Current US FDA Regulation of Cell Therapy

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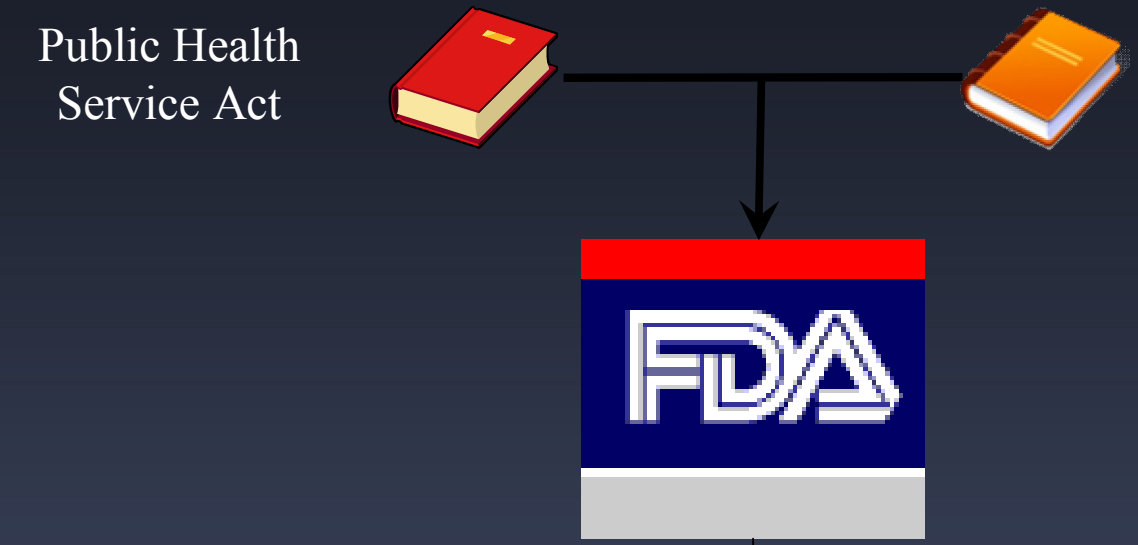
Overview

- FDA Organization
- HCT/P Definition
- Tissue Rules (TR)
- Products regulated only under TR (1271)
- Products also regulated under IND/BLA
  - Preclinical, Product & Quality Expectations
- New Guidance Documents

FDA Review of Medicinal Products



CBER

Center for Biologics Evaluation & Research

CDRH

Center for Devices and Radiological Health

CDER

Center for Drug Evaluation & Research

Center for Biologics Evaluation and Research (CBER)

OBRR Office of Blood Research & Review	**OCTGT** Office of Cells, Tissues and Gene Therapies	**OVRR** Office of Vaccines Research & Review
•Whole blood •Blood components •Blood fractionation •Donor Screening Test Kits	•Human tissues •Cellular therapies •Gene therapies •Combination products •Xenotransplantation •Devices used for cells & tissues	•Prophylactic vaccines •Anti-toxins •Allergenics •Adjuvants

Food and Drug Administration: Regulatory Authority

Laws

- Statutes enacted by Congress outlining binding conduct or practice in the community
    - The Public Health Service Act (PHS Act)
        - Sections 351 and 361
    - The Food Drug and Cosmetic Act (FD&C Act)

Regulations

- Interpretation of Laws (21CFR)
    - Rules for daily business, binding like laws
    - Part 1271 Tissue Rules
    - Part 312 INDs
    - Parts 210 and 211 cGMP

Guidance

- Describes agency's policy and regulatory approach to a specific area or issue
    - Not binding on industry, but usually binding on agency

Regulations for Cell Therapy

Referred to as “Tissue Rules”

21 CFR 1271	Covers
Subpart A	Scope; Definitions
Subpart B	Procedures for Registration and Listing
Subpart C	Donor Eligibility
Subpart D	Current Good Tissue Practices (cGTP)
Subpart E	* Additional Requirements
Subpart F	* Inspection and Enforcement

* Sub parts E and F only apply to establishments described in 1271.10 (regulated solely by the Tissue Rules)

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What are: Human cells, tissues, or cellular or tissue-based products (HCT/Ps)?

- Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient

Examples of HCT/Ps:

- Musculoskeletal
- Skin
- Ocular tissue
- Reproductive tissue
- Heart valves
- Dura mater
- Cellular therapies
- Hematopoietic stem/progenitor cells
- Cells + biomaterials
- Autologous manipulated chondrocytes

Not Classified as HCT/Ps

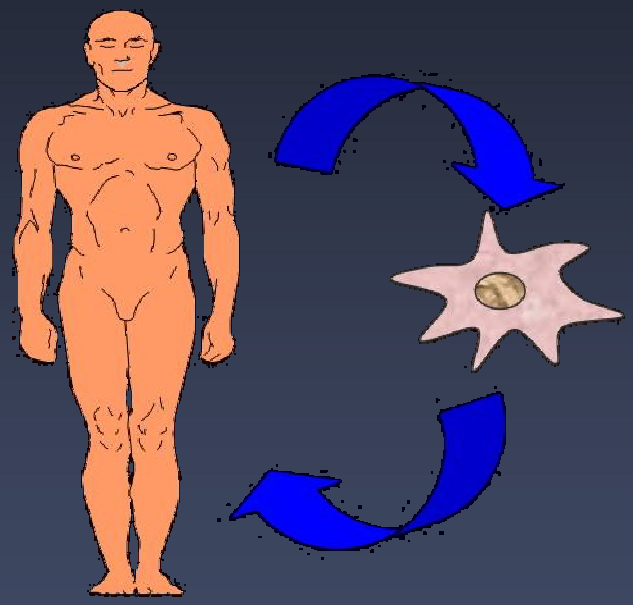
- Vascularized organs for transplant
- Minimally manipulated bone marrow for homologous use
- Cells, tissues, organs derived from other than human (xenografts)
- Blood and Blood Products
- Secreted or extracted products e.g. human milk, collagen, cell factors
- Ancillary products used in manufacture of HCT/P
- In vitro diagnostic products

Framework for Regulation of HCT/P's

Two options and one exception based on risk presented by product:

1. Regulated Solely by Tissue Rules (361 Products)
2. Higher risk products regulated in addition as drug, device or biologic product (351 Products)
3. Exception

Exception: HCT/Ps not Regulated by U.S. FDA



Autologous cells if cells are obtained and returned to patient during same surgical procedure

21 CFR 1271.15(b)

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The “Tissue Rules”

Tissue Rule	Describes
Establishment Registration and Listing	Which establishments must register and list products; Lists criteria for levels of FDA regulation
Eligibility Determination for Donors	Communicable disease test requirements and medical screening requirements
Current Good Tissue Practice (GTP)	Handling and process controls to prevent contamination and preserve integrity of cells; requirements for manufacturing

Establishment Registration & Listing

- Form FDA 3356
  - Can be done online at: http://www.fda.gov/cber/tissue/tisreg.htm.
- Must register within 5 days after beginning operations or subsequent ownership or location change
- An annual update is required in December
- Changes in HCT/P listing within 6 months of the change

Establishment Registration & Listing

- Establishments that perform donor testing or HCT/P testing must also register even if do not manufacture cells or tissue products
- Establishments that only manufacture HCT/P under an IND or IDE don't have to register and list until product is approved for commercial use (351 products)
- Foreign establishments importing HCT/Ps into the US must register

