

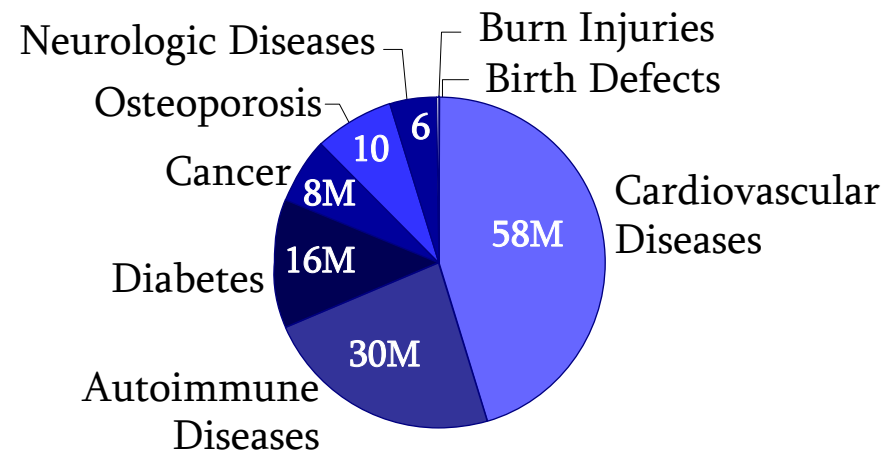
# Cell Therapy Products: Translational Development and Manufacturing

Scott R. Burger, MD  
Advanced Cell & Gene Therapy

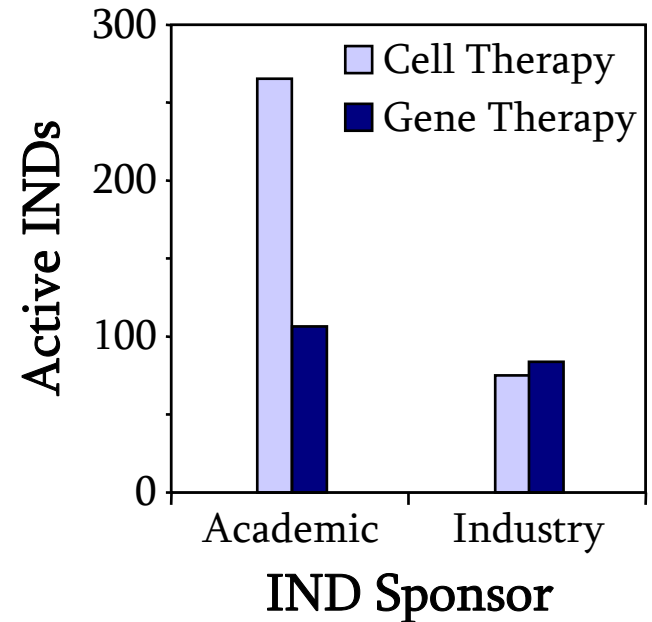
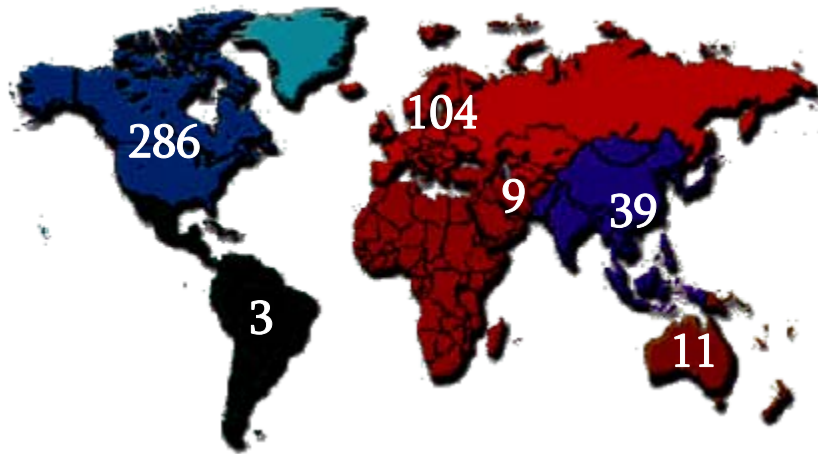
# Cell Therapies - Potential, Promise, and Plenty of Challenges

