

Compliance with cGTPs/cGMPs in Manufacturing Cell and Gene Therapy Products

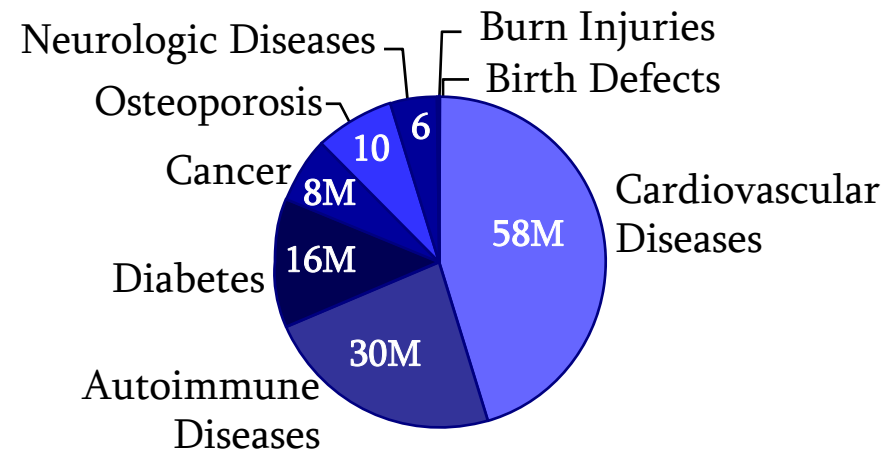
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Advanced Cell & Gene Therapy

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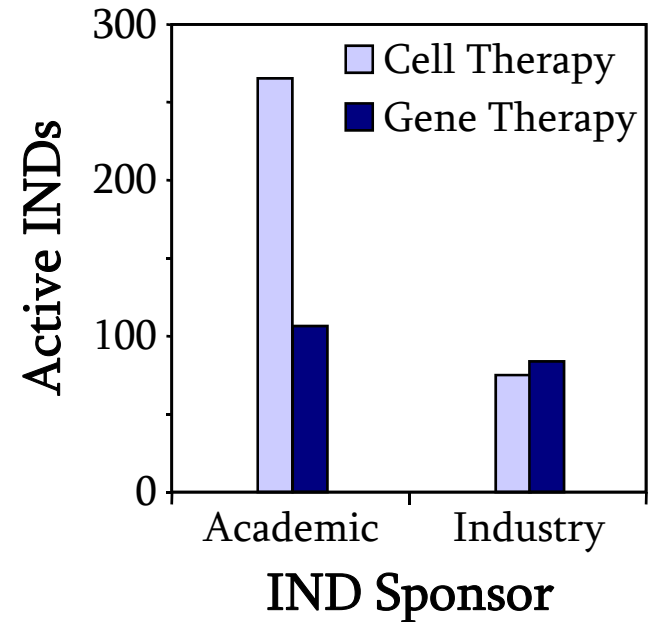
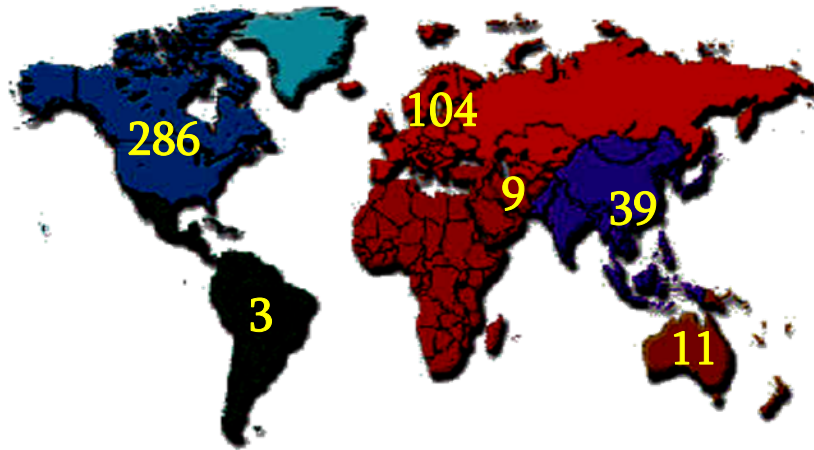
Cell Therapies - Potential, Promise, and Plenty of Challenges

