Regulation of Cell & Gene Therapy Products for Clinical Trials

Adrian Gee
Center for Cell & Gene Therapy
Baylor College of Medicine
Houston, Texas

Thank you for the Invitation

I have no disclosures to make

Aim

To navigate through some of the regulatory issues associated with developing products for cell and gene therapies

A Word of Advice!

- One of today's talks will be given by a speaker from the FDA
- Theirs is the opinion that ultimately matters – not mine!
- Make use of all of the opportunities available for interaction

Why do I need to know this?

- Cell & Gene Therapies are FDA regulated
- Regulations use specialized terminology
- You need to understand the terminology and regulations to know how to:-
  - Make & test the study product
  - Design the clinical trial
  - File the application FDA
  - Move towards licensure of the product

Terminology matters!

- HCT/P's: Human Cells, Tissues, and Cellular and Tissue-Based Products
- FDA: Regulates Cell & Gene Therapies in the USA
  - CBER: Center for Biologics Evaluation & Research
  - CDER: Center for Devices & Radiological Health
  - Who regulates what depends on the cells
- Combination Product: Cells combined with membranes, scaffolds etc.

Regulatory Continuum

Title 21 Code of Federal Regulations

GLP Regulations

Good Laboratory Practices GLP

- Regulations to cover non-clinical laboratory studies to support applications for research or marketing permits for FDA-regulated products
- To ensure quality and integrity of the safety data

Covers Non-clinical Laboratory Studies – "Preclinical Studies"

- Title 21 CFR Part 58
- Changes pending
  - Proposed rule 08/24/16
  - Complete Quality Systems approach

Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products

Good Laboratory Practices Questions and Answers

GLP Components

A General provisions

B Organization & personnel

C Facilities

D Equipment

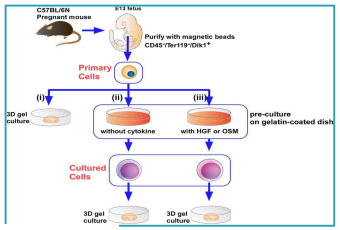
E Facility operations

F Test & control articles

G Study conduct protocol

J Records & reports

K Disqualification of facilities



- Most studies to support Phase 1 IND applications are NOT performed under **FULL** GLP
- What you do need:
  - Well-designed experiments
  - Good documentation
  - FDA advice in a Pre-pre IND meeting

Guidance for Industry

Preclinical Assessment of Investigational Cellular and Gene Therapy Products

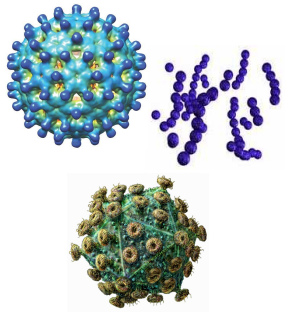
Intent of GMP Regulations

Regulations to ensure that the product is manufactured using a controlled, auditable process that reproducibly results in a safe and effective product

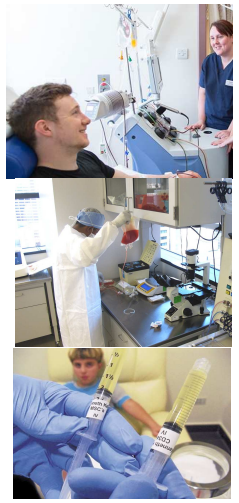
Regulations for Product Manufacturing

- Current Good Manufacturing Practices
  - 21 CFR Part 210/211+
  - HCT/Ps regulated under Section 351 of the Public Health Service Act (Type **351** Products) leading to Biologic Product License Application via an IND mechanism
- Current Good Tissue Practices (2005)
  - 21 CFR Part 1271
  - HCT/Ps regulated under Section 361 of the Public Health Service Act (Type **361** Products)

Type 361 Regulations



- Introduced in 2005 to prevent the introduction, transmission & spread of communicable diseases by HCT/Ps
- Which regulations to follow is based on **risk**:
  - Risk to donor during collection
  - Risks from ex vivo manufacturing
  - Risk to recipient



Which Cover What?

