IND Filing
"Ask the Experts"
PACT Web Seminar
November 14, 2013

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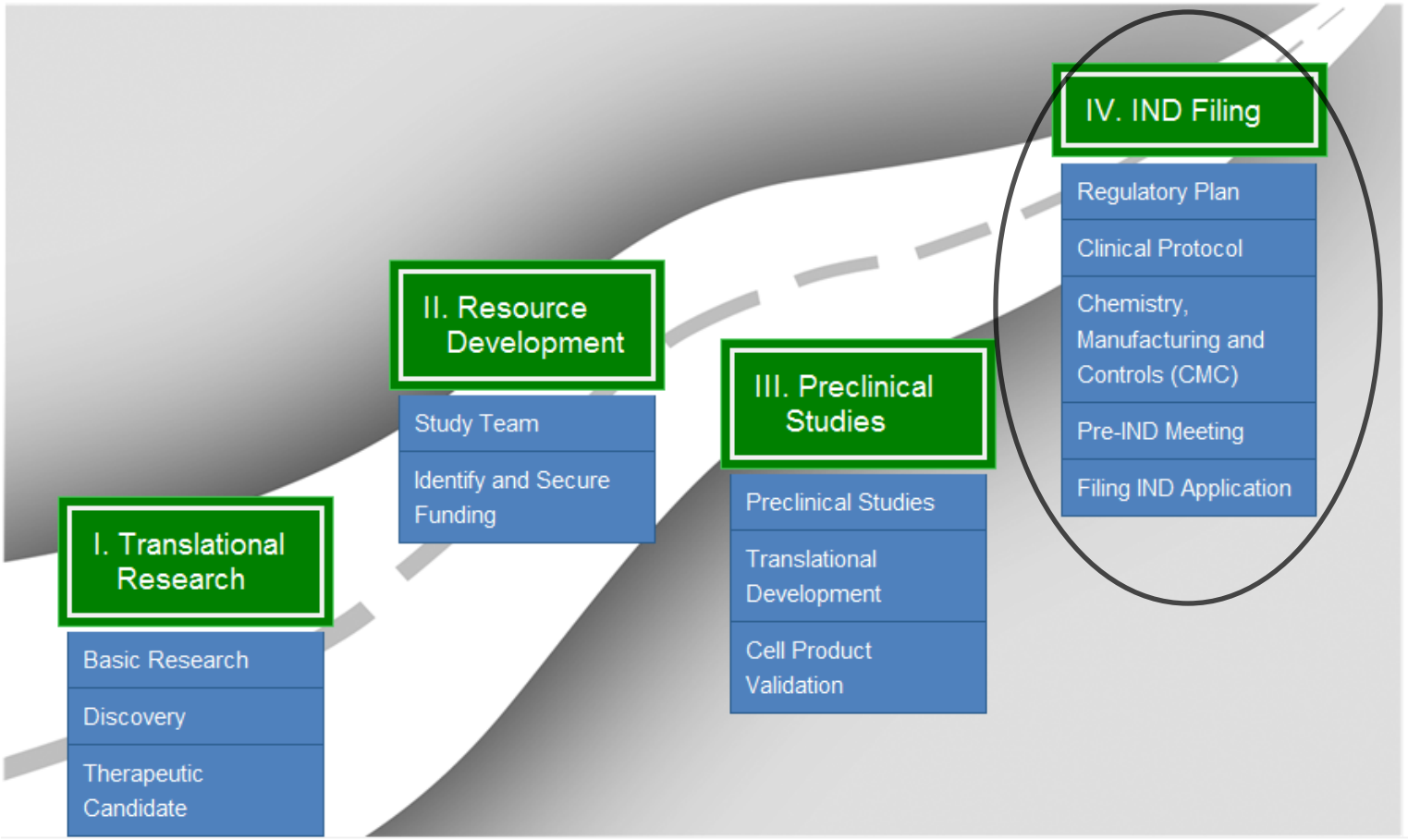