- Numerous potential applications, often for unmet needs
  - Potentially definitive therapies
- Novel uses of cells/genes
  - Difficult to evaluate efficacy, predict clinical risks
- Complex cell/gene engineering
  - Risk of manufacturing problems, product/process characterization challenges

Potential Patients (USA)



# An Emerging Cell Therapy Industry



- Over 400 cell or gene therapy companies worldwide
- Over 500 cell or gene therapy products in clinical development
- Over 1,000 gene therapy clinical trials worldwide
- Industry sponsors 25% of cell therapy INDs

# Challenges of Cell-Based Therapy

## Biotechnology

## Cell Therapy

*Product*

Cultured cells generate product

Living cells *are* product

*Raw Material*

Seed cell lines

Unique, primary tissue

*Variability,  
Heterogeneity*

Limited

Substantial

*Product  
Definition*

Well-defined, definable products

Product defined through trials  
Full definition likely unattainable

*Process, Testing*

Established early

Evolve through trials

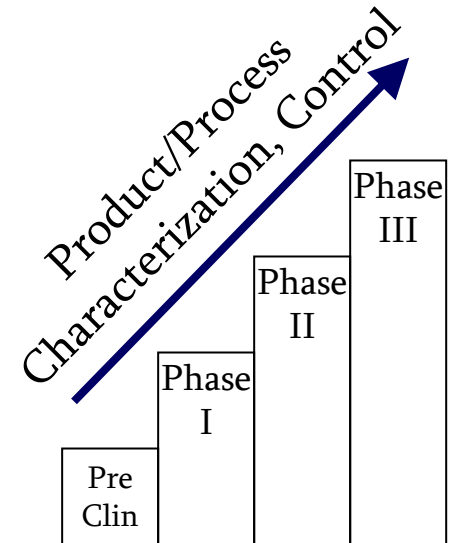
*Process Scale*

Bulk processes predominate

Patient-specific products common

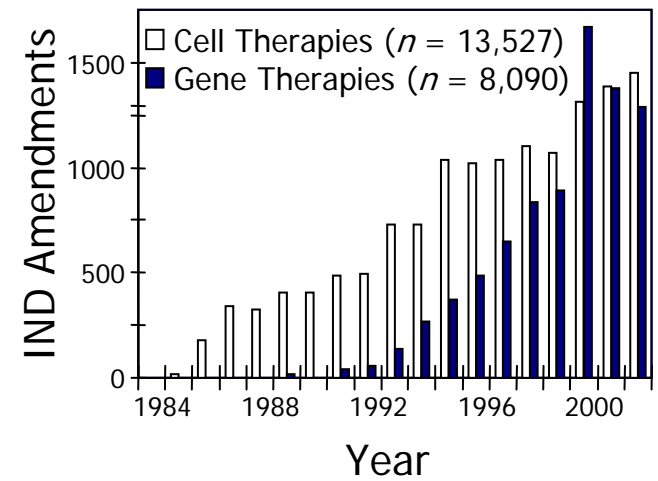
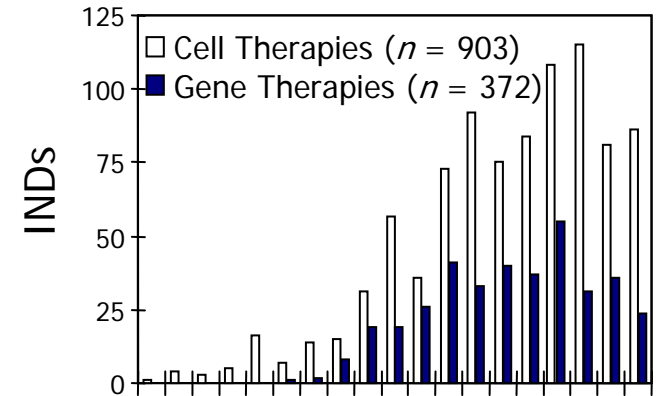
# Development Throughout Clinical Trials