- 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 300 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

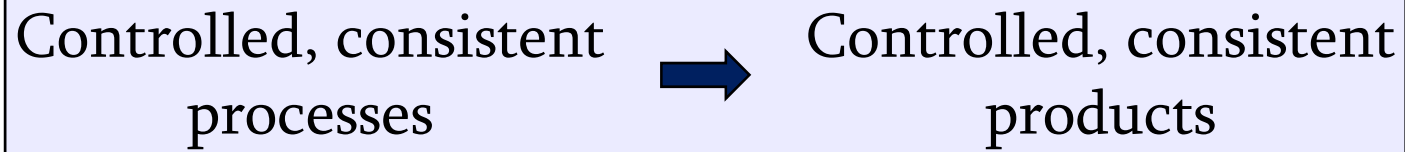
Bulk processes predominate

Patient-specific products common

Strategies for Cell-Based Therapies

- Rigorous process development, characterization
 - Product definition, relevant biological function
 - Ongoing, iterative development throughout clinical trials

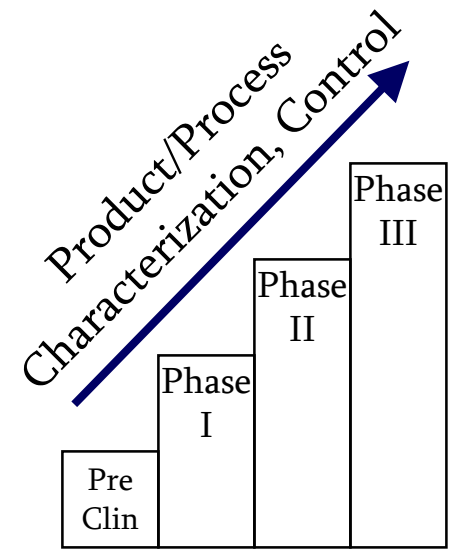
- Focus on manufacturing process control



- High throughput, parallel processing to achieve scale
 - Functionally-closed processing systems, automation
 - Closed-system manufacturing can replace process cleanroom

Manufacturing Process Development Throughout Clinical Trials

- Evolution of manufacturing process, characterization profile
 - Processes, specifications refined based on experience
 - 903 cell therapy INDs
 - Over 13,500 IND amendments
- FDA expects ↑ control, characterization as clinical development progresses



Risk-Based Approach to Cell Therapy Regulation

- Products that present greater risk of adverse clinical outcome require more and better control, and hence more stringent regulation and oversight.
- Risks, and potential risks
 - Complex manufacturing, complex product
 - Unrelated allogeneic clinical strategy
 - Cells/tissues used in a manner unlike natural function
 - Or, cannot assess risk due to extreme novelty
- Higher risk products regulated under Public Health Service Act, Section 351

Application of FDA Regulatory Requirements

“361” Products

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

“351” Products

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 *AND* GTPs required

Nearly any interesting cell therapy meets criteria for the “351” category

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

Current Good Manufacturing Practices (cGMPs)

A set of current, scientifically sound methods, practices or principles that are implemented and documented during product development and production to ensure consistent manufacture of safe, pure and potent products.

21 CFR 210, 211

- General provisions
- Organization and personnel
- Buildings and facilities
- Equipment
- Control of components
- Production and process controls
- Packaging and label controls
- Holding and distribution
- Laboratory controls
- Records and reports
- Returned and salvaged product

GMP Manufacturing

- Elements of GMP

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

- GMP Systems

- Training, proficiency testing
- Monitoring
 - Environment, equipment, personnel
- Process control
 - Instruments, reagents, supplies, assays, specifications
- Qualification, validation
 - Processes, equipment, assays
 - IQ, OQ, PQ
- Document control, data management
 - Format, change/version control, retention, analysis, trending

Current Good Tissue Practices (cGTPs)

- Methods, facilities for manufacture of human cellular and tissue-based products
 - Prevent introduction, transmission and spread of infectious disease
 - Donor screening and testing
 - Prevent mix-ups, cross-contamination
 - Product recovery, processing, storage, labeling, distribution
- Resemble GMPs, but narrower focus
- Quality Program
- Organization, Personnel
- Procedures
- Facilities
- Environmental Control, Monitoring
- Equipment
- Supplies and Reagents
- Process Controls, Changes
- Process Validation
- Labeling Controls
- Storage Requirements
- Receipt and Distribution
- Records
- Tracking
- Complaint File

21 CFR Part 1271

Core GTP Requirements - 1271.150(b)

- *Directly* related to preventing introduction, transmission, or spread of communicable disease.

