

Options for Manufacturing Cell Therapy Products

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Enabling Cell Therapy Manufacturing

- Key elements
 - Manufacturing facility
 - Materials, equipment
 - GMP/GTP systems, other operational support
 - Personnel
 - Ongoing development capabilities
- Established service infrastructure supports biotech manufacturing - what options for manufacturing cell therapy products?

Biotechnology and Cell Therapy: Key Differences

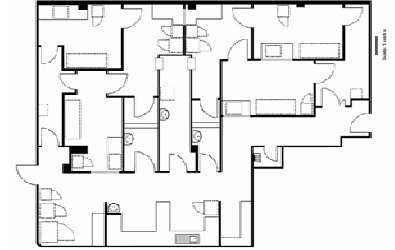
	<i>Biotechnology</i>	<i>Cell Therapy</i>
<i>Product</i>	Cultured cells generate product	Living cells <i>are</i> product
<i>Raw Material</i>	Seed cell lines	Unique, primary tissue
<i>Variability, Heterogeneity</i>	Limited	Substantial
<i>Product Definition</i>	Well-defined, definable products	Product defined through trials Full definition likely unattainable
<i>Process, Testing</i>	Established early	Evolve through trials
<i>Process Scale</i>	Bulk processes predominate	Patient-specific products common

Establishing the Manufacturing Facility

- Do-It-Yourself
- Contract manufacturers, service providers
 - Manufacturing facilities, infrastructure, staff
 - Academic, commercial alternatives
- Other considerations
 - Centralized or distributed manufacturing?
 - Transport and tracking logistics
 - Cells → Facility → Patient
 - Characterization testing

The Do-It-Yourself Path

- New construction
 - Built to suit needs, but time-consuming, costly
 - Need architecture, engineering with effective experience building cell therapy facilities
- Remodel existing facility
 - Potentially less costly, but risk of legacy problems
 - “Why, yes, the landscaping was all done with kudzu. It’s so prolific!”
- Modular cleanrooms
 - Rapid, less costly, soft-wall and rigid-wall options. Longevity?



GMP, GTP Systems Needed

GMPs

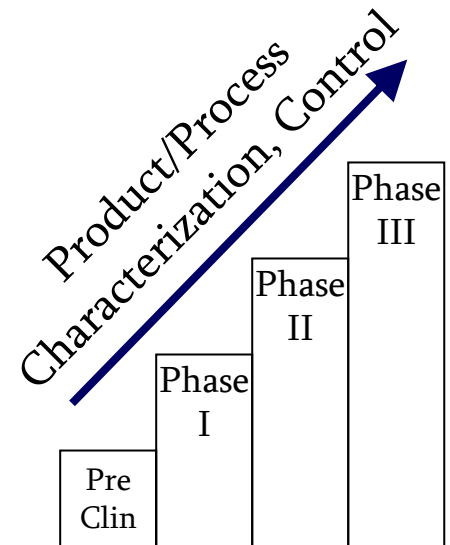
- Organization, personnel, training, evaluation
- Buildings and facilities
- Equipment, reagents and supplies
- Procedures
- Production and process controls
- Finished product control
- Laboratory controls
- Records and reports

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

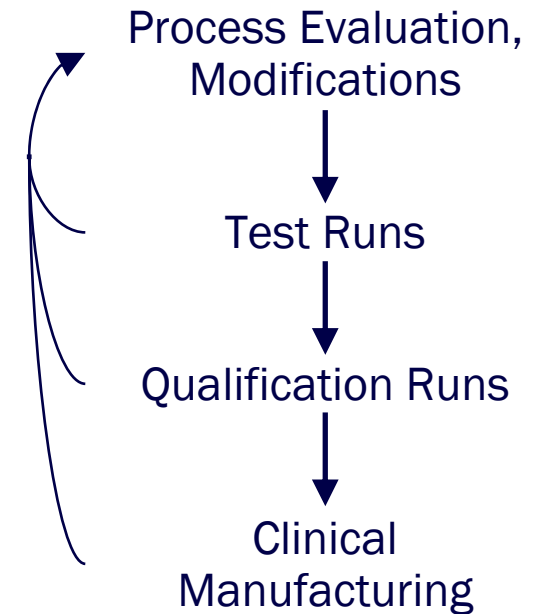
Development Throughout Clinical Trials

- 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



Infrastructure Needed

- Development support
 - Manufacturing process evolves throughout clinical development
 - Cell therapy
 - 903 INDs, 13,527 amendments
 - Gene therapy
 - 372 INDs, 8,090 amendments
- Skilled personnel
 - Need staff trained in cell therapy *and* GMPs, GTPs

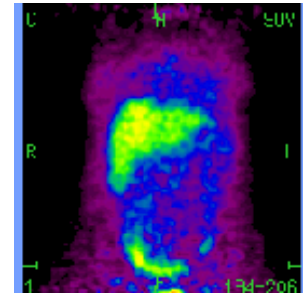
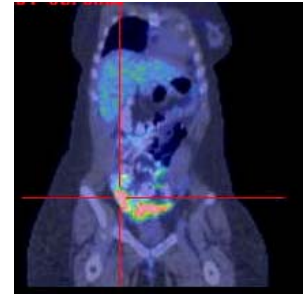


Contract Service Providers

- Academic-based laboratories
 - NIH-PACT, individual university programs
 - Decades of cell therapy experience, state-of-the-art technology
 - GMP, quality programs may be less robust
 - Not primarily contract service labs
- Commercial laboratories
 - Experience typically in cell line and vector production, not clinical cell therapy
 - Strong GMP, quality infrastructure
 - Contract services are primary mission

Approach to Contract Service Providers

- Rigorous vendor qualification, auditing
 - Cell therapy experience, capabilities?
 - Not just growing CHO cells or making antibody
 - Closed-systems, and other litmus tests
 - Characterization testing capabilities?
 - Flow cytometry, cell-based functional assays...
 - GMP, GTP systems, quality program?
 - Related services - training, regulatory support?
 - Capacity, response time, potential conflicts?
- Ongoing monitoring



Cell Therapies Pty
Cell Alliance