

# Cell Therapy Products

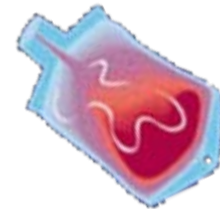
## Regulatory and Manufacturing Strategies

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# Unique Challenges of Cell Therapy

	<i>Biotechnology</i>	<i>Cell Therapy</i>
<i>Product</i>	Cultured cells generate product	Living cells <i>are</i> product
<i>Raw Material</i>	Seed cell lines	Unique, primary tissue
<i>Variability, Heterogeneity</i>	Limited	Substantial

>99% CDX<sup>+</sup> cells



?% CDY<sup>+</sup> cells

?% CDY<sup>-</sup> cells

# Unique Challenges of Cell Therapy

	<i>Biotechnology</i>	<i>Cell Therapy</i>
<i>Product Definition</i>	Well-defined, definable products	Product defined through trials Full definition likely unattainable
<i>Process, Testing</i>	Established early	Evolve through trials

	INDs	IND Amendments
Cell Therapy	903	13,527
Gene Therapy	372	8,090

# Unique Challenges of Cell Therapy

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<i>Process Scale</i>	Bulk processes predominate	Patient-specific products common

# Cell Therapy Product Manufacturing Strategies

- Manufacturing process must protect product, patient
  - Focus on product characterization, process control
  - Controlled, consistent processes → controlled, consistent products
- High throughput, parallel processing to achieve scale
  - Functionally-closed processing systems, automation
- Rigorous process development, characterization

# Making Coffee One Cup at a Time: Automated, Functionally-Closed Systems

Individualized, cup-specific brewing of a variety of coffees, teas, cocoa, *even mochaccino with extra foam*.



Preloaded, disposable,  
individualized raw  
material sets

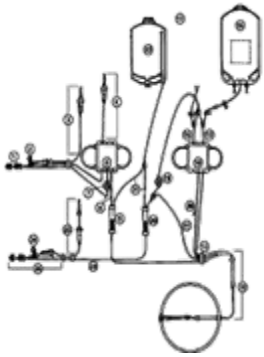


Separate process  
environment  
for each product



Automated  
processing  
device

# High Throughput Cell Therapy Product Manufacturing: Automated, Functionally-Closed Systems



Preloaded, disposable,  
individualized raw  
material sets



Separate process  
environment  
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Automated  
processing  
devices

# Regulations and Standards for Cell Therapy Products

- FDA-CBER OCTGT, CDRH
  - Good Tissue Practices (GTPs)
  - Good Manufacturing Practices (GMPs)
  - Good Clinical Practices (GCPs)
- Institutional Review Board, Biosafety Committee
- Foundation for the Accreditation of Cellular Therapy (FACT)
- American Association of Blood Banks (AABB)
- American Association of Tissue Banking (AATB)
- United States Pharmacopeia (USP)
- College of American Pathologists (CAP)
- Clinical Laboratory Improvement Amendments (CLIA)

# FDA Requirements - GCPs, GTPs, GMPs

Good Manufacturing Practices (GMPs)	Ensure consistent manufacture of safe, pure, potent products
Good Tissue Practices (GTPs)	Prevent infectious disease transmission Donor screening and testing
	Prevent cross-contamination, mixups Product recovery, processing, storage, labeling, distribution
Good Clinical Practices (GCPs)	Ethical, scientific quality standards Protect trial subjects rights, safety, confidentiality Assure credibility of clinical trial data

# Application of FDA Regulatory Requirements

## Minimally Manipulated

*IF* a cell therapy product meets criteria 1 *and* 2 *and* 3, *and* (4a *or* 4b *or* 4c).

- 1 Minimally manipulated (not activated, encapsulated, expanded *ex vivo*, or genetically modified) *AND*
- 2 Intended for homologous use *AND*
- 3 Not combined with a drug or device *AND*
- 4a. Does not have a systemic effect, *AND* Primary function does not depend on metabolic activity of viable cells *OR*
- 4b. Has a systemic effect and is intended for autologous, related- allogeneic, or reproductive use *OR*
- 4c. Primary function depends on metabolic activity of viable cells) and is intended for autologous, related- allogeneic, or reproductive use