Other GTP requirements support core cGTPs

- Facilities - 1271.190(a) and (b)
- Environmental control - 1271.195(a)
- Equipment - 1271.200(a)
- Supplies and reagents - 1271.210(a) and (b)
- Recovery - 1271.215
- Processing and process controls - 1271.220
- Labeling controls - 1271.250(a) and (b)
- Storage - 1271.260(a-d)
- Receipt, pre-distribution shipment, distribution - 1271.265(a-d)
- Donor eligibility determination - 1271.50, 1271.75, 1271.80, 1271.85

GTP-Specific Requirements

- Requirements for GTPs and GMPs overlap in many respects - GMP-compliant operation will meet many of the GTP requirements.
- However, certain requirements are GTP-specific. Either not covered by GMPs at all, or requirement is more HCT/P-specific than in GMPs, so **GMP compliance alone is not sufficient.**
 - Donor eligibility
 - Tracking systems
 - Quality program
 - Predistribution shipment
 - Recovery of HCT/Ps
 - Exemptions and alternatives
 - Records
 - Availability for Distribution
 - Receipt procedures
 - Processing, process controls
 - Reporting requirements

Tracking systems 21 CFR 1271.290(a-g)

- A tracking system for HCT/Ps is a vital GTP element, with specific requirements (relating product to donor, tracking from original to final disposition, distinctive codes) not covered by GMP regulations. GMPs (21 CFR 211.196) address distribution records, but do not require this degree of tracking.

Quality Program

- Although GMPs (21 CFR 211.22) address role of quality control unit, the GTP requirement for a quality program is HCT/P-specific.

Predistribution Shipment

- Addresses shipment of HCT/Ps prior to release for distribution, GTP-specific, not in GMPs. Part of core GTPs.

Recovery of HCT/Ps

- Specific to HCT/Ps and GTPs, and part of the core GTPs (21 CFR 1271.215).

Exemptions and alternatives

- 21 CFR 610.9 addresses equivalent methods, but is not as extensive as GTPs.

Records - 21 CFR 1271.270

- (a)-(c) - Record requirements covered under GMPs (211.180, 211.188)
- (d) requires retention of records for 10 years, not covered under GMPs
- (e) requires records of all contracts and agreements, not required under GMPs

Availability for Distribution - 21 CFR 1271.265 (c)

- (1) Covered by GMPs, 211.22, 211.165, 211.167, 211.192
- (2) Specific to review of donor eligibility, *not covered by GMPs*
- (3) Covered under GMPs, 211.192
- (4) Specific to packaging and shipping of HCT/Ps, not covered by GMPs
- 211.196 cGMP requirement for distribution records is not as specific. Record must contain name and strength of product, description of dosage form, lot or control number.

Receipt procedures for HCT/Ps - 21 CFR 1271.265 (a)

- Requires evaluation of incoming HCT/Ps with respect to presence of microorganisms, damage and contamination. Decision to accept, reject or quarantine. This is distinct from, but complemented by, 21 CFR 211.84 (a) – Procedures for the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components.

Processing and Process Controls

- Pooling 21 CFR 1271.220(b) - human cells or tissue from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing - GTP-specific.
- GMPs are, however, applicable to other production and processing controls (process validation, in-process testing, change control, as apply to identity, strength, quality, purity).

Reporting Requirements - 21 CFR 1271.350 (a)

- Manufacturers must investigate:
 - Any adverse reaction involving a communicable disease related to an HCT/P that they made available for distribution.
- Manufacturers must report to FDA
 - An adverse reaction involving a communicable disease if
 - It is life-threatening
 - It results in permanent impairment of function or permanent damage to body structure
 - It necessitates medical or surgical intervention, including hospitalization

Cell Therapy Manufacturing Processes

- Cryopreservation
- Cell selection
- *Ex vivo* culture
 - Expansion, maturation, selection, other
- Cell activation
- Genetic modification
- Tissue processing
- DNA/RNA purification, amplification