Good Tissue Practices [cGTP]

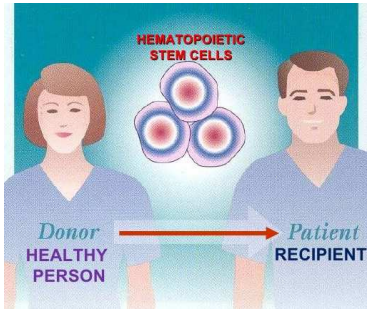
(Lower risk category)

- Cells are **minimally-manipulated**
- Are for **homologous use**
- Are not combined with another article
- Do not have a systemic effect
- **OR:** Do have a systemic/metabolic effect
- **BUT:** Are for autologous use or use in a 1st or 2nd degree relative

Critical GTP Definitions

Homologous use

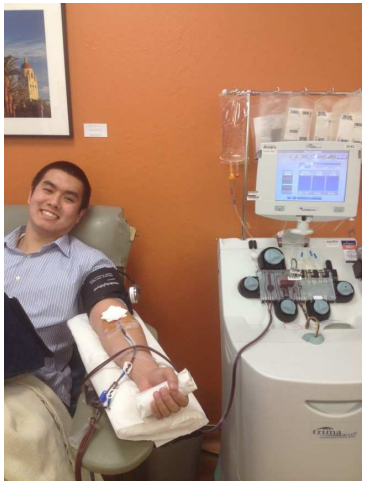
- The cells perform the same basic function in the recipient as in the donor



Minimal manipulation

- Processing that does not alter the relevant biological characteristics of the cells or tissues