- Evolution of manufacturing process, characterization profile
  - Processes, specifications refined based on experience
- FDA expects  $\uparrow$  control/characterization as clinical development progresses
  - Preclinical - basic process control, characterization
  - Phase III - full characterization, GMPs, GTPs



# Process and Product Definitions Develop Through Clinical Trials

- Process, testing, product definition evolve based on manufacturing experience, characterization data, clinical outcome data
  - Refine specifications and thresholds over time
  - Determine biological function, and cells mediating function
  - Final potency assay in place by Phase III



# Cell Therapy Product Manufacturing Strategies

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

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

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



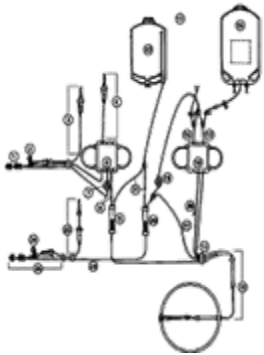
Preloaded, disposable,  
individualized raw  
material sets

Separate process  
environment  
for each product

Automated  
processing  
device

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

Individualized manufacturing, run in parallel for high throughput - cell selection, expansion, activation, centrifugation, cryopreservation.



Preloaded, disposable,  
individualized raw  
material sets



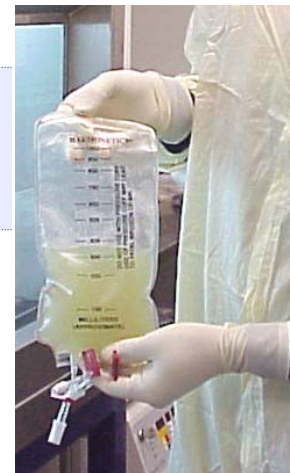
Separate process  
environment  
for each product



Automated  
processing  
devices

# Open vs. Closed-System Manufacturing

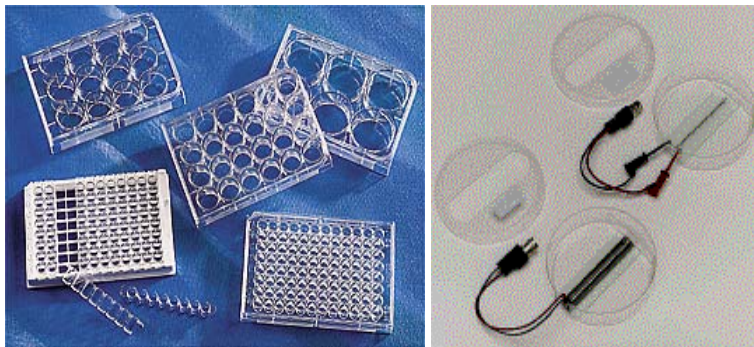
	<u>Open</u>	<u>Closed</u>
<i>Contamination Risk</i>	↑	↓
<i>Cell Yield</i>	↓	↑
<i>Manufacturing Space</i>	Cross-contamination risk limits options	Maximal effective use
<i>Consistency, Control</i>	Limited	↑ ↑ ↑
<i>Throughput Potential</i>	↓ ↓ ↓ Patient-specific	↑ ↑ ↑ Parallel processing Readily automated Presterilized, disposable