Raw Materials

- GMP manufactured materials needed, but complex, often unique reagents
 - Sera, cytokines, vectors, genes, culture media, supplements, mAbs...
- If GMP reagents unavailable?
 - Qualification
 - Physical characteristics, quality control, qualification tests, storage conditions, expiration
 - Manufacturer Service Level Agreements
- Qualify removal of ancillary materials from final product

Human serum (AB-, autologous)
Fetal calf serum, horse serum
Monoclonal antibodies
Recombinant vectors
G-CSF, GM-CSF, EPO, TPO
IL-1 α , IL-1 β , IL-2, IL-3
IL-4, IL-6, IL-7, IL-8,
TNF- α , PG-E₂
SCF, FL, Flt3, VEGF
BMP-4, EGF, IGF
PDGF-BB, MIP-1 α , MCP-1
TGF- β 1, aFGF, bFGF
N-desulfated O-sulfated heparin

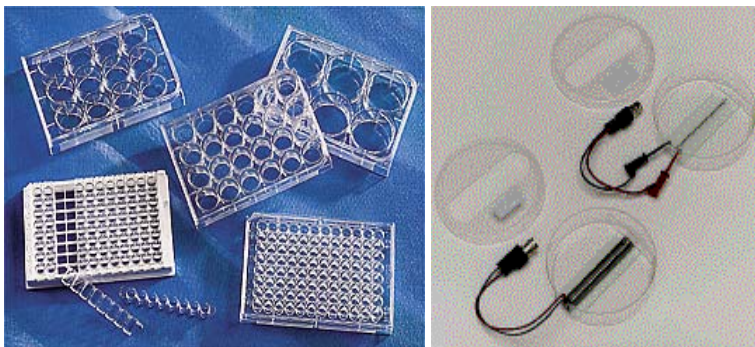


J Immunol Methods 2001

Device Technology

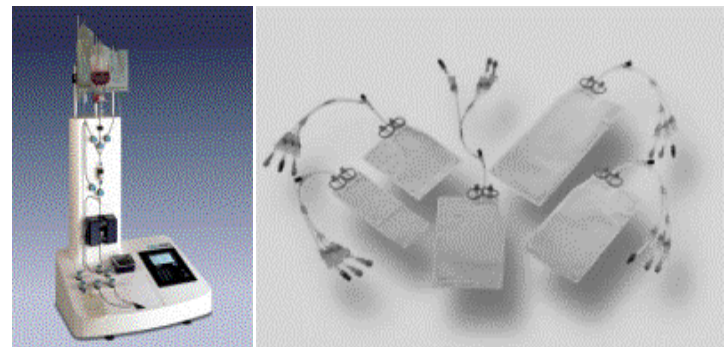
- Pre-clinical

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



- Clinical

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



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*.



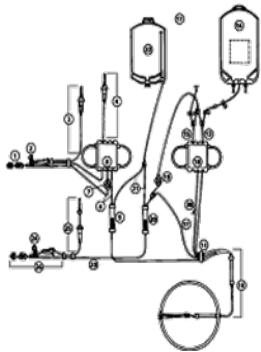
Preloaded, disposable,
individualized raw
material sets

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

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
- Analytical Methods
 - 21 CFR 610 methods, *or demonstrate equivalence*
 - At BLA, 21 CFR 610 methods or *validated* alternative methods

Product Testing - Safety

- Sterility cultures (aerobic, anaerobic, yeast/fungal)
 - Phase I, II - pediatric blood culture bottles. Automated, minimal sample requirements. 14-day culture.
 - Phase III - CFR 610, USP sterility, *or validated equivalent*
- Endotoxin (21 CFR 610.13)
 - Specification <5 EU/Kg/hr for i.v. administration
- Mycoplasma (21 CFR 610.30)
 - Validated PCR-based assay acceptable alternative to PTC
- Adventitious agents
 - Follows practice for blood donor testing, more extensive if using xenogeneic reagents
- Logistics, release policies
 - Results pending, or QCT failure. Clinical release?