Example of Form 3356

Establishment Functions

☑ Recover	☑ Test	☑ Process	☑ Label
☑ Screen	☑ Package	☑ Store	☑ Distribute

Establishment HCT/P Listing

	Types of HCT/P's	HCT/P's Described in 21 CFR 1271.10	HCT/P's Regulated as Medical Devices, Drugs or Biological Drugs	Proprietary Names
a.	Bone			
b.	Cartilage			
c.	Cornea			
d.	Dura Mater			
e.	Embryo			
f.	Fascia			
g.	Heart Valve			
h.	Ligament			
i.	Oocyte			
j.	Pericardium			
k.	Peripheral Blood Stem Cells	X		
l.	Sclera			
m.	Semen			
n.	Skin			
o.	Somatic Cells			
p.	Tendon			
q.	Umbilical Cord Blood Stem Cells	X		
r.	Vascular Graft			
s.	TC, Apheresis	X		

Donor Eligibility

- Based on Donor Screening and Donor Testing for relevant communicable disease agents and disease

Donor Screening

- Review relevant medical records for risk factors for, and clinical evidence of:
  - relevant communicable disease agents and diseases;
  - risks associated with xenotransplantation
- Physical exam of donor for signs or symptoms of relevant communicable diseases
- Guidance Document:
  - Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), Aug 8, 2007

Donor Testing

Relevant communicable disease agents or diseases

- All HCT/P Donors:
  - Human immunodeficiency virus, type 1 and type 2
  - Hepatitis B and C viruses
  - Treponema pallidum
- Viable leukocyte rich HCT/P, in addition to above:
  - Human T-lymphotropic virus, type I and type II
  - CMV
- Reproductive tissue, in addition to above:
  - Chlamydia trachomatis
  - Neisseria gonorrhea
- Additional relevant diseases:
  - West Nile Virus
  - Sepsis (screening only)
  - Vaccinia

GTP Requirements

- Govern the methods, the facilities and controls used for the manufacture of HCT/Ps
  - Prevent introduction, transmission and spread of infectious disease
  - Prevent mix-ups and cross-contamination
  - All steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution
  - Narrower focus than GMPs

GTP Requirements

- GTP's ensure that the HCT/P do not:
  - Contain communicable disease agents
  - Are not contaminated and
  - Don't become contaminated during manufacture

GTP Requirements

- Donor Screening & Testing
- Exemptions and Alternatives
- Quality Program
- Personnel
- Procedures
- Facilities
- Environmental Control and Monitoring
- Equipment
- Supplies/Reagents
- Recovery
- Processing and Process Controls
- Process Changes
- Process Validation
- Labeling Controls
- Storage
- Receipt, Pre-Distribution Shipment, Distribution
- Records
- Tracking
- Complaint File

= Core cGTPs

How to Comply with GTPs

- Register Establishment & List HCT/Ps
- Perform Donor Screening & Testing as applicable
- Ensure manufacturing facility and quality system address GTPs
- U.S. FDA verifies compliance by inspection as necessary