Homologous Use



Stem Cell Apheresis

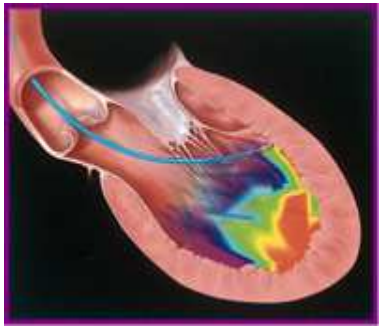
Homologous

GTP

Stem Cell Transplant

GMP + IND

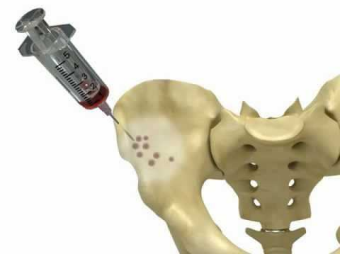
Non-Homologous



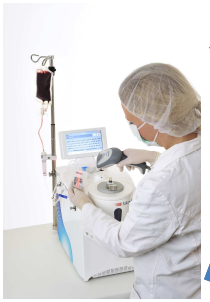
Cardiac Regeneration

Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products

Homologous Use



Bone Marrow Harvest



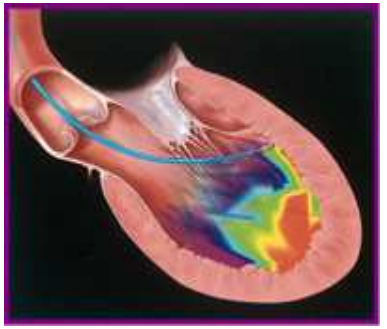
Homologous

Not regulated

Stem Cell Transplant

GMP + IND

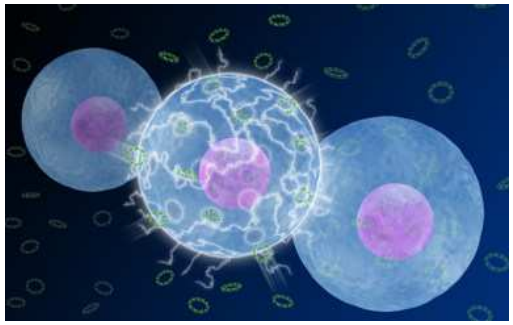
Non-Homologous



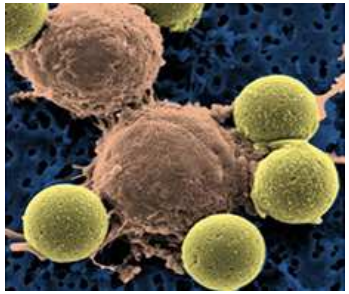
Cardiac Regeneration

Manipulation

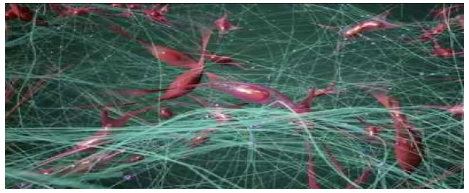
Cell Culture



Genetic Modification



Cell Activation



Cells on Matrix

Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance

Summary of Differences

Type 361 Cells	Type 351 Cells
No IND Needed	**IND Required**
Minimal Manipulation	**More than Minimal Manipulation**
Homologous Use	**Non-Homologous Use**
No Combination Products	**Combination Products**
Good Tissue Practices	**Good Manufacturing Practices**
Example: PBPC	**Example CAR-T Cells**
Minimally-manipulated Marrow	

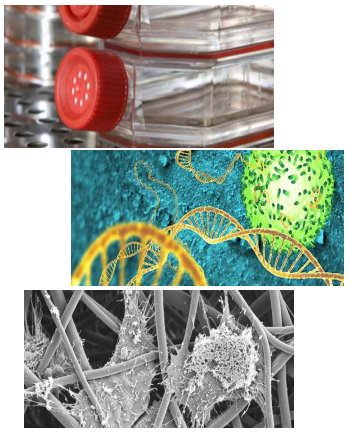
Summary of Differences

GTP	GMP
Register Establishment with FDA	Register Establishment with FDA
Perform Allo Donor Eligibility Assessment	Perform Allo Donor Eligibility Assessment
Exceptions for Ineligible Donor Use	***Very Few Exceptions for Ineligible Donor Use***
Quality Program Required	Quality Program Required
Slightly less documentation of all phases of Manufacturing	***Extensive documentation of all phases of Manufacturing***

In Most Cell & Gene Therapies

The cells are:

- More than minimally-manipulated
- Are for non-homologous use
- May be a combination product



GMP/GTP Requirements

Facilities

Environmental Control

Equipment

Reagents & Supplies

Recovery

Process & Process Controls

GTP Core requirements

Labels & Control

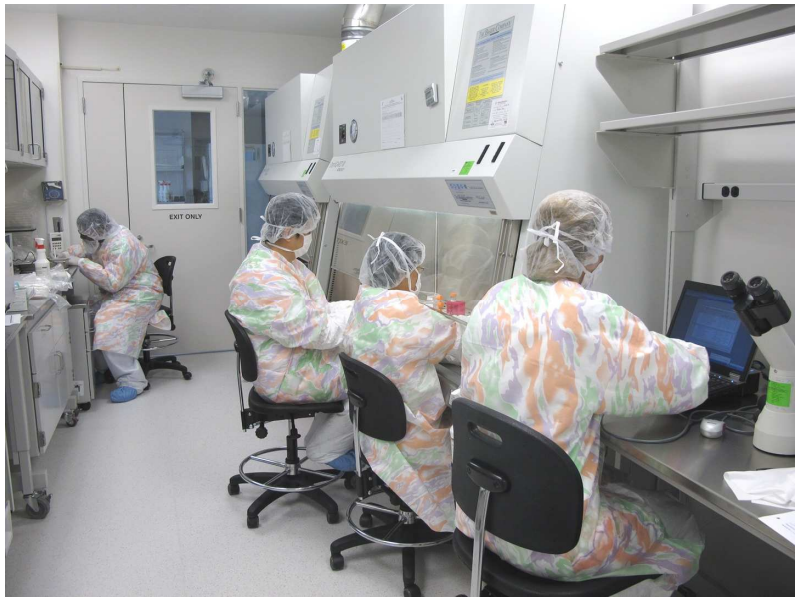
Storage

Receipt & Distribution

Donor Eligibility

Other requirements:

Staff



Sufficient in Number

Appropriate Education

Experienced

Trained

Competent

Quality Program

- Comprehensive system for manufacturing & tracking products
- Designed to prevent, detect and correct deficiencies
- Approves and rejects incoming materials, in-process materials & final products
- Records control & management
- Reviews production records & investigating any unexplained discrepancies

Quality Control

- Tests incoming materials, containers, closures, labeling & monitors the manufacturing environment
- Evaluates manufacturing adherence to proper specifications and limits (in-process & release testing)

Quality Assurance

- Review and approval of all procedures related to production and maintenance
- Review of all associated records
- Auditing and performing & evaluating trend analyses

As the Manufacturer:
What & How Much do I Need?

