INTRODUCTION

Cell Therapy (CT) is the transplantation of human or animal cells to replace or repair damaged tissue and/or cells. CT thus encompasses Regenerative and Repair Medicine, areas rapidly evolving with better understanding of the basic biology of embryonic and adult human stem cells. Cell therapy technologies and novel methods have already begun to change the practice of medicine. Traditional bone marrow transplantation is rapidly being replaced by hematopoietic stem cell transplantation utilizing different cell sources (i.e., peripheral blood stem cells and umbilical cord blood cells). This rapid advance of cell therapy which encompasses regenerative and repair medicine is destined to become mainstream medical practice. Unlike organs, cells are a potentially renewable resource for body repair.[1]

The two most important areas where cell therapy is used are in hospitals and in the clinic.[2] Important growth areas of high interest for cell therapy include bio-platforms and novel applications of stem/progenitor cells in non-traditional settings (e.g., cardiac, neurologic, orthopedic, solid organ, etc). Also critical to the success of cell therapy is the identification of suitable cell sources, the ability to grow or expand cells and the development of methodologies and reagents to support these activities.

Tertiary medical facilities such as medical schools and associated hospitals offer a unique opportunity in which to conduct cell therapy. Several critical factors necessary to carry out meaningful cell therapy treatments are present in such settings. A robust patient population is available with a multitude of medical problems amenable to cell therapy treatment. These patients are mobile, well educated with regard to new medical breakthroughs and this group of patients frequently seeks cutting edge treatments compared with less well educated patients. The medical school faculty is also highly motivated to provide novel treatments in support of their clinical and research priorities and their affiliated institutions capitalize on these circumstances to help distinguish themselves from their peers.

This approach is attractive for several reasons including provision of cutting edge technology, attraction of new patients and increased clinical revenues. To successfully achieve these goals requires a comprehensive and well implemented action plan to establish a cell and tissue manufacturing facility compliant with current regulations. At Northwestern University in Chicago, IL USA, we partnered with Northwestern Memorial Hospital to develop and implement such a facility to deliver breakthrough CT applications to our university medical school-

based patients. We describe in detail the comprehensive planning, facility design and construction, coordination among operators and users, commissioning and validation strategies employed and the funding requirements necessary to meet the goals of providing a state-of-the-art cell therapy manufacturing facility in a hospital setting that is compliant with current good tissue practices (cGTPs)/current good manufacturing practices (cGMPs) regulations.

References:

1. Cell Therapy Markets, TriMark Publications, July, 2007
2. Cell Therapy Business-Market Summary, July 2008

METHODOLOGY

This project was originally conceived to provide cell manufacturing support for the Hematopoietic Stem Cell Transplantation Program at Northwestern Memorial Hospital. It became immediately apparent that the cost of construction and operation of a cell therapy facility for the sole use of the HSCT Program was not sustainable. The concept of building a shared facility for identified cell therapy stakeholders (stem cell transplantation, islet cell transplantation, solid organ transplantation and regenerative and repair medicine programs) was a logical next step in the progression of this project. A "big picture" approach provided a number of advantages compared with individual program approaches to development of a first rate cell therapy manufacturing facility:

- Program cost sharing (wise allocation of resources)
- Tight facility budget control
- Decreased redundancy
- Improved quality assurance and quality control measures
- Dedicated, trained workforce

Funding for the project was initially obtained through an investigator-initiated Northwestern Memorial Faculty Foundation grant awarded to Jayesh Mehta, MD and Richard C. Meagher, PhD ($2 million dollars) in conjunction with a cell therapy application to manufacture T-lymphocyte-reduced stem cell products to help prevent graft-versus-host disease (GVHD) in allogeneic stem cell transplant recipients. When the decision to build a shared cell therapy facility was finalized, Northwestern University contributed an additional $2 million dollars and NMH also contributed $2 million dollars for initial facility construction and implementation costs.