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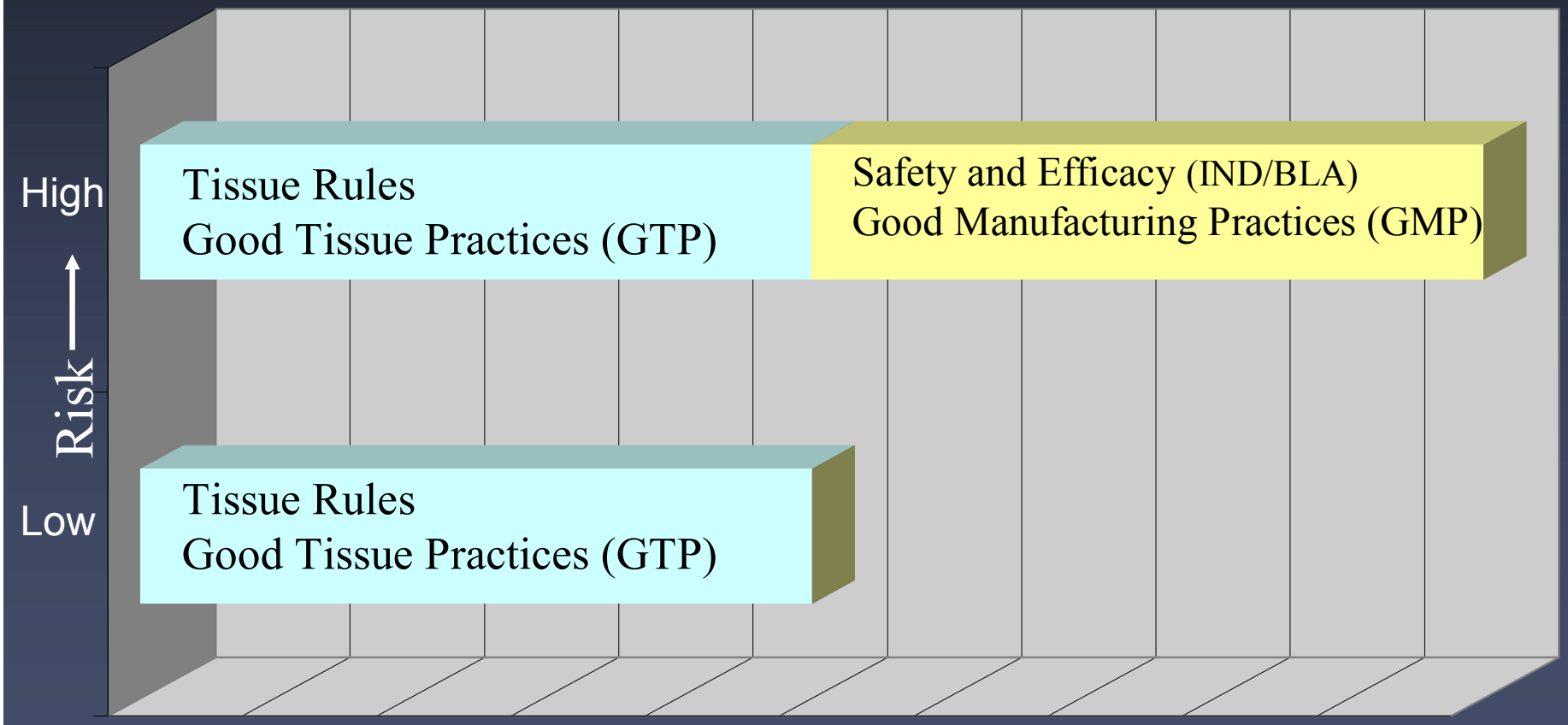
Two Regulatory Tiers



Regulatory Requirements

- For HCT/Ps regulated only under Tissue Rules
  - No clinical safety or efficacy studies required
  - No premarket approval (BLA)
  - |Emphasis is on preventing transmission or introduction of disease
  - An establishment must follow all of the cGTP requirements applicable to the operations that it performs