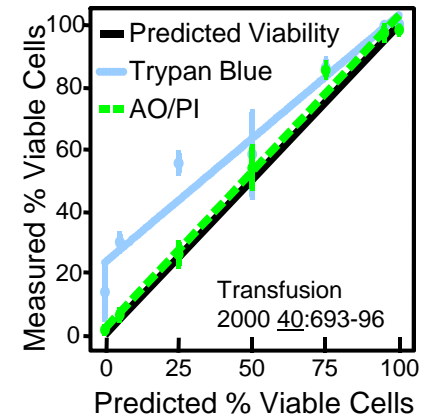
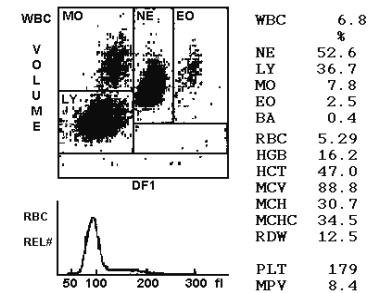
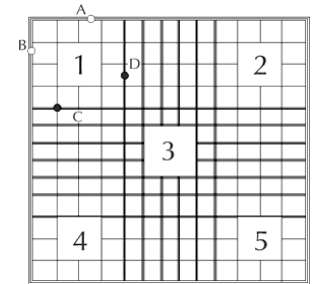
Safety Testing Strategy

- Cryopreserved products - preferred
 - Thaw and administer product when release testing complete
 - Release testing performed on pre-cryopreservation product
 - Validate cryopreservation and thaw
 - Product thawed and administered *without further testing (!)*
- Products administered fresh
 - Culture 24-48 hr pre-harvest, repeat at harvest
 - Stat Gram stain and endotoxin, at harvest
 - Release based on negative 48-hr culture, Gram stain, endotoxin, final results pending
 - Policy and action plan for positive culture results, other QCT failures, obtained after product administration

Product Testing – Purity, Identity

Cell Counts, Viability, Morphology

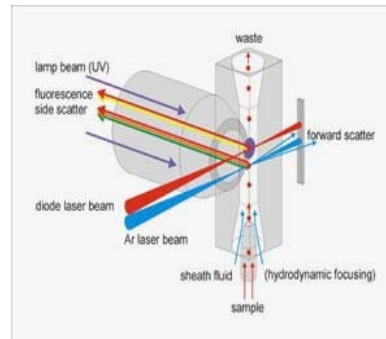
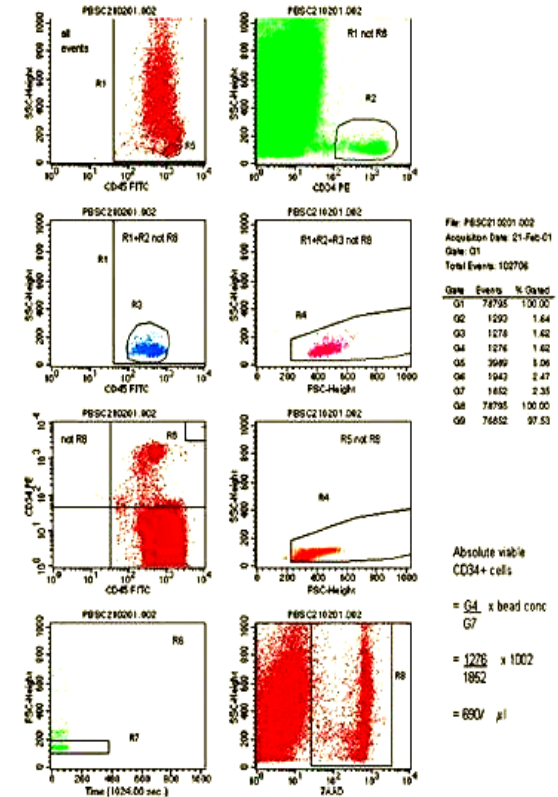
- Manual hemacytometer
 - Impedance technology
 - Other
- Automated electronic cell counters
 - Beckman ViCELL - Trypan blue
 - Guava Technologies PCA - fluorescent dyes
- Qualify viability assay!
 - Trypan blue, acridine orange-propidium iodide, 7-AAD



Product Testing – Purity, Identity

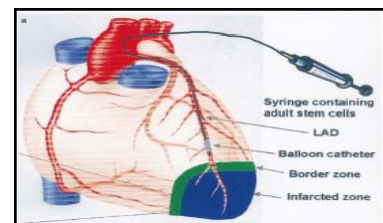
Immunophenotype Determination – Flow Cytometry