Several important business decisions were made prior to initiating the project:

- An operational Advisory Board comprised of cell therapy stakeholders was established
- Defined cost structure and workflow priorities were established
- NMH was designated as the operational administrator for the facility
- The range of cell therapy products to be manufactured within the facility was determined
- A team approach was implemented to complete the project

The business decisions were the project drivers for subsequent decisions regarding the design and implementation of the facility. The project was divided into sections to assist with project implementation and to speed the completion of the project within a defined time limit (assuming no interruptions or lengthily construction delays). The following sections were established and defined:

- **Project Team**
  The project team consisted of the following members selected by the Project Director from the various contractors and NMH internal personnel:

  - Richard C. Meagher, PhD, Director, CTPF, Project Director
  - Thomas Shook, MT (ASCP), Laboratory Manager, CTPF
  - Mehboob Merchant, SLS (ASCP), Quality Assurance Officer, CTPF
  - Joe Wentz, NMH Project Manager
  - Leonard Deputla, Project Construction Manager, Bulley & Andrews Construction Co.
  - Brett Kelly, PE, Senior Project Leader, Henneman Engineering Co.
  - Charles T. Meagher, EIT, Project Manager, Henneman Engineering Co.
  - Brain D. Pittas, Manager, Hill Mechanical Group
  - Michael Seeyle, Commissioning & Validation Engineer, Senior Project Leader, Aquatech Solutions, Inc
  - Dinora Najera, Validation Engineer, Commissioning & Validation Project Manager, Aquatech Solutions, Inc

  Throughout the entire project the team met on a weekly basis to:

  - Review construction progress
  - Discuss problems and possible solutions
  - Examine new issues as they arose (for example, the use of cold cathode ray tube lighting to replace conventional fluorescent tube lighting)
  - Establish a working knowledge regarding cell therapy applications, current manufacturing technology and the central role of the manufacturing facility in provision of such services (the Project Director provided mini-seminars to bring those individuals who were not familiar with Cell Therapy up to speed)

Although this approach was slow-moving in the early stages of the project, it helped speed the final stages of the project since team members understood the fundamental role of the facility and collectively we achieved an excellent outcome. The team members behaved as individual contributors with regard to their own area of expertise, but they were encouraged to consider overall project impact. This approach was highly successful as it yielded several technical improvements during the course of the project that were effectively implemented with minimal up-grade charges. Installation of a larger air handling unit for projected future growth, introduction of a "wall of fans" instead of a conventional single unit design, adopting single-pour epoxy flooring, provision for an "exterior utility corridor" and use of dedicated building automation system (BAS) are some of the important improvements that were a result of the Project Team interactions.

- **Design**
  The design phase of the project addressed the following issues that were deliberated and discussed in detail, and decisions were made that directly impacted the remaining sections and the final outcome of the project:

    - Facility location
    - Architectural plans and drawings
    - Construction materials (cleanroom manufacturers)
    - Cleanroom classifications & specifications
    - Proposed manufacturing processes
        - Critical flows
            - Workflow considerations
            - Raw material and final product flow considerations

- **Planning**
  Project planning was also conducted in a team fashion, giving due consideration to the following issues and areas of concern. The items listed below represent the major concerns that were addressed during the different phases of the project. Each of these items presented their own unique problems with regards to the project. For example, space considerations were a major challenge, placement of the air cooling (condenser) unit for the Cold Room resulted in suspending the unit from the ceiling due the lack of floor space. Some of these items caused design changes that resulted in a significant time delays that were not originally anticipated and they put the entire project off its original timeline.

- Demolition of existing space
- State and city permits
- Major equipment logistics
- Coordination of mechanical, electrical and plumbing (MEP) activities and general construction activities
- Work stoppages for rest of building
- Master validation plan
- Regulatory perspective
- Contracted services
  - Cleaning
  - MEP support
  - Commissioning & Validation

- **Construction**
  The construction phase of the project proceeded smoothly since we hired a very experienced construction company that was familiar with cleanroom applications. It was also very helpful that the Project Team regularly met and identified potential problems early in each phase of the construction. This section of project was assisted by use of:

  - Construction schedules and timelines
  - Coordination of major equipment installation
    - Building automation system (BAS)
    - Rooftop air handler unit
  - Following cleanroom construction process

- **Commissioning Activities**
  The team approach permitted Commissioning activities to be easily addressed by cooperation between the construction contractors and the Commissioning agents. We employed the following methods to ensure smooth transition:

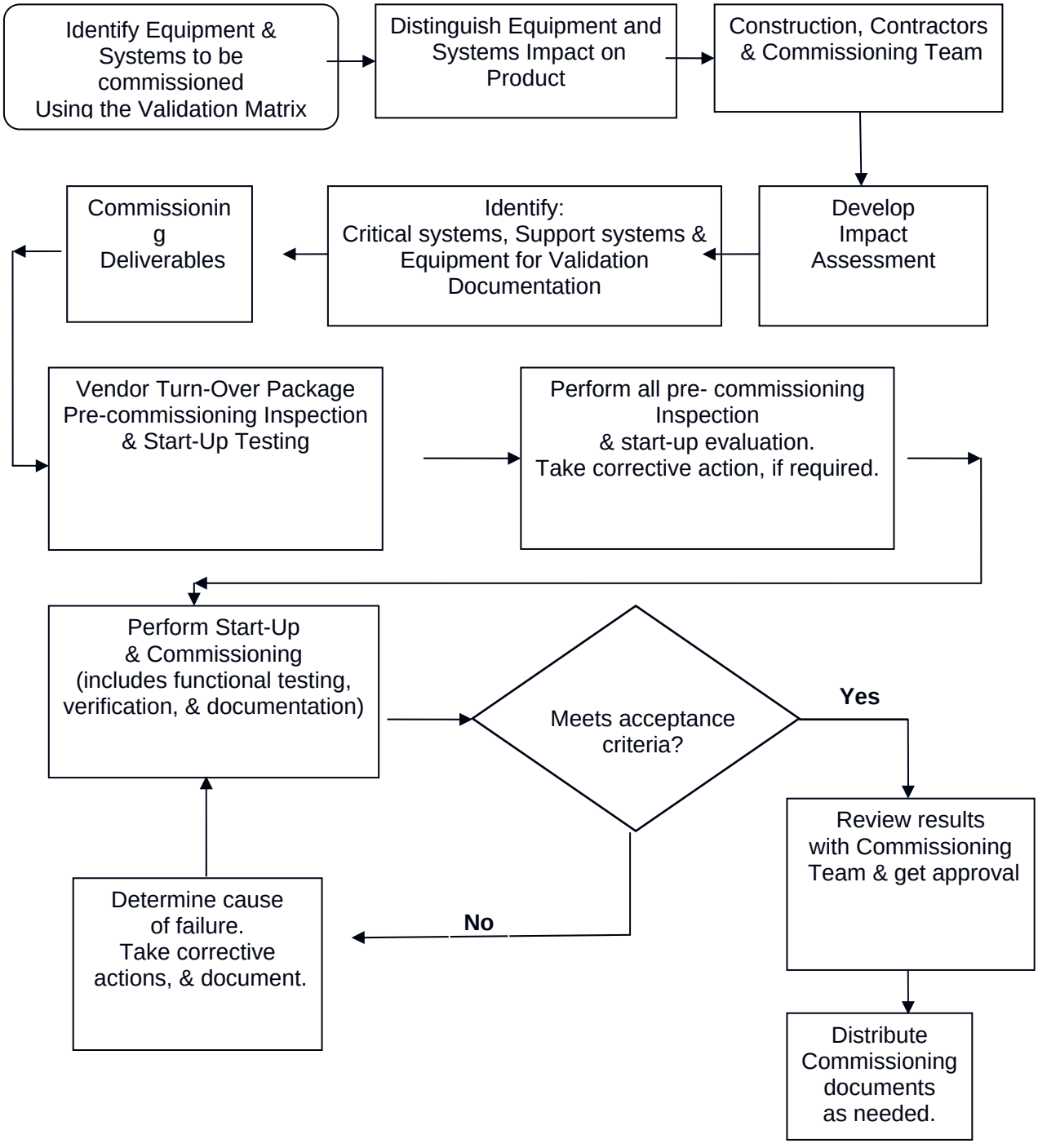
  - Traceability matrix
  - Commissioning flow chart
  - Commissioning deliverables