Classification as Lower Risk

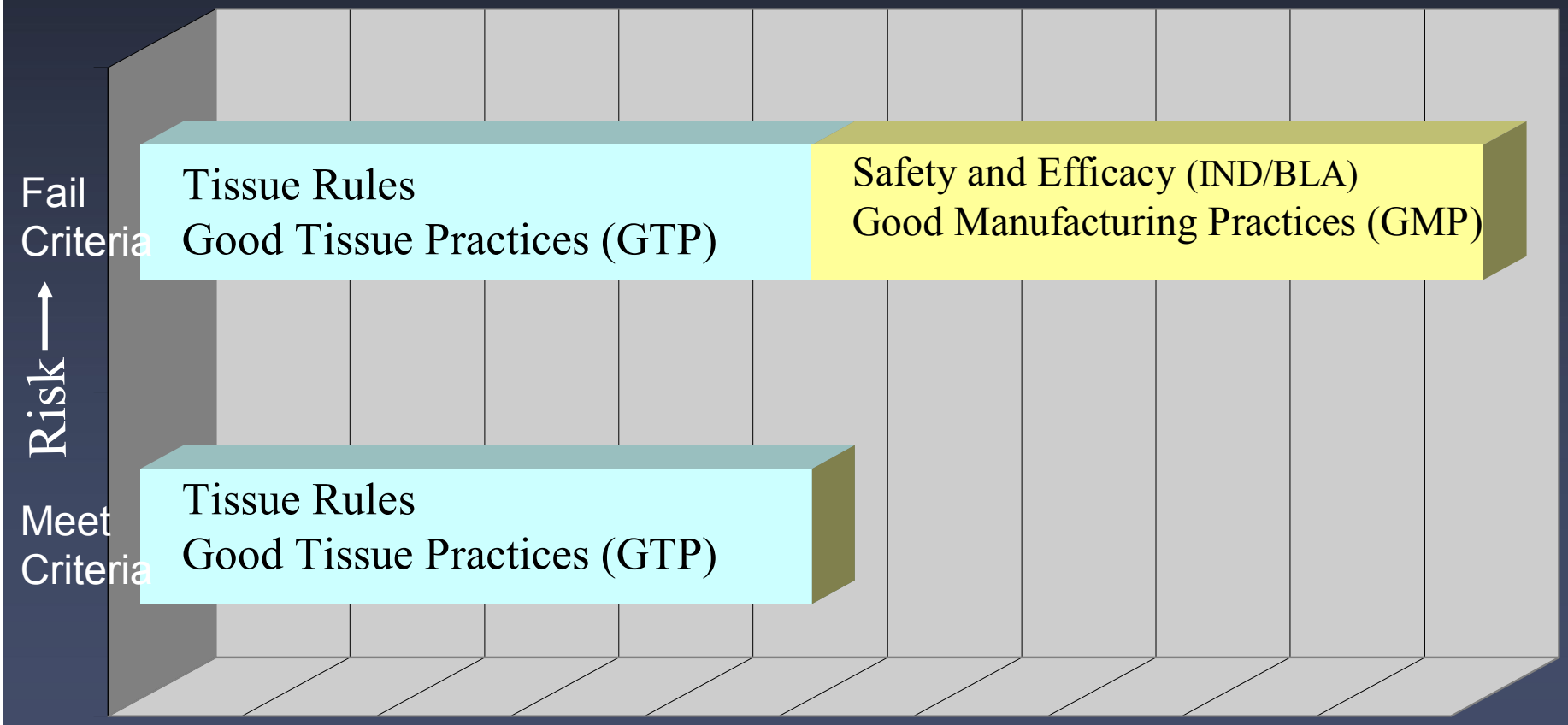
- For a lower level of regulation HCT/P must meet all the specified criteria
  - If ‘yes’ to all criteria: regulated under TR
  - No: clinical studies for safety and efficacy (IND)
  - No: premarket approval (BLA)

4 Criteria for Lower Level of HCT/P Regulation

The cells/tissues are:

1. Not more than minimal manipulation
2. Not combined with another article
   - drug, device, biologic or tissue
3. Intended for homologous clinical use
4. Primary function in recipient is not systemic or dependent upon the metabolic activity of the cells
   - Unless for autologous or family-related, or reproductive uses

Two Regulatory Tiers



Definition of HCT/P Terms

- Minimal manipulation
  - What it is
  - What it is not
- Homologous use
  - What it is
  - What it is not

Minimal Manipulation - Defined

- For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement

- For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

Minimal Manipulation – Examples Structural

- Fascia or dermis processed into particulate form
- Dehydrated and decellularized amniotic membrane intended for wound covering
- Cutting, grinding, shaping of bone

Minimal Manipulation – Examples Non-structural

- CD 34+ selection of peripheral blood stem cells (PBSCs)
- Density gradient separation to remove a particular type of cell from a mixture of cells

Not Minimal Manipulation – Examples

- Decellularization of human arteries, veins, heart valves, or valve conduits
  - Regulated as medical devices
- Dehydrated and decellularized amniotic membrane intended for wound healing
- Culture expansion of cells
  - Autologous or allogeneic
- Genetic modification of cells

Homologous Use - Defined

- The repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor

Homologous Use - Examples

- Demineralized bone matrix used as a void filler during orthopedic surgery
- Bone recovered from a limb, used as a bone dowel for spinal surgery
- Allogeneic cord blood used for hematopoietic reconstitution
- Pancreatic islet cells used for treatment of type 1 diabetes

Non-Homologous Use - Examples

- Allogeneic veins or arteries intended for use as arteriovenous access (A-V shunts) for hemodialysis
- Cartilage tissue used in the bladder for treatment of reflux
- Autologous bone marrow cells used for myocardial repair
- Nasal mucosal cells used to regenerate nerve tissue

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Which HCT/Ps are also Regulated as Biological Products?

