Development of Cellular Therapies: Clinical Perspective

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Learning Objectives

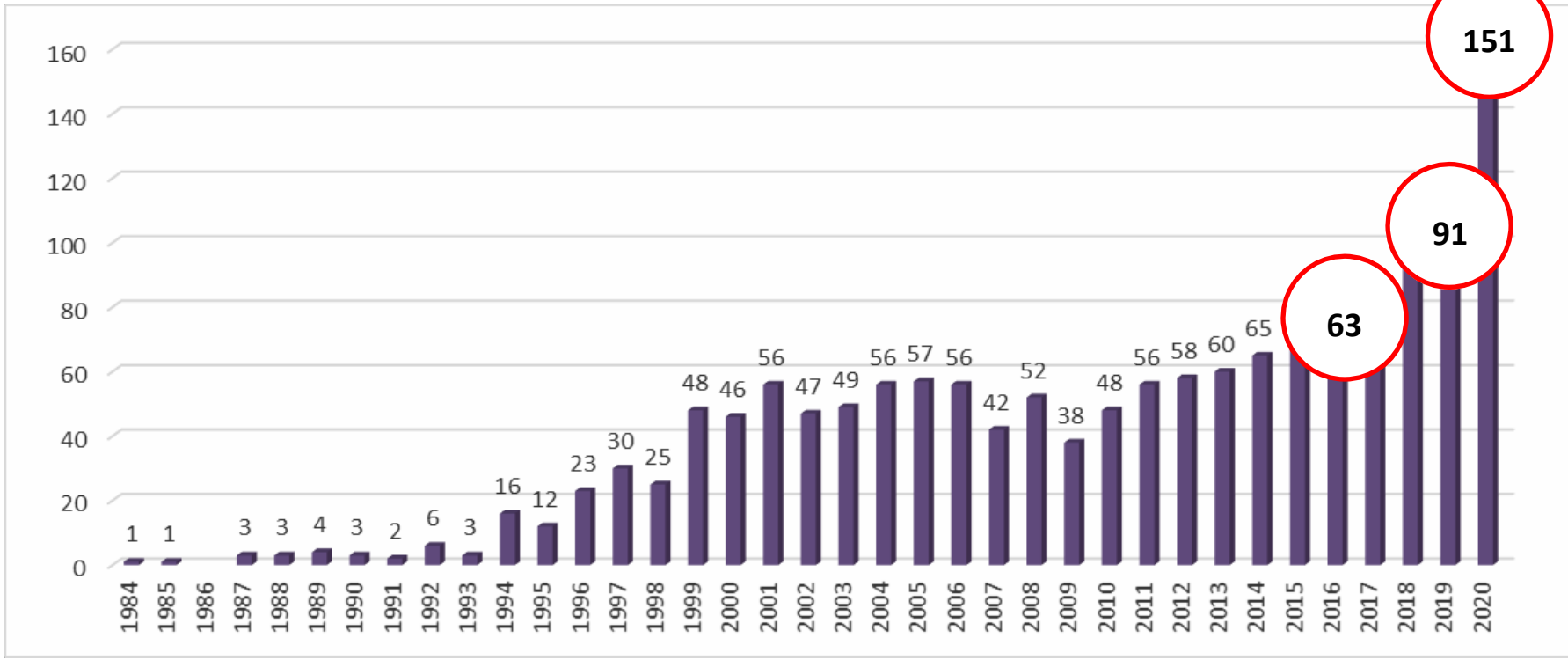
- Identify safety considerations for clinical trials for cellular products
- Understand strategies to mitigate safety risks in clinical trials for cellular products
- Understand strategies for efficient clinical development for cellular therapy products

Background

Examples of OTAT-Regulated Cell Therapy Products

- Pluripotent stem cells
  - Embryonic stem cells (ESCs)
  - Induced pluripotent stem cells (iPSCs)
- Adult stem/progenitor cells
  - Origins: hematopoietic, neural, cardiac, adipose, mesenchymal
- Perinatal
  - Placental, umbilical cord blood
- Fetal
  - Neural
- Functional mature/differentiated cells
  - Origins: Chondrocytes, islets, hepatocytes, retinal pigment epithelial cells, keratinocytes, etc.

Research INDs: Cell Therapy
(highlighting 2016, 2019, 2020)



Cell Therapy Clinical Development: Not A One Size Fits All Approach

- Product
- Route of administration
- Indication
- Target population

Safety: Focus on First in Human & Early Phase Studies

Safety is Always Primary

"FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety…"

[IND Regulations [21 CFR 312.22 (a) - General Principles of the IND Submission]

Examples of Potential Safety Concerns for Cell Therapy Products

- Immune response to the administered cellular product
- Inappropriate cell proliferation and differentiation (e.g., tumor or ectopic tissue formation)
- Cell migration to non-target areas/tissues
- Transmission of infectious disease
- Risks of the delivery procedure
- Interactions/complications from concomitant therapies (e.g. immunosuppressants)

Risk Mitigation in Early Phase Clinical Trial for Cellular Therapy Products

Who

What

When

Who: Choice of Study Population

- Favorable risk-benefit for the study population
  - Healthy subjects are very rarely appropriate for cellular therapy
  - Early vs advanced disease
  - Co-morbid conditions