- **Validation**
  Validation activities proceeded smoothly due to the good communication between the validation agents, the Project Director and the support personnel (e.g., Laboratory Manager and Quality Assurance Officer). Everyone was

aware of the ultimate goal of the project and validation became a straightforward set of steps to be followed. Validation is confirmatory testing, not exploratory testing. Validation delivers legal documentation that documents the actual equipment (or process), its purpose, function and performance against design intent. Validation determines how robust the system is, and if the system fails, will help to correct the failure without an FDA violation (483). Validation activities include:

- Defining fundamental requirements and policies to be followed for all validation activities throughout the qualification lifecycle of the project and in consideration of risk management
- Defining the roles and responsibilities for the various validation activities
- Describing the interrelationship between the commissioning effort and the qualification activities
- Identifying the facilities, utilities, equipment on which Installation, Operational, and Performance qualification (IQ, OQ, PQ) and computer validation testing will be performed
- Providing guidance in an organized, methodical manner to those administering and performing validation activities in order for successful project completion
- Providing documented assurance to regulatory agencies of the facilitie's commitment and approach to compliance with the current Good Tissue Practices (GTPs) and current Good Manufacturing Practices (cGMP), where applicable, and adherence to the Food and Drug Administration (FDA) regulatory requirements

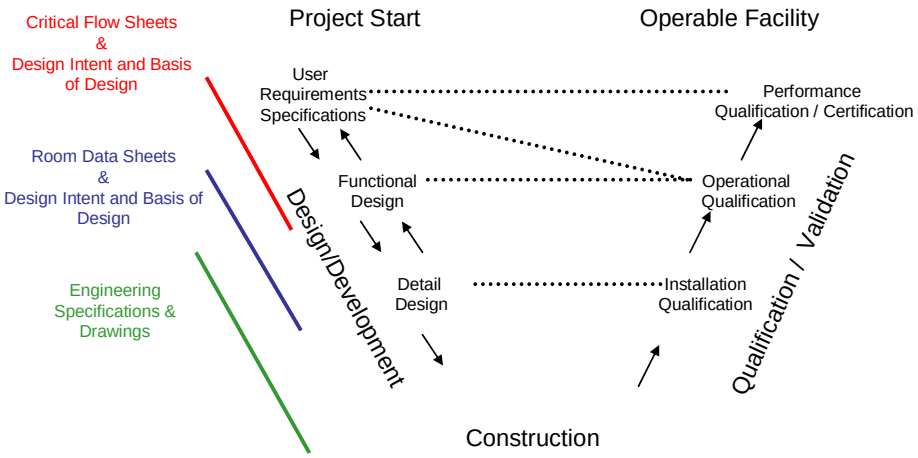
Commissioning Flowchart



Validation Sequence

Document	1st Requirements	2nd Design	3rd Construct	4th Test	5th Implement / Go Live
Contractor Qualification (*if applicable*)	order				
Vendor Assessment(s)					
Change Control Request					
Part 11 Gap Analysis (*if applicable*)					
User Requirements Specification					
Validation Strategy Plan		order			
Functional Requirements Specification					
Design Requirements Specification					
Risk Assessment(s)					
IQ Validation Protocol(s)			order		
OQ Validation Protocol(s)					
PQ Validation Protocol(s) (*if applicable*)					
IQ/OQ/PQ Incident Report(s)				order	
Traceability Matrix					
Operating Procedure(s)					order
Validation Summary Report(s)					

