Production Assistance for Cellular Therapies

Educational Web Seminar

Cell Therapy GTP and GMP Facilities: Design and Operation to Optimize Space to Meet Manufacturing Needs

Friday, 17 July 2020

12:00 PM – 1:00 PM ET

Speakers

Linda Kelley, PhD

Director, Cell Therapy Facility

Moffitt Cancer Center

Amittha Wickrema, PhD

Director, Advanced Cellular Therapeutics Facility

Director, cGMP Cell and Tissue Based Processing Facility

University of Chicago Medical Center

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Objectives

- Identify FDA regulatory guidelines for cellular therapy facility design, validation and operations.
- Describe the steps needed to incorporate FDA guidelines for cellular therapy facility design, validation and operations.
- List examples of ways to best utilize existing facilities and expansion for the greatest flexibility.
- Identify key design features to successfully accomplish the functional requirements of the facility.
- Describe the steps needed to organize and manage the project from planning to commissioning.

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Cell Therapy GTP and GMP Facilities: Design and Operation to Optimize Space to Meet Manufacturing Needs

Linda L. Kelley, PhD
Senior Member
Director, Cell Therapy Facility

July 17, 2020

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Webinar Objectives

Linda L. Kelley, PhD

Assess current and future cell and gene therapy manufacturing needs, regulatory requirements, and modifications to workflows to meet the needs.

Amittha Wickrema, PhD

Describe project planning, budgeting and implementation process for new facility design.

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Cell & Gene Therapy Manufacturing

1. What are the manufacturing needs?
2. What are the regulatory requirements as they pertain to facility design?
3. How do we meet the manufacturing needs and the regulatory requirements?

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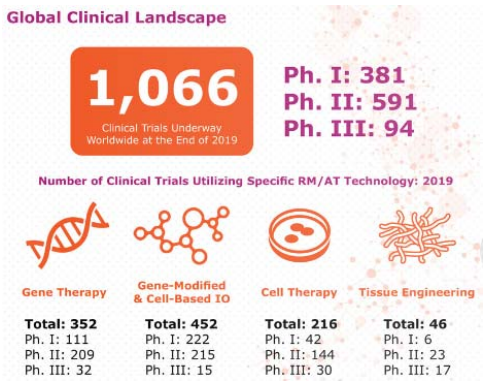

https://alliancerm.org/sector-report/2019-annual-report

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21st Century Cures Act

The 21st Century Cures Act is a United States law enacted by the 114th United States Congress in December 2016. It authorized $6.3 billion in funding, mostly for the National Institutes of Health.

FDA drug approval process

The 21st Century Cures Act modified the FDA drug approval process by mandating new rules that direct the FDA to approve drugs and devices with greater urgency.

- RMAT (Regenerative Medicine Advanced Therapy)
- Fast Track
- Breakthrough Therapy
- Priority Review
- Accelerated Approval

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Moffitt Cell Therapy Facility

- BMT standard-of-care (≈450 txps/year)
- IND phase 1 & 2 (≈10-20 active at any given time)
  - Investigator-initiated (50%)
  - Sponsor-initiated (50%)
    - Most on FDA accelerated approval pathways
- NHLBI/PACT Contract Manufacturing Facility
- 50+ employees
- 10,000 sf facility

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Facility Blueprint As Built 2012

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HCT/Ps Regulation

(Human cells, tissues or tissue-based products)

Title 21 Code Federal Regulations

Part 1271	Part 210, 211
GTPs	**GMPs**
PHSA Section 361	PHSA Section 351
no IND	IND
no BLA	

https://www.fda.gov/medical-devices/medical-device-databases/code-federal-regulations-title-21-food-and-drugs

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361 HCT/Ps

- Amniotic membrane when used alone or without added cells
- Bone
- Cartilage
- Cornea
- Fascia
- Ligament
- Pericardium
- Peripheral or umbilical cord blood stem cells (for autologous use or use in a first or second degree blood relative)
- Sclera
- Skin
- Tendon
- Vascular graft
- Heart valves
- Dura mater
- Reproductive cells and tissues (e.g., semen, oocytes, embryos)

All of the above are minimally manipulated, intended for homologous use only, and not combined with another article, with some exceptions.