*THEN...*

- IND or IDE *NOT* required
- GTPs *ARE* required

## More-Than-Minimally Manipulated

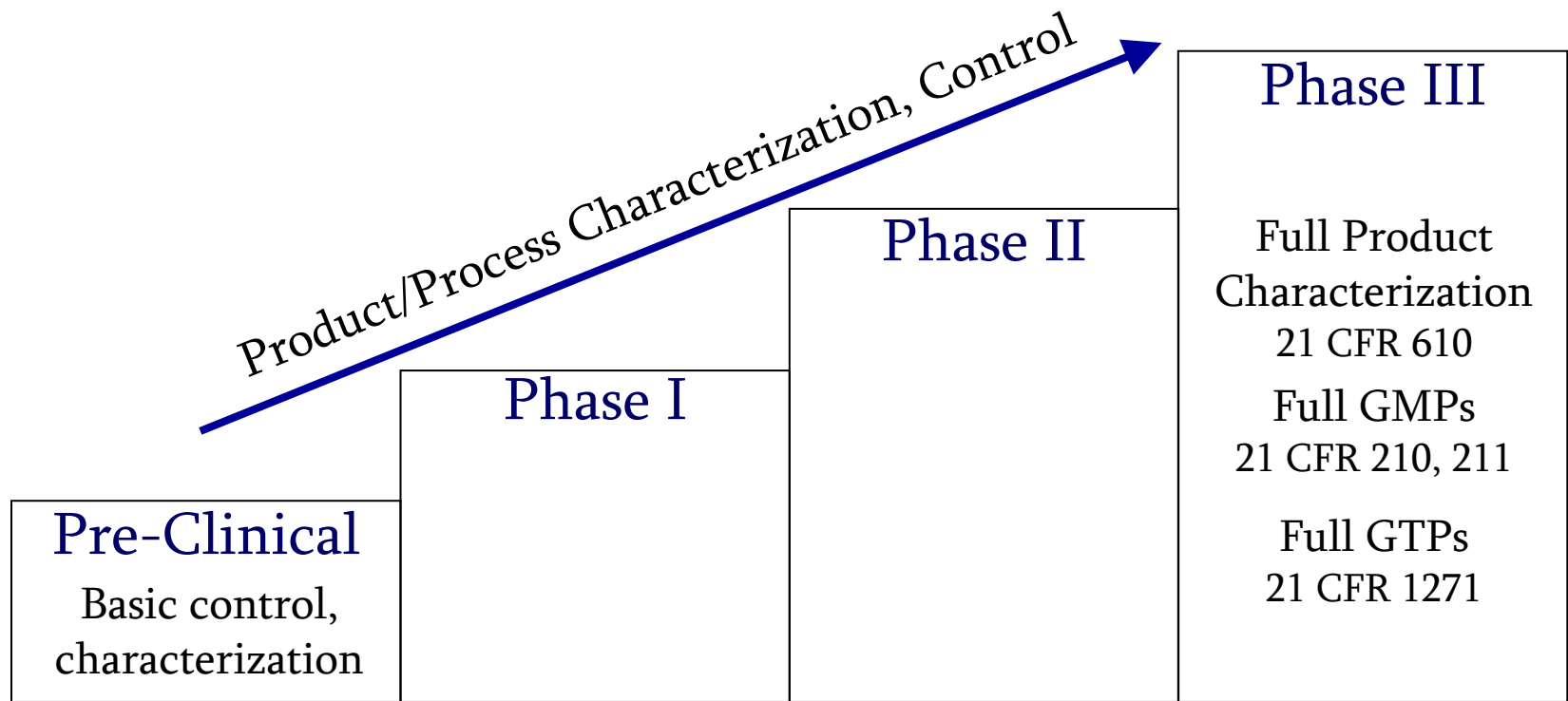
*IF* a cell therapy product does not meet one or more of the four major criteria defining minimally manipulated products

*THEN...*

- Regulated using IND/IDE framework, clinical trial pathway
- GMPs, GTPs, GCPs required

*Nearly any interesting cell therapy meets criteria for the more-than-minimally manipulated category*

