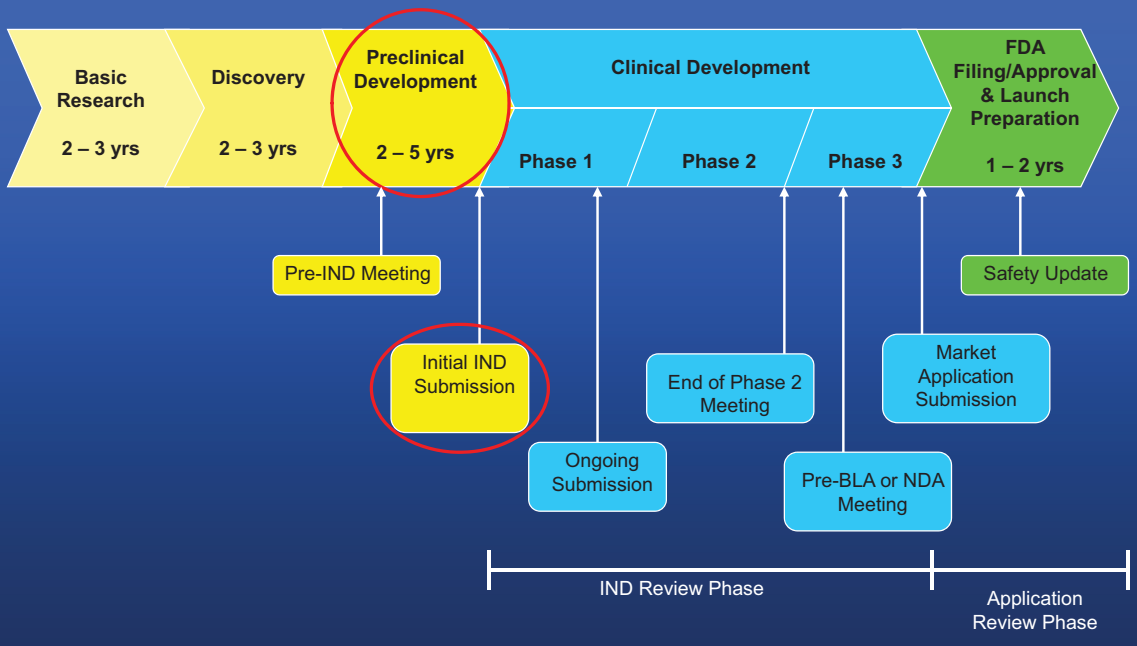


Drug versus Biologic Development

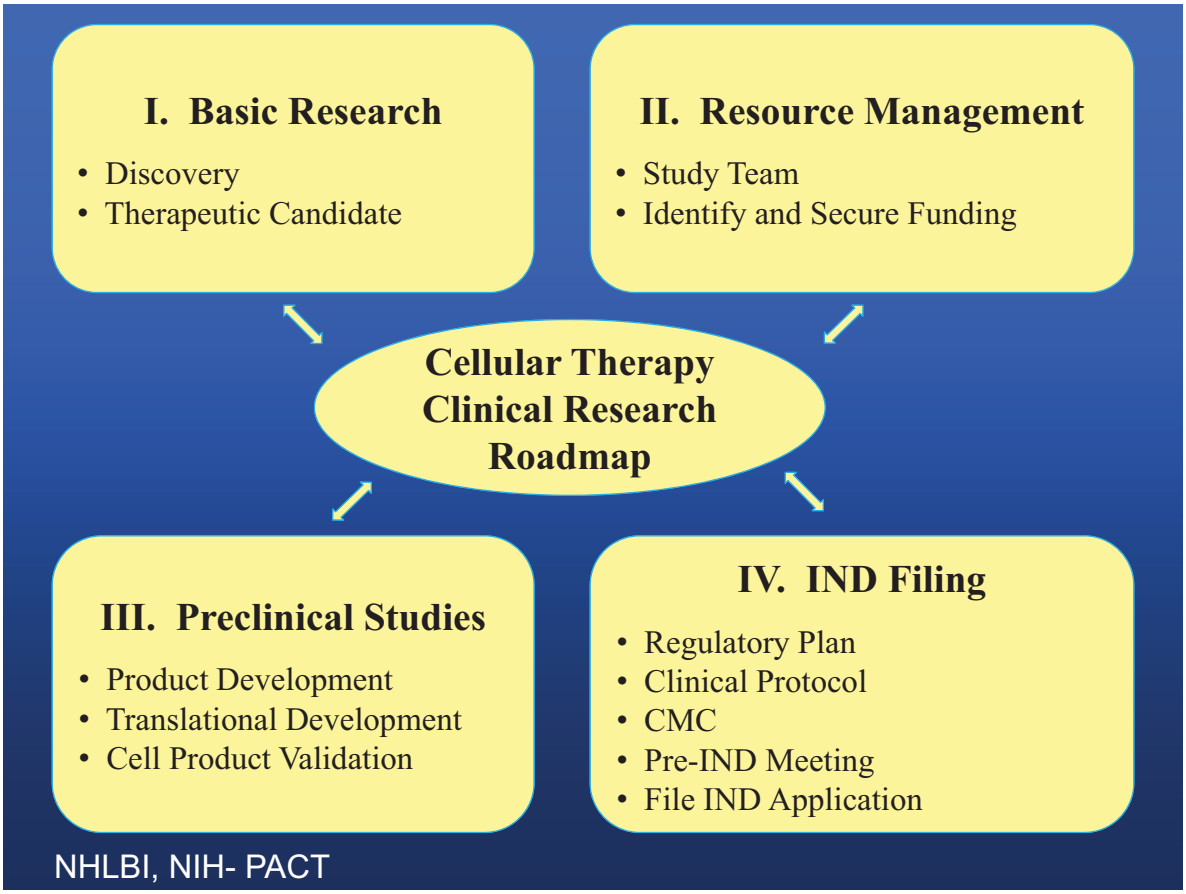
	Drugs	Biologics (Cell Therapy)
Properties:	Fixed- traditional decay	Dynamic- gene expression
Manufacturing:	Fixed/automated/closed	Complex/manual/open "the process is the product"
Batch size:	Large- 1000's of doses	Small- 10-Tray cell factory
Mode of action:	Some known	Mostly unknown
Active ingredient:	Typically single	Host of factors
Average daily treatment cost:	$ 2/day*	$ 45/day*