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351 HCT/Ps

- Cultured Cartilage Cells
- Cultured Nerve Cells
- Lymphocyte Immune Therapy
- Gene Therapy Products
- Human Cloning
- Human Cells Used In Therapy Involving The Transfer Of Genetic Material (Cell Nuclei, Oocyte Nuclei, Mitochondrial Genetic Material In Ooplasm, Genetic Material Contained In A Genetic Vector)
- Unrelated Allogeneic Hematopoietic Stem Cells
- Unrelated Donor Lymphocytes For Infusion

All of the above are more than minimally manipulated, not intended for homologous use only, may be combined with another article, with some exceptions.

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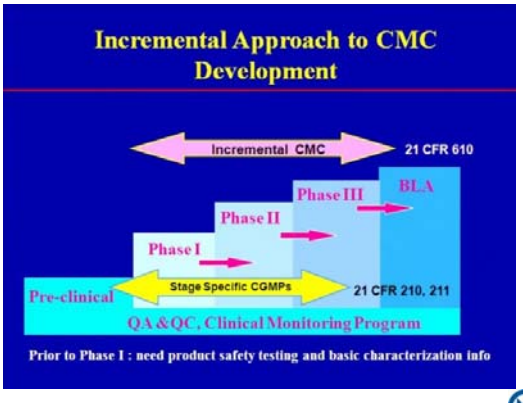

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FDA Guidance Documents

cGMPs

- CGMP for Phase 1 Investigational Drugs (2008)
  https://www.fda.gov/media/70975/download
- INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information (2003)
  https://www.fda.gov/media/70822/download

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cGMPs

21 CFR Parts 210-226, 600-680

PART 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

A. General Provisions
B. Organization and Personnel
C. Buildings and Facilities
D. Equipment
E. Control of Components and Drug Product Containers and Closures
F. Production and Process Controls
G. Packaging and Labeling Control
H. Holding and Distribution
I. Laboratory Controls
J. Records and Reports
K. Returned and Salvaged Drug Products

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211

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FDA Guidance Documents

cGMPs

- CGMP for Phase 1 Investigational Drugs (2008)

"....investigational new drugs (IND) used in phase 1 clinical trials are exempt from complying with 21 CFR part 211"

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CGMP for Phase 1 Investigational Drugs (2008)

VI. SPECIAL MANUFACTURING SITUATIONS

A. Multi-Product Facilities

- manufacture only one phase 1 investigational drug at any given time in an area or room separate from unrelated activities
- However, same area or room can be used for multiple purposes, including manufacture of other investigational products or laboratory research **if appropriate cleaning and procedural controls are in place to ensure no carry-over of materials or products, or mix-ups**
- the design or layout should promote orderly handling of materials and equipment, the **prevention of mix-ups, and the prevention of contamination** of equipment or product by substances, previously manufactured products, personnel, or environmental conditions
- **SOPs for clearing the room of previous product materials**, product segregation, component segregation, and use of unique product identifiers

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CGMP for Phase 1 Investigational Drugs (2008)

VI. SPECIAL MANUFACTURING SITUATIONS

C. Sterile Products/Aseptically Processed Products

- Conduct aseptic manipulation in an aseptic workstation (e.g., laminar air flow workbench, **biosafety cabinets**, or barrier isolator system) under laminar airflow conditions that meet Class A, ISO 5
- Conduct a **process simulation using bacterial growth media** to demonstrate that the aseptic processing/controls and production environment are capable of producing a sterile drug
- Performing **environmental monitoring** of the aseptic workstation during processing to ensure appropriate microbiological control (settling plates or active air monitoring)

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Facility Blueprint As Built 2012