# FDA Regulatory Requirements Increase With Product Development



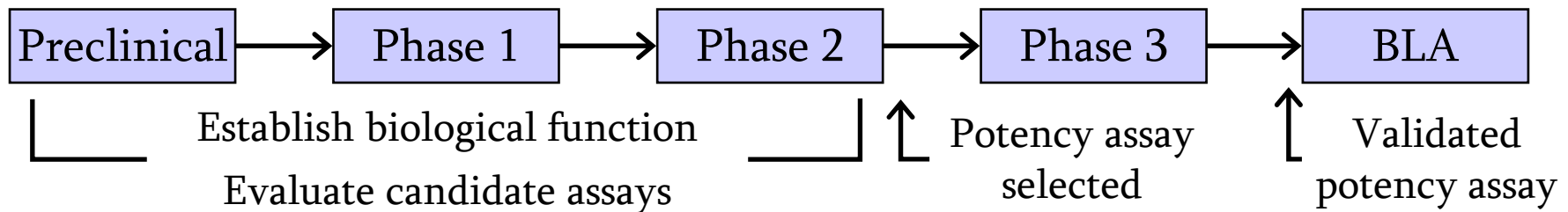
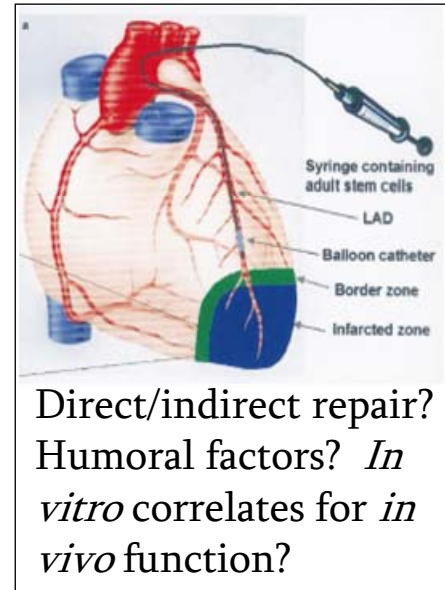
GMPs expected throughout clinical studies

↑ control as clinical development progresses

Sufficient control (GMP) at early stages to enable development to licensure

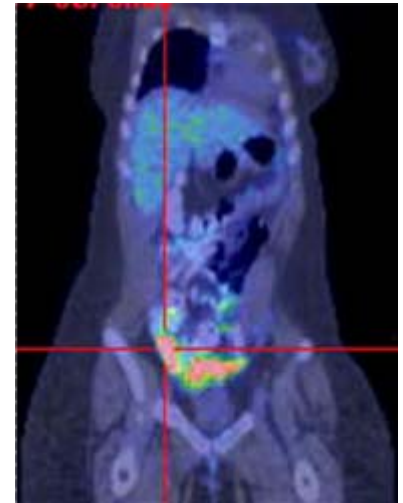
# Product Characterization - Potency

- Testing “relevant biological function”
  - Understanding product function refined from preclinical to Phase III
- Potency assays
  - Evaluate candidate assays across Phase I, II trials, assess in light of clinical data
  - Qualify surrogate assays giving real-time results

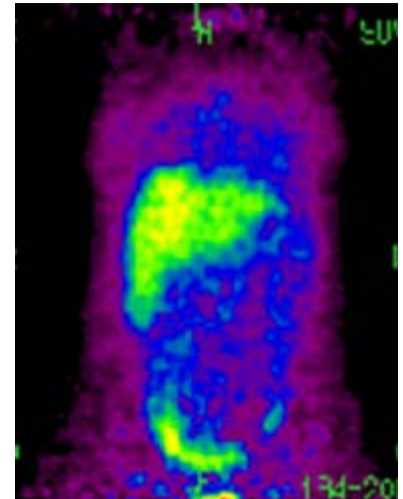


# Cell Distribution *In Vivo*

- Imaging technology for *in vivo* cell tracking
  - Cell distribution, kinetics
  - Fluorescence, magnetic particle-based imaging
  - Isotopic imaging - PET-CT, SPECT
- Development and regulatory applications
  - Clues to biological function
  - Animal model qualification
    - Human cells? Animal cells?
  - Bridge manufacturing changes
    - Fresh *vs.* frozen/thawed? Serum *vs.* serum-free?
  - Patient monitoring



Pre-Rx PET



FDG-labelled MAK cells  
t = 3 hr., PET-CT

# Summary

- Unprecedented numbers of cell therapy products are in development for a remarkable range of clinical applications. These living biological products present unique challenges in development, manufacturing, characterization, and delivery.
- Regulatory aspects of cell therapy products differ from those of biotechnology products. *All* cell therapy products are regulated under GTPs; most must comply with GMPs as well. Requirements for product characterization and process control grow more stringent with advancing clinical development.