Guidance for Industry

CGMP for Phase 1 Investigational Drugs

What Information will the FDA require in the IND?

Guidance for Reviewers

Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs)

Good Clinical Practices

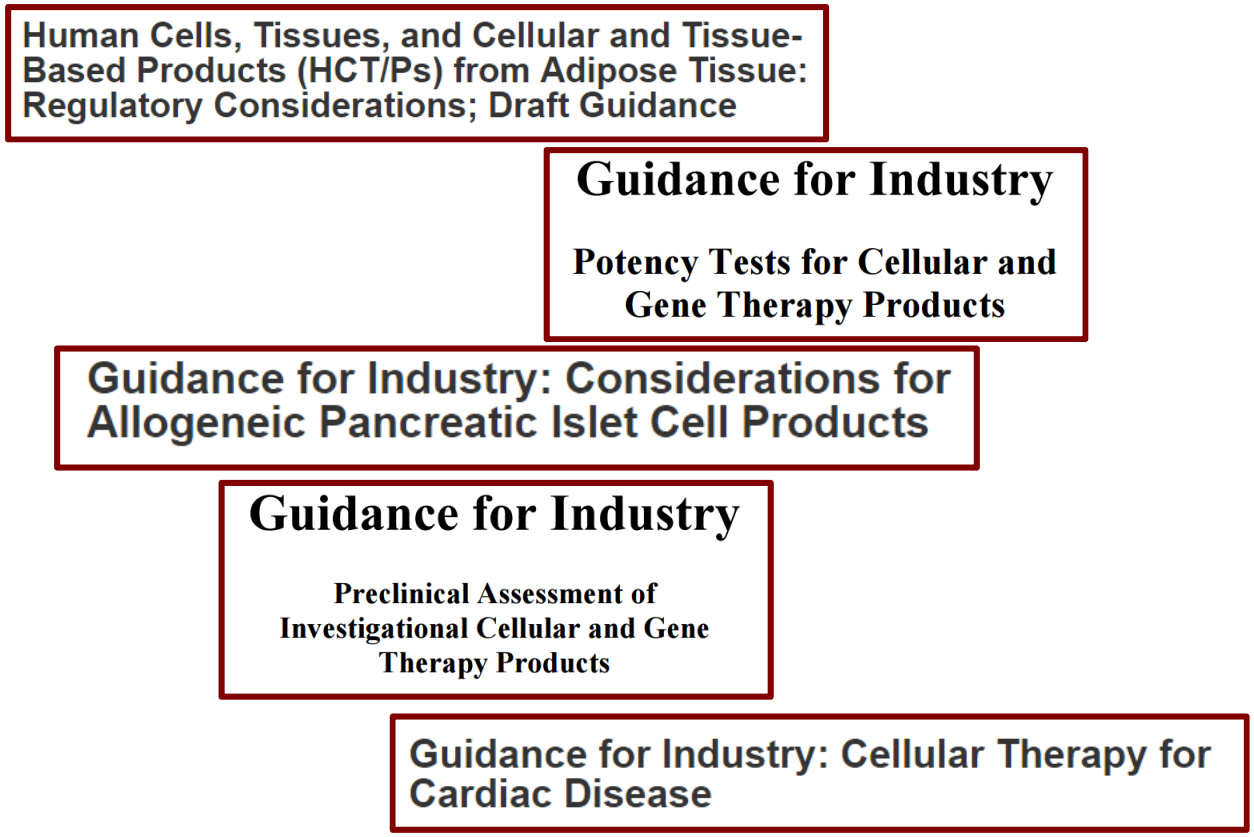
Good Clinical Practices GCP

An international ethical & scientific quality standard for designing, conducting, recording, & reporting trials that involve participation of human subjects.