- More than minimally manipulated
  - Examples: Cells/tissues from human organs that have been expanded or activated (islets, hepatocytes)
- Genetically modified cells
- Intended for Non-homologous use
  - Example: HPC for cardiac repair
- Combined with another article
  - Examples: drugs, devices “Combination Products”

Examples of HCT/P Also Regulated as Biological Products

Cellular Product	Tissue Source	Function/Use
Chondrocytes Šmore than MM	Cartilage biopsy	Cartilage repair
Pancreatic islets- more than MM	Cadaveric donor pancreas	Produce insulin in type I diabetics
Cells combined with biomaterial matrix (Combination Product)	Chondrocytes, epithelial cells, fibroblasts (with collagen matrix)	Structural repair
HPC	BM, cord or peripheral blood	• Allogeneic, unrelated transplant • Expanded, activated • Gene modified
Gene modified smooth muscles cells	Vein segment	Angiogenesis

HCT/P Also Regulated as Biological Products

- Require pre-market approval by US FDA
- Data are submitted in a Biologics License Application (BLA)
- Approval based on data from US (IND) or foreign studies that are:
  - Well designed
  - Performed by qualified investigators
  - Conducted in accordance with ethical principles
- Data must demonstrate safety & efficacy

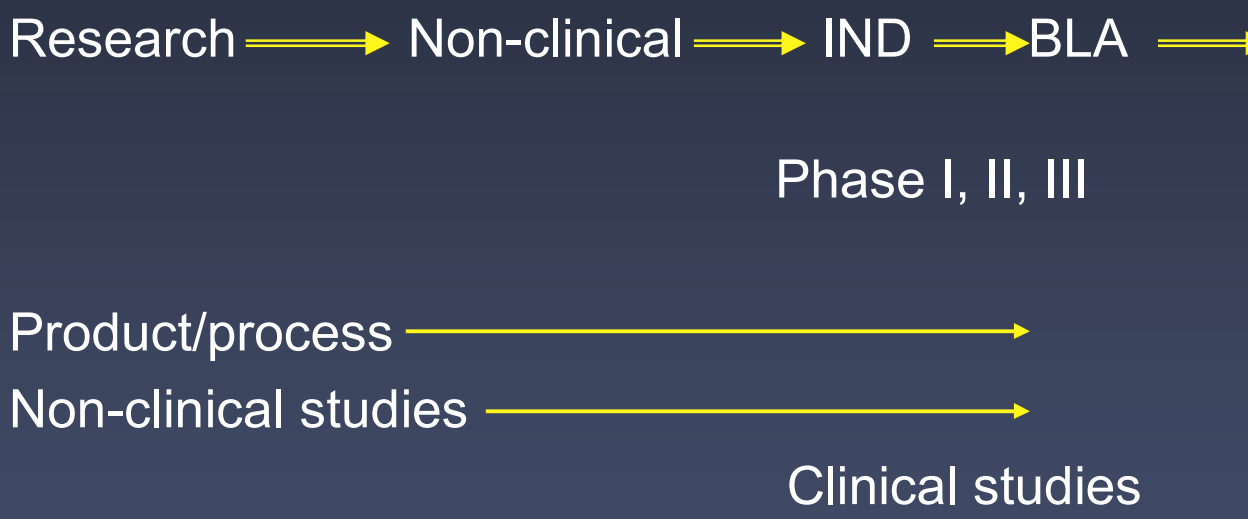
Investigational New Drug (IND) Application