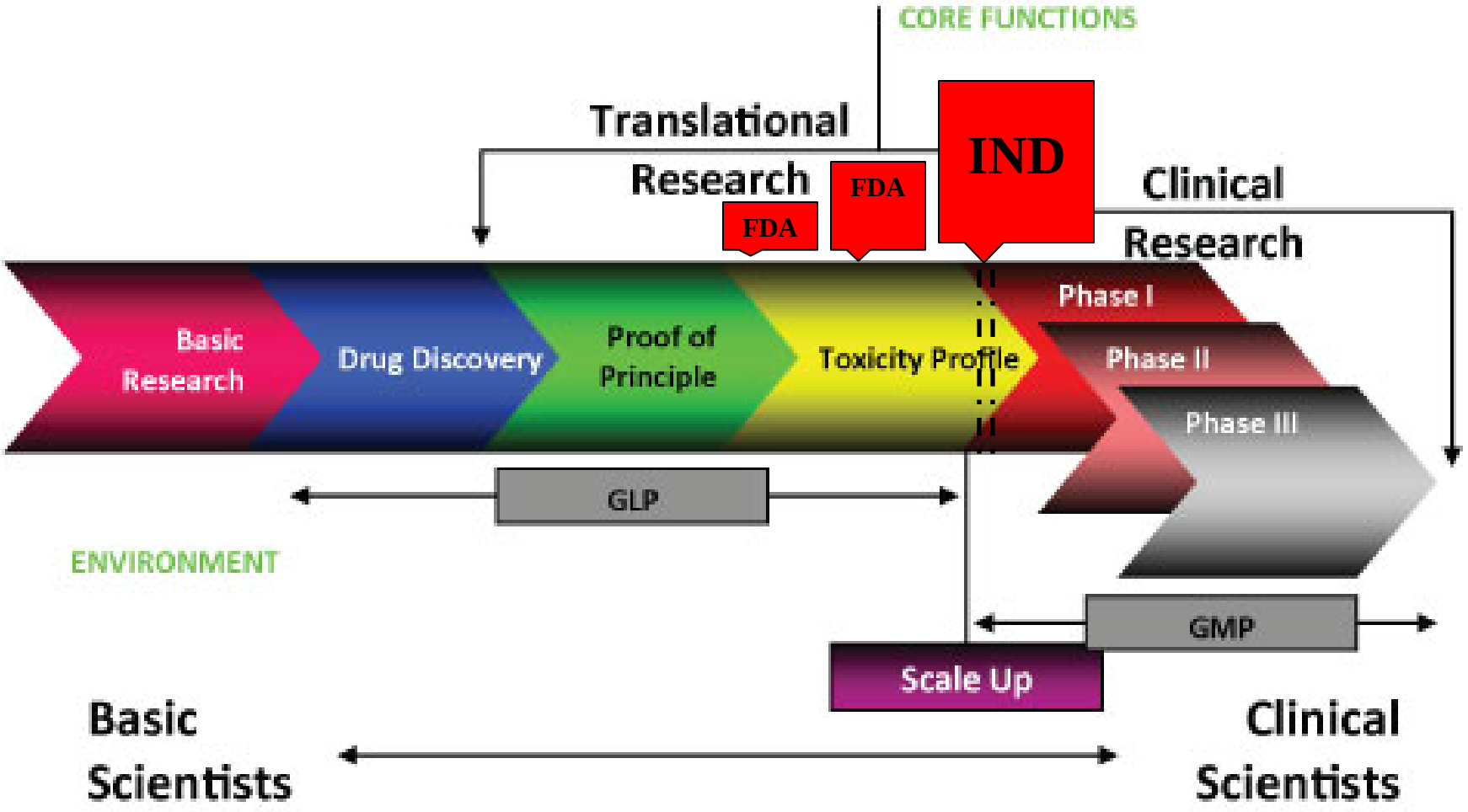
PACT
Production Assistance for Cellular Therapies
National Heart Lung and Blood Program