# Device Technology

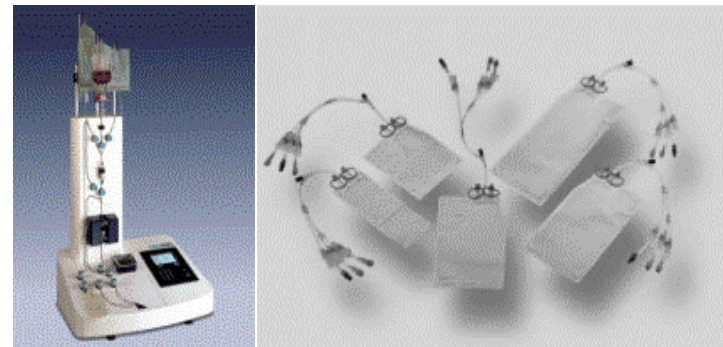
- Pre-clinical

- Open plates, tubes
- Small-scale
- Unique instruments



- Clinical

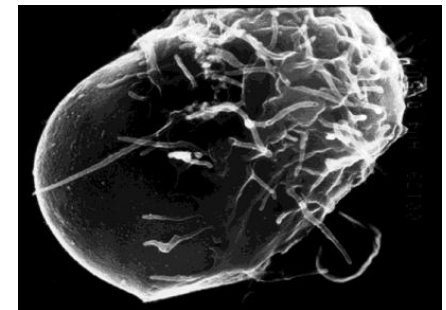
- Closed system
- Larger-scale
- Validated devices
- Presterilized, disposable



# Raw Materials

- Viable, functional biological raw material
  - Cell/tissue source for development studies?
- Reagents and supplies
  - Complex, often unique - cytokines, vectors, genes, culture media, supplements, mAbs...
  - Need for GMP manufactured reagents
  - Develop reagent specifications, qualify
    - Physical characteristics, quality control, qualification tests, storage conditions, expiration
  - Manufacturer Service Level Agreements

Human serum (AB-, autologous)  
Fetal calf serum, horse serum  
Monoclonal antibodies  
Recombinant vectors  
G-CSF, GM-CSF, EPO, TPO  
IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, IL-3  
IL-4, IL-6, IL-7, IL-8,  
TNF- $\alpha$ , PG-E<sub>2</sub>  
SCF, FL, Flt3, VEGF  
BMP-4, EGF, IGF  
PDGF-BB, MIP-1 $\alpha$ , MCP-1  
TGF- $\beta$ 1, aFGF, bFGF  
N-desulfated O-sulfated heparin



J Immunol Methods 2001

# 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

# GMP, GTP Systems Needed

## GMPs

- Organization, personnel, training, evaluation
- Buildings and facilities
- Equipment, reagents and supplies
- Procedures
- Production and process controls
- Finished product control
- Laboratory controls
- Records and reports

## GTPs

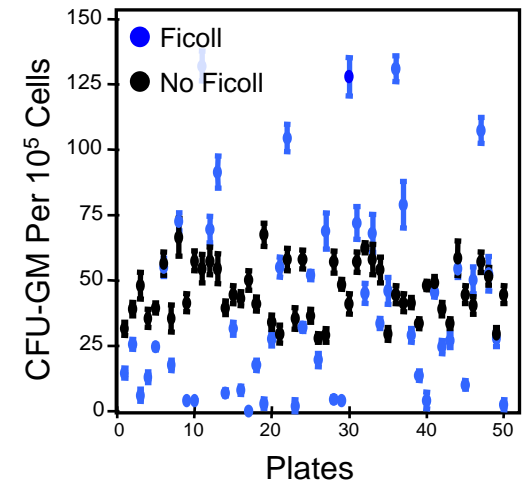
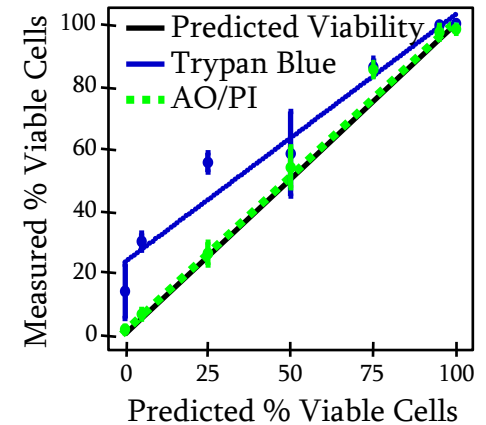
- Organization, personnel
- Facilities, monitoring
- Equipment, supplies and reagents
- Quality program
- Procedures
- Process validation, controls, changes
- Storage, receipt, distribution
- Tracking
- Labeling controls, records, complaint file