- An application to test an unapproved drug or biologic in human clinical trials
- Three IND phases:
  - Phase I- initial introduction to humans, primary objective is safety
  - Phase II- optimize dose, route, regimen, patient population and endpoints, controlled
  - Phase III- pivotal safety and efficacy, randomized,controlled, support labeling claims

Investigational New Drug (IND) Application

- The IND must provide:
  - Preclinical Pharmacology/Toxicology data
  - Manufacturing description and product safety & characterization data
  - Clinical protocol and investigator information

Biological Product Development Process



Non-clinical Studies Expectations

Support the safety and rationale for use of the product in humans

- Efficacy/ Proof-of-concept
  - Demonstrate ability to correct or alleviate target disease in relevant model
- Safety/Toxicology
  - Potential for adverse events
  - Escalating doses (MTD)
  - Delivery method
- Design of Non-clinical program based on clinical expectations
- GLP or “spirit of GLP”

Non-clinical Studies Expectations

- Cell Fate Post-transplant
  - Tumorigenicity
  - Cell migration and trafficking
  - Cellular differentiation
  - Persistence and cell survival

Manufacturing and Product Testing Expectations

- Product Safety Testing
  - Sterility, mycoplasma, endotoxin, adventitious virus
  - Must be assessed at all stages of product development
- Product Characterization
  - Purity, viability, identity, potency
  - Step-wise approach applies
- Manufacture under GMP / GTP
- Process Control and Consistency
  - Demonstrated based on accumulating data from product testing

HCT/P Lot Release Challenges

- Sterility
  - Result not available prior to release. Release based on 48-72 assay results & negative Gram Stain. May still need to obtain post-release results on sample of final product. Rapid test methods
- Mycoplasma
  - Result not available prior to release. May need to develop alternative test methods or procedures (PCR)
- Purity
  - Endotoxin/pyrogenicity -results typically obtained prior to release (LAL)
- Potency
  - Often a single quantitative assay is not possible for a cell product. Matrix of qualitative and quantitative assays can be used.

HCT/P Lot Release Challenges

- Identity
  - Assays should be product specific and may include phenotypic markers, morphology, specific staining
- Viability
  - Function of product depends upon living cells; recommend at least 70% viability
- When final lot release results are not available prior to use, in-process testing will be critical and may need to examine product after use to verify safety, function, performance, etc.

Quality Expectations

- GCP, GLP, GMP, GTP provide the framework (controls) for conduct of high quality:
  - Research
  - Pre-clinical safety studies
  - Product manufacture
  - Clinical trials

GCP, GLP, GMP/GTP

- Principles apply to the entire product/clinical development process
- For GMP level of compliance increases with phase of study
- For GTP 100% compliance is expected prior to manufacture
- Ensure integrity and quality of data/ product
- Very important for all:
  - DOCUMENTATION !!