*Himchlor, Ben, "FDA Rebuffs Novartis Over Delay to Biogeneric Drug," *Reuters News* 15 November 2005.

Product Development Timeline



Adopted from www.fda.gov Industry - FDA Interactions During Development



I. Basic Research

- Discovery and Therapeutic Candidate
  - Research and Development
  - Proof-of-concept studies
  - Animal studies
  - Cellular product and disease interaction
- Goals
  - Publications
  - Identify clinical potential
  - Define cellular product
  - Intellectual Property Landscape, “freedom to operate”

II. Resource Management

- Assemble Study Team
  - Clinician, biostatistician, regulatory, technology transfer, Project Manager, manufacturing staff
- Identify Source of Funding
  - Preclinical, technology transfer, scale-up, IND filing, clinical development
- Goals
  - Establish a study team
  - Secure funding for preclinical and clinical research

III. Preclinical Studies

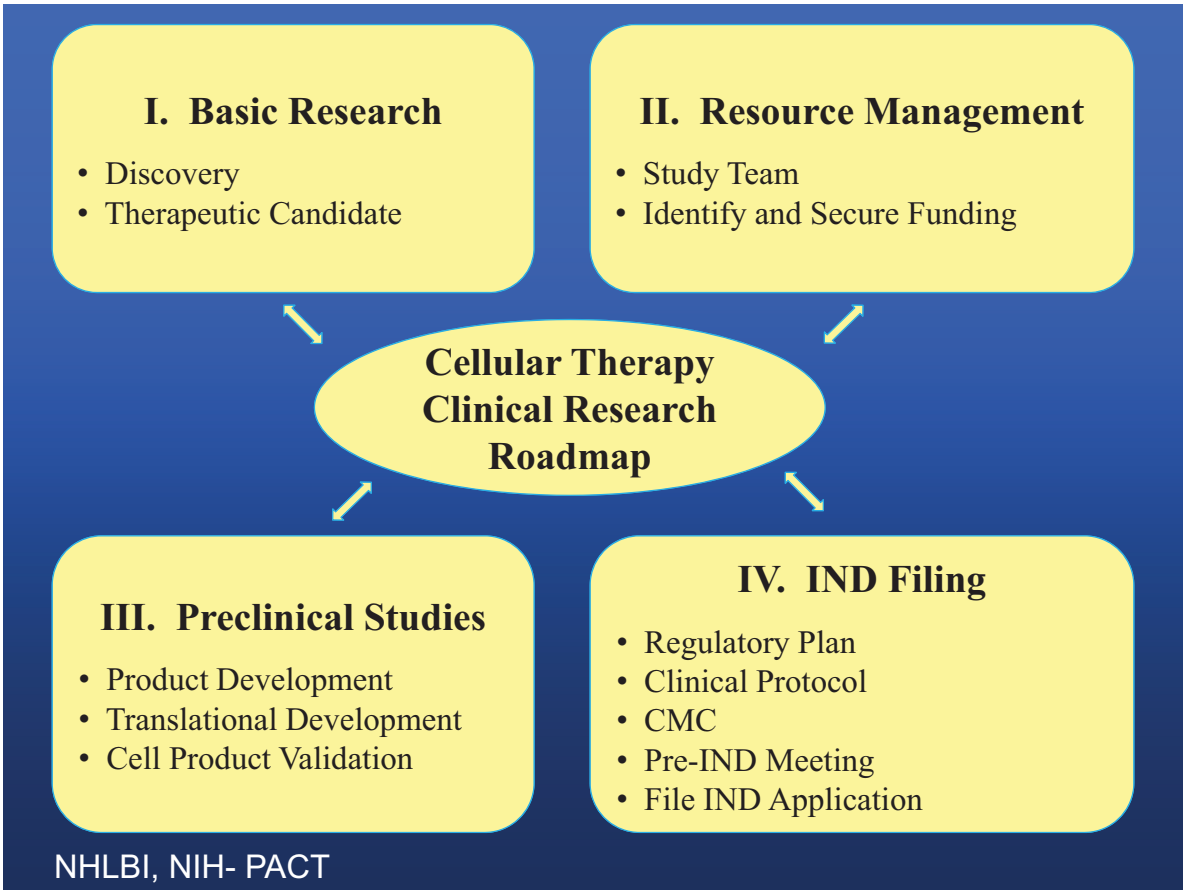
- Product Development
  - Preclinical safety studies, animal model, dose escalation, scale-up, other studies to support IND
- Translational Development & Product Validation
  - Cell product characterization, safety testing, assay development, packaging/shipping, release criteria
- Goals
  - Documentation: SOPs, batch production record, qualification/validation protocols, CMC for IND