# Product Characterization Testing (21 CFR 610)

- Safety
  - Sterility, endotoxin, mycoplasma, adventitious agents
- Purity, Identity
  - Cell viability, concentration, morphology, immunophenotype
- Potency
  - Relevant biological function, real-time surrogates for functional assays
- Stability
- Tumorigenicity
- Reagents, Ancillary Materials

# Product Characterization Strategy

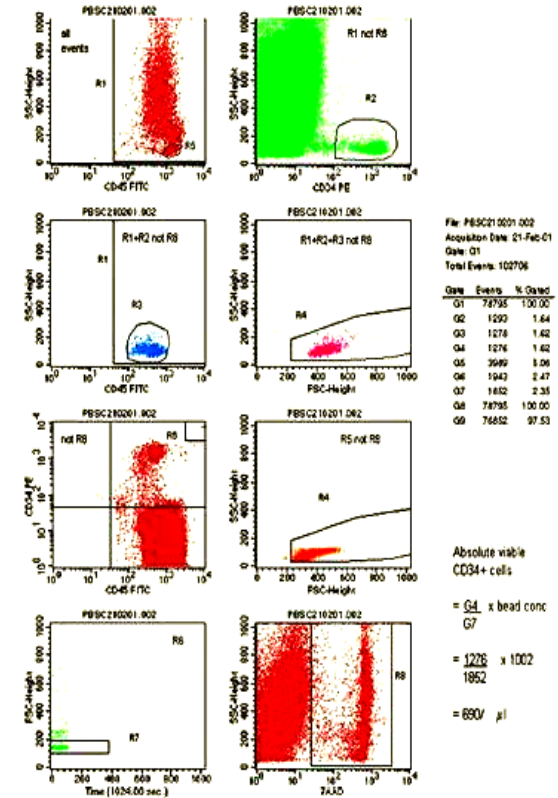
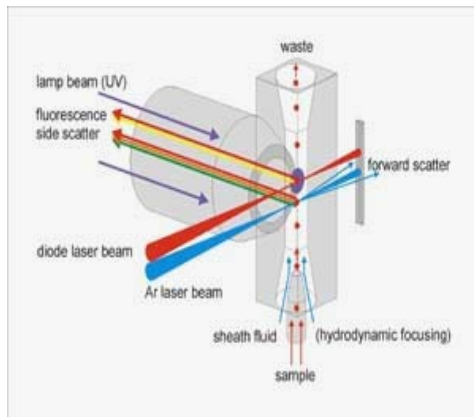
- Test multiple parameters, establish *pattern* of product characterization data, *refine over time*
- May need novel analytical tools
- Robust, qualified analytical methods
  - Documented reproducibility, predictive value, sensitivity, specificity



# Product Testing – Purity, Identity

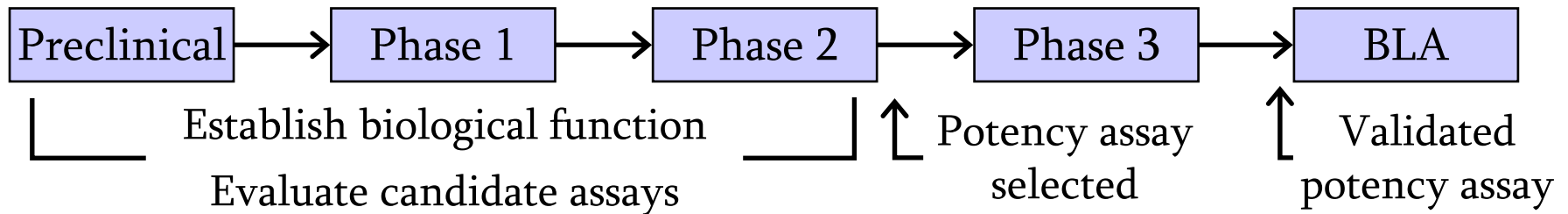
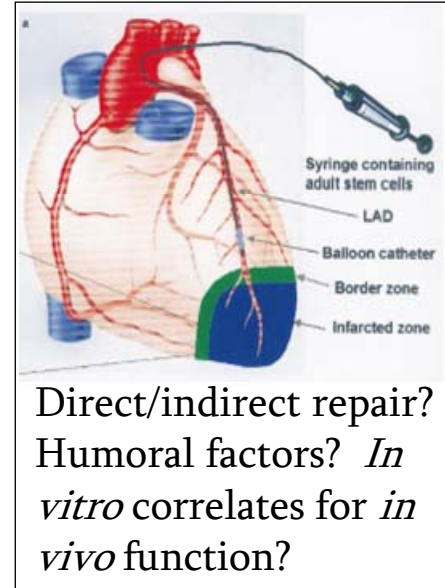
## Immunophenotype Determination – Flow Cytometry