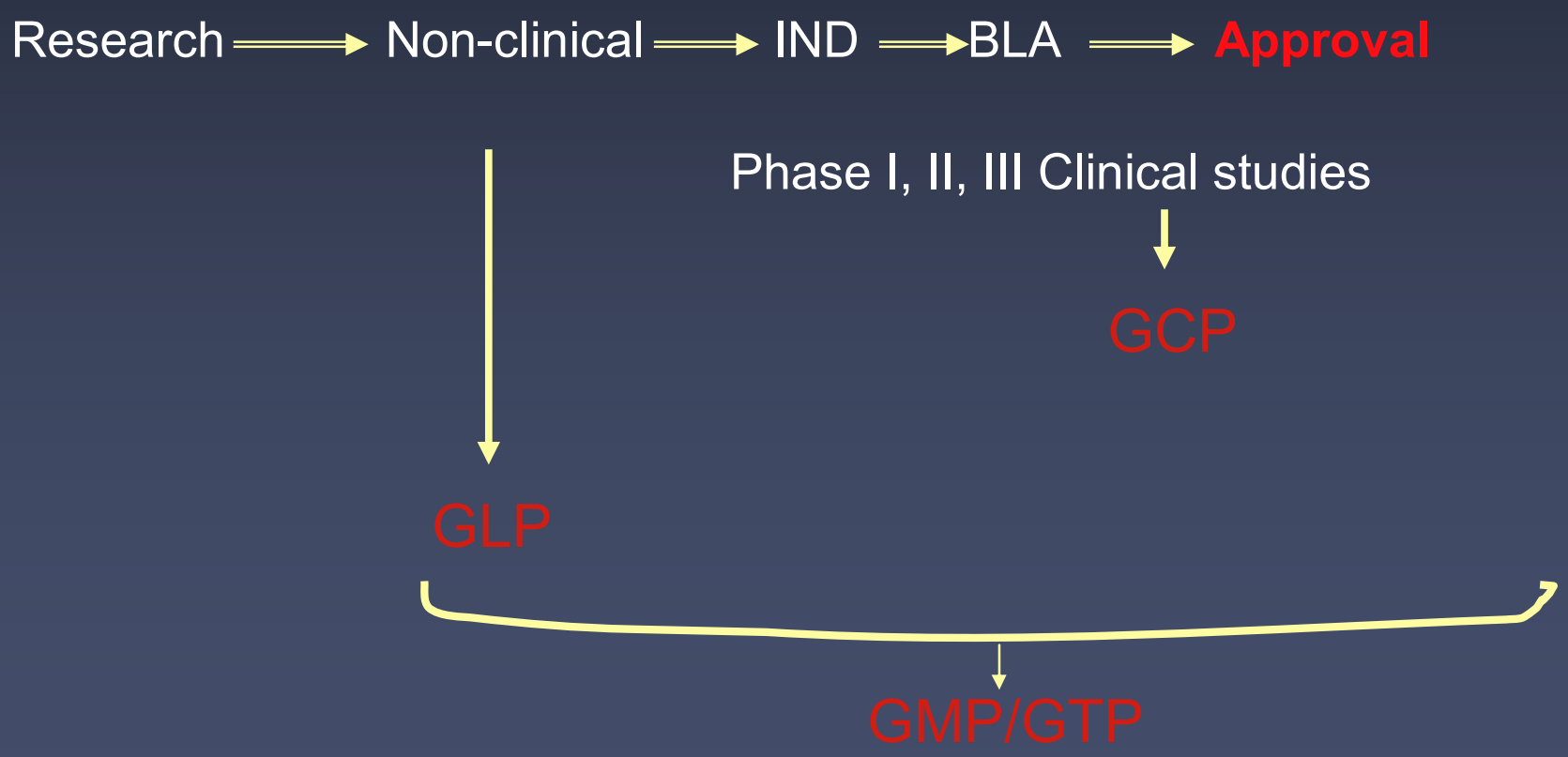
GCP,GLP, GMP/GTP

- Good Clinical Practice (ICH E6)
  - Applies to design, conduct and reporting of clinical trials
- Good Laboratory Practice
  - Applies to nonclinical laboratory studies that are intended to support an investigational or marketing permit
  - Not to manufacturing or quality of test material used in preclinical studies
    - GMP not GLP

GCP, GLP, GMP/GTP

- Good Manufacturing Practice
  - Applies to the manufacturing process and the facility for HCT/P regulated as biological products, QC activities
- Good Tissue Practice
  - Applies to all human cellular and tissue-based products
  - Supplements but does not supersede GMPs

Quality Expectations for Biologics



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CBER Guidelines

- http://www.fda.gov/cber/guidelines.htm
- Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) - Small Entity Compliance Guide August 2007
- Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs) July 2007
- Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)
- Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products Feb 2008

Summary

- HCT/P are regulated under 21 CFR 1271, referred to as Tissue Rules
- Tissue rules consist of instructions for:
  - Establishment Registration
  - Donor Eligibility
  - Good Tissue Practices
- 4 criteria define the level of potential product risk
- Low risk products follow TR only
- Higher risk products follow TR + Biologics Regulations (IND/BLA, GMP)