cGMP Cell Therapy Processing Facility
Commissioning & Validation Methodology

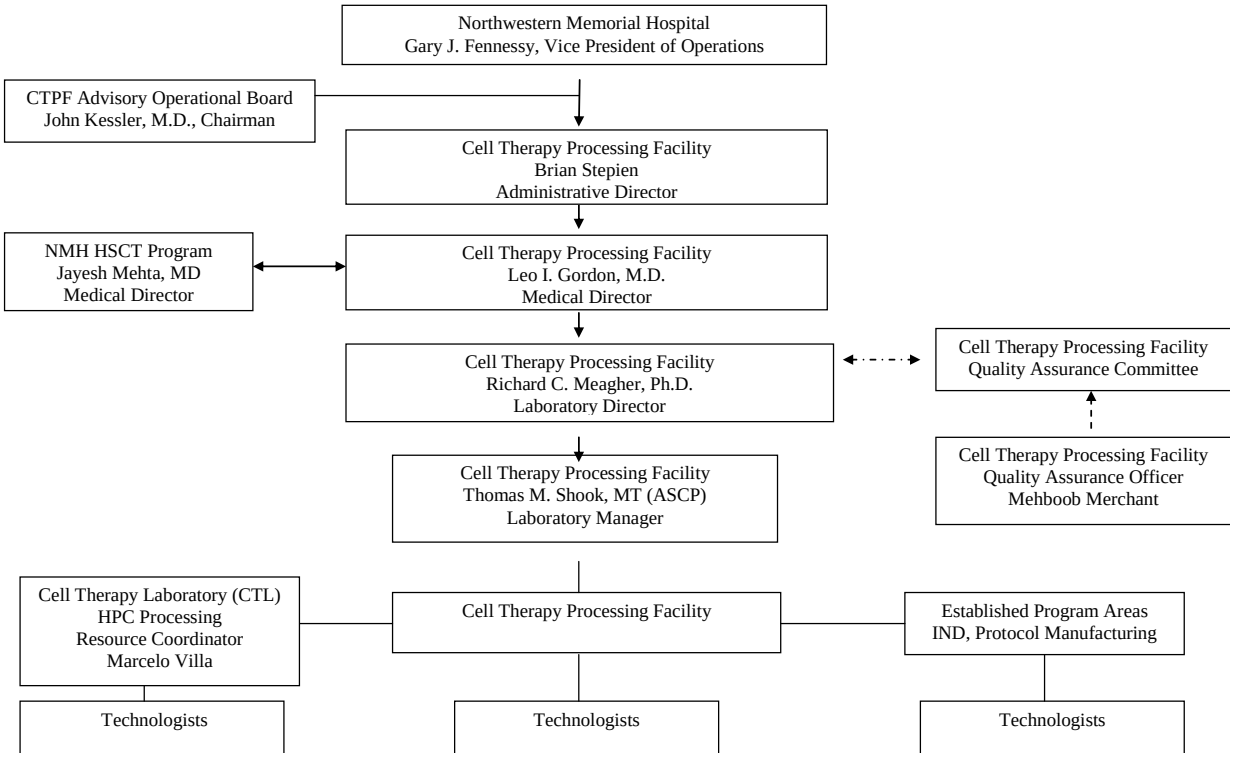


RESULTS

CTPF Advisory Board

Name	Title	Department
John Kessler, MD, Chairman	**Department Chairman**	**Neurology**
Jayesh Mehta, MD	**Director, Adult HSCT Program**	**Hematology/Oncology**
Leo I. Gordon, MD	**Medical Director, CTPF**	**Hematology/Oncology**
Richard C. Meagher, PhD	**Director, CTPF**	**Hematology/Oncology**
Morris Kletzel, MD	**Director, Pediatric BMT Program, CMH**	**Hematology/Oncology**
Dixon B. Kaufman, MD	**Director, Islet Cell Program**	**Transplant Surgery**
Josh Miller, MD	**Research Professor of Medicine**	**Transplant Surgery**
Joseph Leventhal, MD	**Associate Professor of Medicine**	**Transplant Surgery**
Richard Burt, MD	**Director, Autoimmune Diseases**	**Medicine**
Douglas Losordo, MD	**Director, Cardiac Transplant Program**	**Cardiology**