- Essential analytical tool for most cell therapies
  - Purity, identity
  - Applications in potency testing
- Multiple potential sources of error, variability, subjective interpretation
- Requires optimization, rigorous control, *validation*
  - IQ/OQ/PQ - reagents, *cytometer*, software, procedures, analysis



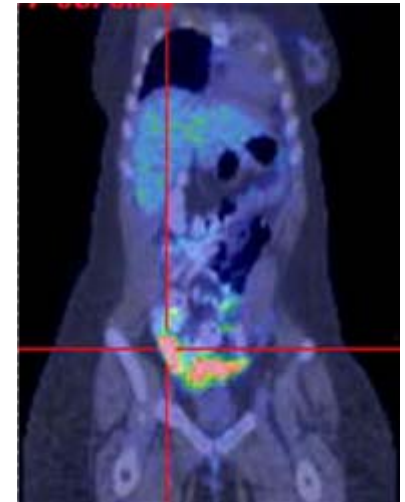
# Product Characterization - Potency

- Testing “relevant biological function”
  - Understanding product function refined from preclinical to Phase III
- Potency assays
  - Cytotoxicity, cytokine release, antigen presentation, proliferation, differentiation...
  - Evaluate candidate assays across Phase I, II trials, assess in light of clinical data
  - Functional assay turnaround time problematic, qualify real-time surrogate assays

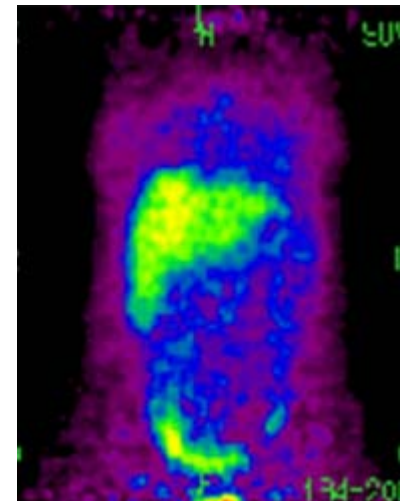


# Cell Distribution *In Vivo*

- 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

# Formulation - Stability - Shelf-Life

- Fresh (non-cryopreserved) products
  - Product stability drives release, distribution, administration
  - Release on 24/48 hr sterility culture, endotoxin, Gram stain
  - Need effective rapid sterility testing
- Cryopreserved products
  - Manufacturing and administration flexibility, but...
  - Thaw and administer product with cryoprotectant
  - Thaw, wash, administer - manufacturing at clinical site
    - Post-wash, stat Gram stain and endotoxin
    - *Need functionally-closed device for thaw/wash/resuspension*
- Novel preservation alternatives
  - Possibilities for DMSO-free, non-frozen preservation



# 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

- Rigorous, evolving characterization and process control vital to address biological heterogeneity, variability, incomplete definition.
- Begin preparing for manufacturing *early*, and expect changes. Processes/analytical methods/product definition must evolve over multiple clinical trials.