Cellular Therapy Clinical Research Roadmap



From Basic to Clinical Research



NHLBI, NIH- PACT Manual of Procedures (MOP)

Regulatory Plan

- Develop a plan early in the development process
- Identify Regulatory Team
  - Regulatory Liaison, Principle Investigator (1571), Lead Clinical Investigator (1572), Manufacturing & Quality Assurance representation
- Become familiar with regulatory resources
  - Code of Federal Regulation (CFR), Guidance for Industry, ICH, GXPs
- Prepare for FDA interactions
  - Understand types of meetings/obligations/time constraints

Clinical Protocol

- Develop a Clinical Protocol Schema
  - Clinical indication, patient population, Standard of Care
  - Study design, multicenter/single center, number of subjects, I/E criteria
  - Route of administration, administration schedule, summary of subject visits
- Generate a Clinical Protocol
  - Consent Form, schedule of study procedures/visits, safety endpoints/stopping rules, Data Management Plan, Data Monitoring Plan, and Case Report Form
- Develop a General Investigational Plan
  - Current clinical need, currently approved products, proposed future studies

Chemistry, Manufacturing, and Controls

- Manufacturing Process
  - Process flow diagram, manufacturing scale, and summary of product development activities, storage/stability studies
- Quality Assurance/Quality Control
  - Documentation control, review, and approval
  - Critical Raw Materials (e.g., animal derived components), in-process and final product testing, specification setting, and establishing lot release criteria
- Quality Systems
  - Documentation system: Test Method (TM), Batch Production Record (BPR), Standard Operating Procedure (SOP), Certificate of Analysis (COA)
  - Prospectively design and executed studies
  - Preclinical phase of product development and testing

Preclinical Studies

- Product Characterization
  - Process flow diagram, manufacturing scale, and summary of product development activities
  - Comparability of preclinical material to that intended for clinical use
- Product Safety Testing
  - Critical Raw Materials, in-process and final product testing, specification setting, and lot release criteria
- Pharmacology/Toxicology Studies
  - Proof of concept studies demonstrating efficacy
  - Adequate documentation to include: Protocols, Final Study Reports, Product Development Reports, TMs, BPRs, and SOPs

Pre-IND Meeting

- Identify Meeting Type
  - Type A, B (pre-IND), or C (pre,pre-IND)
  - Meeting format: Face-to-face or teleconference
- Reason for FDA meeting
  - Discuss critical Raw Materials, in-process and/or final product testing, specification setting, lot release criteria, clinical study design
- Scheduling the meeting with FDA
  - Formal meeting request with purpose and anticipated outcome, draft specific questions, list of meeting participants, pre-meeting materials packet

File IND Application

- Format of an IND Application
  - Traditional or Common Technical Document (CTD) format
  - 21 CFR 312.23 IND Content and Format
  - FDA presentation (*see* Relevant Guidance Documents)
- Content of the IND application
  - Modular, complete yet succinct, provide summary information with supporting final reports in the Appendix
- FDA Project Manager
  - Assign IND number, number of copies to submit, Serial Submission #
- Potential outcomes of an IND submission

In summary

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 (e.g., 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

Relevant Guidance Documents

Investigational New Drug (IND)/Preclinical/Quality

1. Formal Meetings Between the FDA and Sponsors or Applicants 2009
2. Preclinical Assessment of Investigational Cellular and Gene Therapy Products Draft 2012
3. Preclinical assessment of cell and gene therapy products, see OCTGT Learn Video Series, at: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm23282.htm
4. Quality Systems Approach to Pharmaceutical CGMP Regulations 2006
5. Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND 2013
6. Exploratory IND studies 2006
7. Process Validation: General Principles and Practices Draft 2008
8. Target Product Profile—A Strategic Development Process Tool Draft 2007

Relevant Guidance Documents

Chemistry, Manufacturing, and Controls (CMC)

1. cGMP for Phase 1 Investigational Drugs 2008
2. Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs) 2008
3. Potency Tests for Cellular and Gene Therapy Products 2011
4. ICH Q5D: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products 1997.
5. ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process 2004.

Relevant Guidance Documents

Clinical

1. Frequently Asked Questions—Statement of Investigator (Form FDA 1572) Draft 2008
2. Guidance for IRBs, Clinical Investigators, and Sponsors 2013
3. MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) 2005
4. Information Program on Clinical Trials for Serious Life-Threatening Diseases and Conditions Draft 2004
5. How to Comply with the Pediatric Research Equity Act Draft 2005
6. ICH E6: Good Clinical Practice: Consolidated Guidance 1996.

Q & A Session