Regulatory Considerations in the United States Associated with Cell Therapy

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Overview

- Summary of FDA Cell Therapy Regulations
- Case Study #1: Epicel
- Case Study #2: Autologous Cell Therapy – PROVENGE
- Case Study #3: Autologous Gene/Cell Therapy – CAR T-cell

US FDA Regulations for Cell Therapies

- Medical Device
- Biologic
  - Cell Therapy drug
- Gene Therapy
  - Gene/Cell therapy drug

FDA Regulations

- Mode of Action
  - Inert – Regulated as a Medical Device
  - Chemical – Regulated as a Drug or a Biologic
- Gene Therapy Component
  - No Added Genetic Element – Regulated as a Biologic
  - Added Genetic Element – Regulated as a Gene Therapy

Case Study # 1

- Epicel® - Cultured Epidermal Autografts

Medical Device - Epicel® - Cultured Epidermal Autografts

- Skin replacement therapy for the treatment of life-threatening burns
- Made from patient's own skin cells
- Regulated as a device
  - Primary mode of action is not through chemical action
  - not dependent upon being metabolized

Medical Device Definition

- "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:
  - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
  - intended to affect the structure or any function of the body of man or other animals,
  - and which **does not achieve any of its primary intended purposes through chemical action** within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Marketing Submission to FDA CDRH

- PMA
- HDE (Humanitarian Device Exemption)

Case Study # 2

- PROVENGE
  - Autologous cellular immunotherapy for the treatment of prostate cancer

Cell Therapy - PROVENGE

- PROVENGE
  - Primary mode of action
    - Induces immune response targeted against an antigen (PAP) expressed in most prostate cancers

FDA Definition of Biological Product

- Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies

  – Primary mode of action is via “chemical action”

FDA Definition of Cell Therapy

- Cellular therapy products include cellular immunotherapies, and other types of both autologous and allogeneic cells for certain therapeutic indications, including adult and embryonic stem cells.

Additional Nonclinical Requirements of Cell Therapies Regulated as Biologics

- Tumorigenicity through the same route of administration in patients
  - Stem cell therapy – evaluated more rigorously for tumorigenicity
- Cell fate studies (trafficking, survival, differentiation)
- No Genotoxcity studies

Additional Clinical Requirement of Cell Therapies Regulated as Biologics

- FDA often requests a Data Safety Monitoring Committee in the First-in-human clinical trial

PROVENGE Regulated as a Biologic

- Under purview of the FDA Office of Cell and Gene Therapy within CBER
  - Similar requirements as an investigational biologic (recombinant protein or monoclonal antibody)
    - Two Phase 3 studies
    - File BLA as Marketing Application

Case Study # 3

- CAR T-Cell
  - Chimeric Antigen Receptor T cell Therapy
  - Patients' own immune cells engineered to recognize and attack their tumors
  - In one clinical trial, 18 of 21 patients with advanced acute lymphoblastic leukemia had complete responses
  - Gene Therapy Component

FDA Definition of Gene Therapy

- Human gene therapy refers to products that introduce genetic material into a person's DNA to replace faulty or missing genetic material, thus treating a disease or abnormal medical condition.

Regulatory Oversight

- Clinical studies involving gene transfer are regulated by the FDA and in nearly all instances by the NIH.

- FDA
  - Office of Cellular, Tissue, and Gene Therapies, CBER

Submission to the US Regulatory Authorities for Clinical Trials

- NIH/RAC
- IBC
- FDA
- IRB

Regulatory Oversight

National Authority	FDA – Office of Cellular, Tissue and Gene Therapies	NIH/RAC
Responsible party	Sponsor	Principal Investigator
Local Authority	IRB	IBC
AE reporting	MedWatch form	MedWatch form or NIH Reporting Template
Nature of Review	◆Confidential ◆Safety/Non-clinical review by FDA reviewers	◆Public ◆Critical scientific review by leading gene therapy researchers

NIH Oversight

- NIH oversight is required under the following conditions:
  - Clinical Investigators participating in clinical trials who receive NIH funding or
  - Clinical Investigators who are affiliated with institutions that receive NIH funding or
  - Clinical trials conducted at institutions that receive NIH funding

NIH Oversight

- Recombinant DNA Advisory Committee (RAC) in the office of Biotechnology Activities (OBA) within the NIH oversees gene therapy
  - RAC does not have oversight over vaccines
  - RAC meets quarterly for public discussion of gene transfer clinical studies that are deemed novel
  - Accelerated review process for clinical studies that are deemed not to be novel and not to represent significant risk
    - Clinical protocols and Informed Consent documents are subject only to written reviews by several members of the RAC committee

Evolving Gene/Cell Therapy Regulations

- As of 2014
  - No requirement to submit to RAC Committee for routine investigational gene therapy treatments
  - First CAR T cell clinical trial is non-routine and had been reviewed by the RAC Committee
  - Subsequent CAR T cell clinical trials may be deemed “routine”

Institutional Biosafety Committee (IBC)

- Review body appointed by the institution of the proposed clinical trial site
- Review and approves all experiments involving gene transfer in human research participants
- Must consider issues raised and recommendations made during RAC review

Unique FDA Clinical Requirement for Certain Gene Therapy Drugs

- 15-year follow-up Monitoring Plan for subjects in clinical trials with integrating vectors – CAR T cells
  - Retrovirus
  - This monitoring plan must be in the initial IND or the FDA will put the IND on hold

Unique Manufacturing Aspect

- Pre-competitive cooperation
  - FDA, industry and academia

▼ Request by FDA for CAR T-cell therapies at the 2014 American Society for Cell and Gene Therapy

▼ Assess the potential for replication competent lentivirus in their cellular product

FDA Review Division

- Office of Cellular, Tissue and Gene therapies (OCTGT)
  - Division of Cellular and Gene Therapies (DCGT)
  - Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT)
- CMC Review – DCGT
- Pharmacology/Toxicology and Clinical Review - DCEPT

Starting a Cell Therapy Clinical Trial in the United States

- Is it a Medical Device?
  - CDRH
- Is it a Biologic?
  - CBER
- Is it Gene Therapy?
  - CBER
  - RAC Committee