IV. IND Filing

- Develop a Regulatory Plan
  - Identify FDA contacts, plan FDA communications
- Chemistry, Manufacturing, and Controls (CMC)
  - Production process, cell source/donor testing, sourcing and testing of reagents/components
  - Testing product stability, safety and quality
- Complete the Clinical Protocol
  - Study summary, preclinical safety data, summary data

IV. IND Filing (cont.)

- Pre-IND Meeting
- Filing an IND Application
  - Cover Letter, Form 1571, TOC, Introductory Statement, General Investigational Plan, Clinical Protocol, CMC, Safety data (pharmacology/toxicology), Form 1572
- Goals
  - Identify documentation to support IND filing
    - SOPs, batch production record, qualification/validation protocols
    - Clinical protocol and synopsis, CMC information, other documents
  - Submit IND application to FDA



Pre-IND Preparation

1. Have key clinical elements defined
   - Identify Lead Clinical Investigator
   - Draft clinical protocol - indication, dose, delivery, inclusion/exclusion criteria, standard of care
   - Defined- study objectives, anticipated outcome, trial duration

2. Preclinical study data defined
   - Assemble basic research and POC study data
   - Define manufacturing process - evaluate scale, COGs, RMs
   - Describe assays - characterization, QC, and lot release
   - Assemble product characterization profile – define specs

3. Initiate a Type C or Type B FDA meeting
   - Present manufacturing process, preclinical data, clinical plan, develop specific questions to solicit FDA feedback

Submit an IND Application

1. Generate additional data as a result of FDA feedback on pre-IND materials

2. Submit an IND application to FDA
   - FDA Review team consists of experts from many disciplines - Project Manager, CMC, microbiology, pharmacology/toxicology, clinical, and biostatistician
   - Original is archived; FDA has a 30 day review period

3. Potential outcomes of a submission (on or before 30 days)
   - Receive a "Clinical Hold" letter indicating deficiencies
   - FDA request for "Additional Information or Clarification"
   - No response from FDA - technically free to enroll subjects

FDA Communications…

1. FDA encourages interactions early in the development process and often throughout development

2. Formal Process - written meeting request, pre-read materials packet, FDA written response, meeting (time sensitive)

3. FDA embraces good science & peer review (e.g. publications, grants); adherence to these principles is powerful in winning FDA support

4. FDA expects adequate documentation and controls- sound experimental design, reproducible results, accurate interpretation of results, and use of complimentary assays is often helpful

Expedite product development…

1. Engage in early communications with FDA
2. Identify sensitive topic areas through early FDA interactions (e.g., Informal or pre-IND meeting)
3. Be aware of preclinical expectations - product characterization, data collection, and documentation
4. Get acquainted with regulatory requirements for your product
   - FDA and ICH Guidance documents
   - FDA workshops/meetings/Webcasts/interest groups
   - Code of federal regulations
     - Tile 21 CFR 312 - IND Application

Questions?

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Contact Information

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10-Tray Cell Factory

API Manufacturing