NMH CELL THERAPY PROCESSING FACILITY
ORGANIZATIONAL CHART



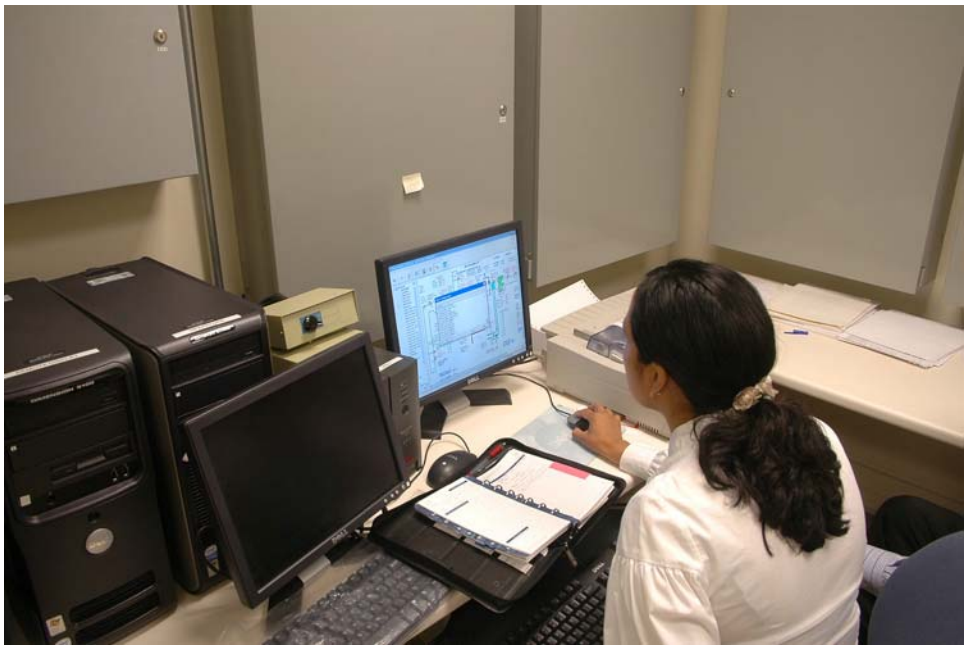
SOP Estate
Section Headings & Descriptions

CTPF Master Number Index of Documents

Section Heading / Document #	Document Title	Ver. 1.0 Implementation Date	Ver. 2.0 Implementation Date	Ver. 3.0 Implementation Date	Ver. 4.0 Implementation Date	Ver. 5.0 Implementation Date	Removal Date
	Validation Master Plan	02/17/06	10/12/07	09/30/08	09/03/09		
Section 0	**Governance**						
Section 1	**Organization** (Roles and Responsibilities)						
	Section 1 Forms						
Section 2	**Resources** (Personnel, Training)						
	Section 2 Forms						
Section 3	**Equipment** (Sourcing / Purchase, Preventive Maintenance, Calibration)						
	Equipment Operation						
	Calibration / Preventive Maintenance						
	Section 3 Forms						
Section 4	**Supplier Assessment** (Purchasing / Inventory / Contracts)						
	Section 4 Forms						
Section 5	**Process Control**						
	Section 5 Forms						
Section 6	**Documents / Records**						
	Section 6 Forms						
Section 7	**Adverse Events** (Deviations, Nonconformances)						
	Section 7 Forms						
Section 8	**Audits** (Internal & External)						
	Section 8 Forms						
Section 9	**Process Improvement** (Corrective & Preventive Actions)						
	Section 9 Forms						
Section 10	**Service & Satisfaction** (Complaint Management)						
Section 11	**Facilities & Safety**						
Section 12	**Donor / Patient Information**						
Section 13	**Environmental Management**						
	Section 13 Forms						
Section 14-20	**Reserved for Program Area SOPs**						
Appendix							

Cell Therapy Processing Facility
Completed Facility Pictures

ISO 5 Cold Room



Building Automation System Control Room

Work Suite 4 – ISO 7 Islet Cell Work Suite

Materials / Product Pass-Thru

Material Staging Area – ISO 7

Clean Corridor – ISO 7

CONCLUSIONS

To successfully establish a cell therapy manufacturing facility in a medical school hospital setting it was necessary to have a strong partnership between the medical school administration and the affiliated hospital administration, adequate funds to build and validate the facility and substantial input from the stakeholders *prior to* and *repeatedly during* the construction phase of the project. In addition, the following recommendations should be taken into consideration:

- Comprehensive planning is a must to ensure proper construction, operation and maintenance of facility
- The team approach was very critical to ensuring project success
- Start up trouble shooting by the project team mitigated many problems
- Establishing a minimum knowledge base regarding project goals resulted in more efficient project implementation and validation. Tailoring the project to stakeholder needs trumps the "one size fits all" strategy
- Qualified contractors (project partners) ensured project success

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