What: Safety Monitoring & Risk Mitigation

- Careful product administration
- Monitoring for immediate reactions to cellular therapy
- Monitoring for sub-acute reaction to cellular therapy
  - For example: Graft-versus-host disease, autoimmune phenomena, cytokine release syndrome, infection
- Evaluation of product persistence and long-term effects
    - Duration of follow-up to be tailored to individual products

When: to Proceed or Stop

- Staggering within & between cohorts
  - Monitor acute and subacute toxicity
- Stopping rules subject & study
  - Specify conditions (e.g., incidence and/or nature of observed adverse events) for temporary suspension of enrollment and dosing
  - Stopping rules are not necessarily intended to lead to study termination, but may necessitate protocol and Informed Consent revisions
- Purpose is to limit the number of patients put at risk, if early experience uncovers important safety problems

Efficient Product Development

Regulatory Requirements for BLA Approval

- Approval of drugs and biologics must be based on **substantial evidence of effectiveness** and evidence of safety.
- Evidence of effectiveness should be obtained from **adequate and well-controlled studies**.
- Certain aspects of product development that are feasible for common diseases may not be feasible for rare diseases. FDA regulations provide **flexibility** in applying regulatory standards (21 CFR 314.105).

Evidence of Effectiveness – Rare Disease

- No specific minimum number of patients to be studied to establish effectiveness and safety for a treatment for a rare disease.
- The number of patients to establish effectiveness and safety is determined on a case-by-case basis, taking into consideration
  - Persuasiveness of the data (e.g., comprehensiveness and quality)
  - Nature of the benefit provided (or expected in the case of surrogate endpoints)
  - Length of treatment or exposure
  - Patient population that would be treated after marketing approval
  - Concern for potential of harm from the treatment

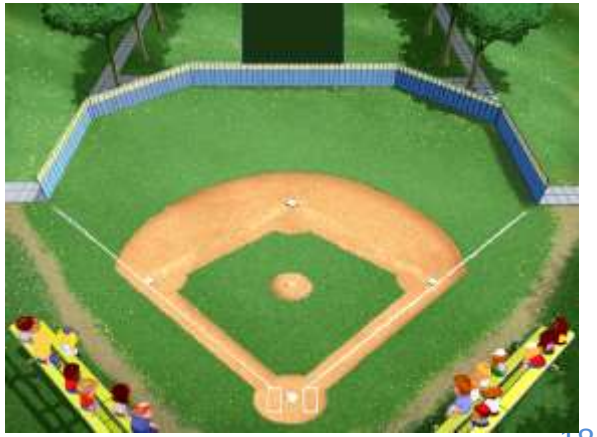
Product Development:

Start with the end in mind

Try to Hit a Home Run

- Design first-in-human clinical trial to provide evidence of effectiveness
  - **Randomized controlled trials** beginning with first study
  - **Concurrent control with blinding**, whenever feasible

- **Resolve manufacturing issues**, as much as possible, before initiating clinical trial



Careful Planning throughout Development

- Basic Research/Discovery
- Proof of Concept (POC) Studies
- Toxicology/Safety
- Cell Fate/Vector Biodistribution (BD)
- Development of companion diagnostics or devices
- **Natural History Studies**
- **Endpoint Tool Development (e.g. Fit for Purpose Clinical Outcome Tools)**
- **Patient Engagement**

- IND Submission
- Early Phase Clinical Trials
- Late Phase Clinical Trials
- Biologics License Application
- Product License Granted

Natural History Studies

- **A well-designed Natural History (NH) study is a golden opportunity to prospectively collect credible data**
  - Full spectrum of disease phenotypes & genotypes
  - Variability in disease course and prognostic factors
  - Clinical endpoints
- **NH study objectives should include**
  - All anticipated purposes study data are intended to serve
  - Plans to refine data collection to advance the study objectives

Patient Engagement

- Understanding impact of disease
- Inform endpoint selection based on what is clinically meaningful to patients
- Risk tolerance in the context of specific diseases and available treatments
- Benefit-Risk assessment

Dosing Considerations Cell Therapy Products

- Adequate and complete investigation of the effective and safe dose range to ensure accurate recommendations in product labeling
- Cell therapies are often mixtures of different cell types
  - The total number of cells delivered, cell viability
  - The total number of a specific cell type per all cells delivered
- Appropriate dose measurements
- Pre-specified range of exposure; rationale for re-dosing

Pediatric Considerations

- 21 CFR 50.52 Subpart D: Requires evidence of Prospect of Direct Benefit for each child when there is more than a minor increase over minimal risk (e.g. cellular therapy products)
  - Non-clinical data from animal model of disease or clinical data from adults

- When feasible obtain safety data from adults prior to initiating studies in children

Summary

- For subject safety consider Who, What and When
- Plan ahead, with thoughtful design risks can be minimized & expeditious product development is possible
- Communicate early with the FDA and collaborate with scientists, clinicians, patients, & advocacy groups

Guidances

- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015) http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM359073.pdf

Challenge Question #1

First-in-Human study for a cellular product should always be in otherwise healthy adults.

A. True

B. False

Challenge Question #2

Which of the following statements is NOT true?

A. A clinical study should only be paused for an expected SAE that is attributed to a cellular product.

B. An appropriate staggering interval can mitigate safety risks to subsequent subjects from a cellular product.

C. A safety signal identified during long-term monitoring following administration of a cellular product can inform benefit-risk for potential future subjects and continued product development.

D. A blinded, randomized controlled study should be considered for a first-in-human study to improve interpretability of safety and efficacy data and expedite product development.

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