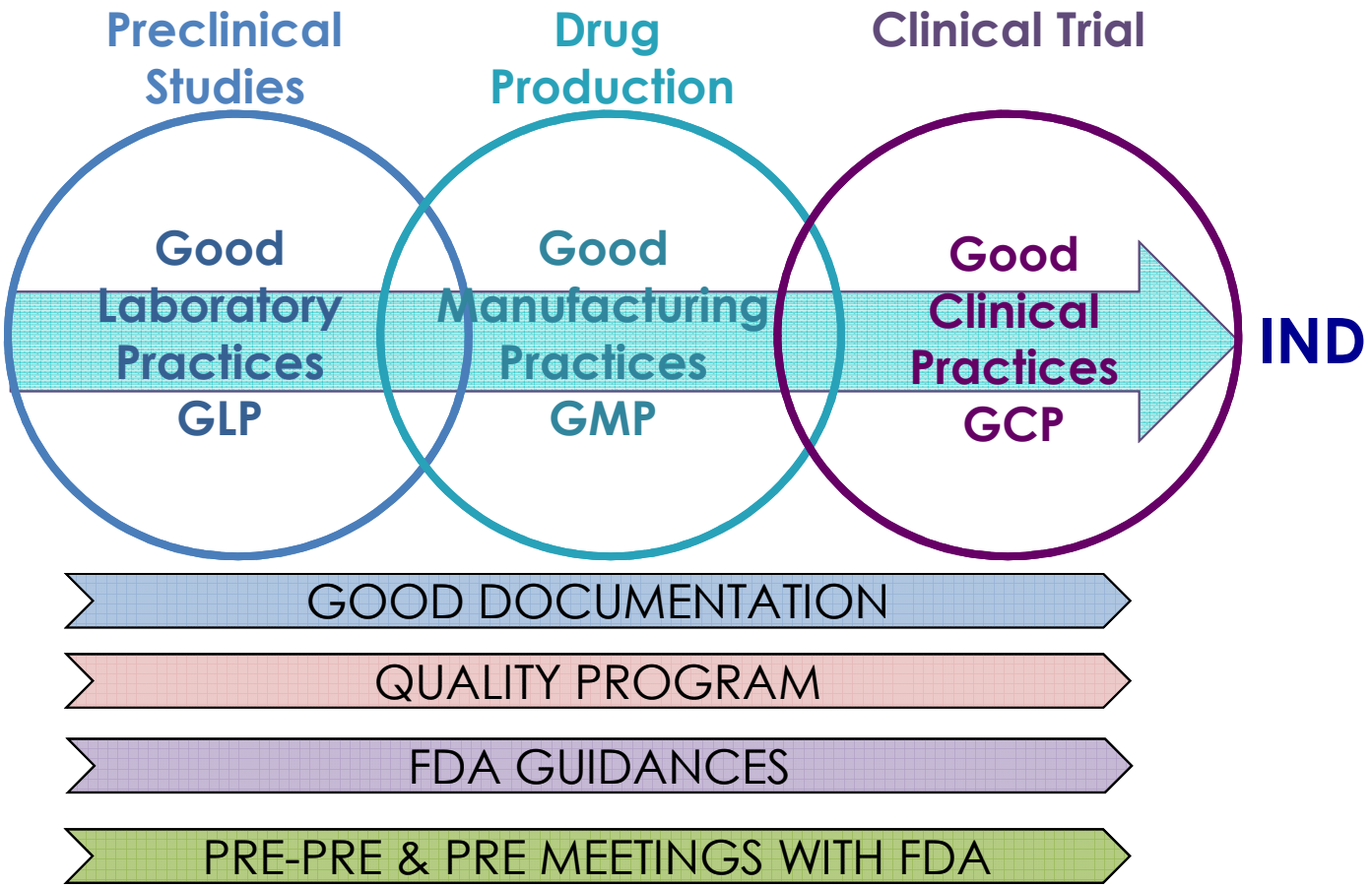
Guidance for Industry
E6 Good Clinical Practice: Consolidated Guidance

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products

The Best Tips – FDA Guidances



Pathways to Success



Thank You!