- 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

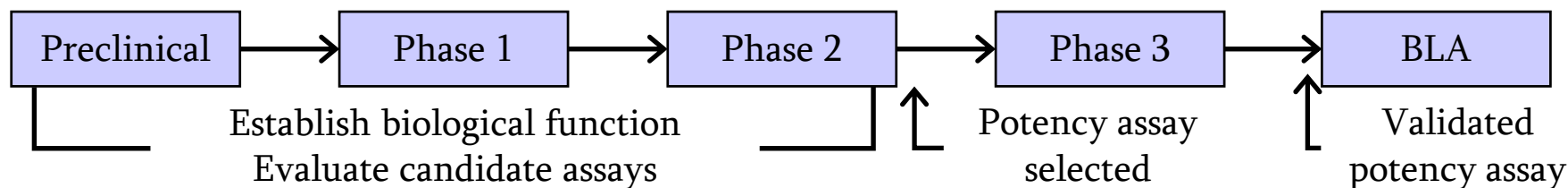
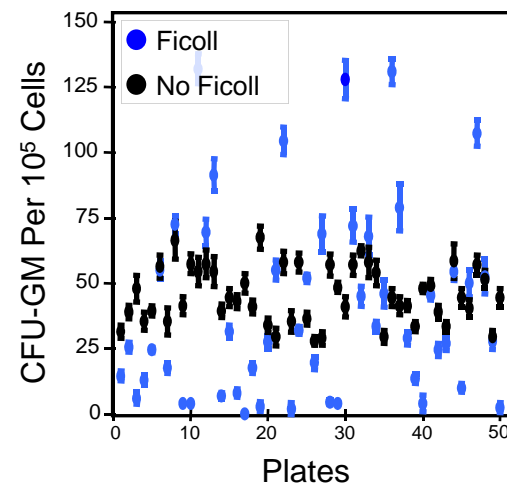


Product Testing - Potency

- 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

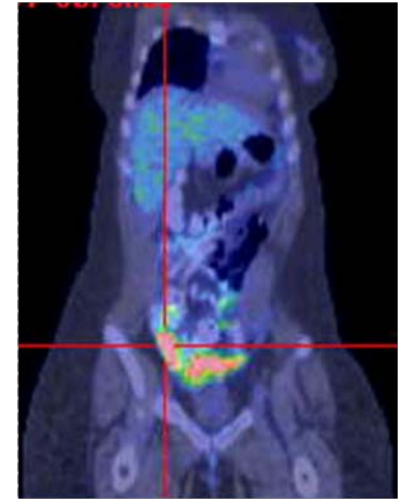


Direct/indirect repair? Humoral factors? *In vitro* correlates for *in vivo* function?

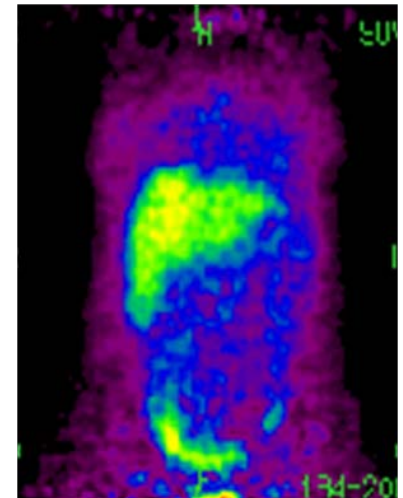


Cell Distribution *In Vivo*

- 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

- Living biological products present unique challenges in development, manufacturing, characterization, and delivery.
- Compliance with GMPs and GTPs fosters both good science and good clinical medicine, and (mostly) makes good business sense.
- Rigorous, evolving characterization and process control are vital to address biological heterogeneity and variability. Processes, analytical methods, and product definition must evolve over multiple clinical trials.

Save the Date!

May 17-20, 2008

14th

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International Society for Cellular Therapy

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Program Format:

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Oral and Poster Abstract Presentations

Preliminary Program Topics:

- Gene Therapy
- Cell Therapy Commercialization
- Lab Practices
- Hematopoietic Stem Cells
- Immunotherapy
- Dendritic Cells
- Mesenchymal & Tissue Stem Cells
- Legal & Regulatory Affairs

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