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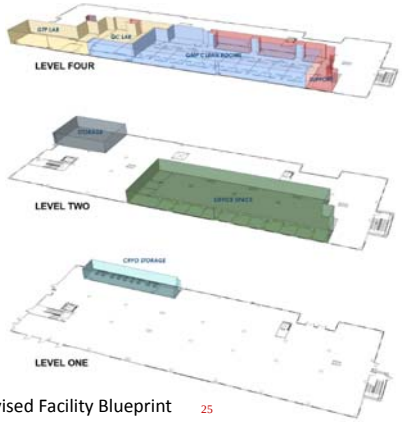

2020 Revised Facility Blueprint 25

ISO 8 GTP Lab

Number	Room Name:	ISO Classification:
464C	GTP PROCESSING FACILITY	ISO Class 8
Description: This room is where processing of human tissue regulated under 21 CFR Part 1271 is performed. Materials processed in this room are administered to patients only within the United States. Occupancy: 5 - 7 people		
Environmental Ranges:		72ºF +- 2ºF; NMT 65%RH
Minimum Total ACPH:		NLT 20 From HVAC
Fresh ACPH:		By the engineer
Cleanroom Finishes Required:		Yes. Must be easily cleaned.
Terminal HEPA Filtration Required:		Yes
Low Wall Exhaust or Return Required:		Yes. Existing
Specialty equipment requiring wider door or taller ceiling?		Yes. BSCs.

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Conclusions

- Doubled square footage (10,000 ➡ 20,000)
- Reagent & supply & LN2 freezer storage (3x)
- Administrative offices & tech workstations (3x)
- Quality Control Lab (+300 sf)
- New ISO 8 GTP Lab
  - Transition all IND-enabling pre-clinical work
  - Adequate for SOC BMT & Phase 1 clinical trials
  - Decreased manufacturing and monitoring costs
  - Improved working environment for staff
- Total new construction cost = $1.4 M

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Design, Construction and Commissioning of an Academic Cellular Manufacturing Facility

June 17th 2020

Amittha Wickrema, Ph.D
Director, Advanced Cellular Therapeutics Facility
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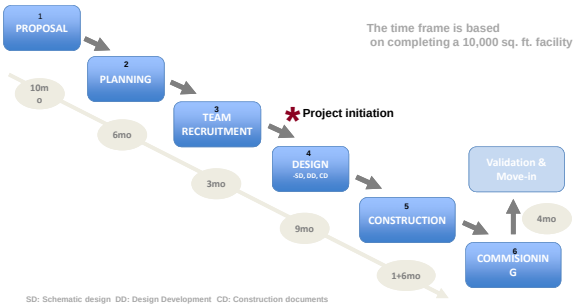
SCOPE AND GOAL OF THE PROJECT

- Build a hybrid facility capable of manufacturing 361 and 351 categories of cellular therapy products.
- Spaces consisting ISO8 (GTP), ISO7 (cGMP) and other ancillary areas.
- Overall facility that supports a 350 standard of care stem cell transplants per year and approximately 700 cellular therapy products including novel cell therapies for the next 10 years.
- A facility with product development capabilities for IND filings.
- To build a facility consistent with FDA requirements (21CFR 1271, 211,610) for manufacture of human cellular therapy products (HCTPs) that meet basic criteria of cellular potency, viability, sterility and stability.

THE ROAD MAP FOR ACHIEVING GOAL



SD: Schematic design DD: Design Development CD: Construction documents

PROPOSAL

JUSTIFICATION OF NEED TO THE LEADERSHIP

- **Need**
  - Information regarding current volumes and projected growth over 5-10 yrs.
  - Information regarding increasing efficiency (new technologies and automation).
  - Information regarding the need for developing novel cell therapies.
  - Information on potential new revenue.
  - Approximate/estimate cost of the new facility (ie: $ all-in1,000/sq feet).
- **Method of communication**
  - A program workshop with hospital leadership on hand.
  - A detailed proposal and follow up face-to-face meeting.

PLANNING

ELEMENTS INCLUDED IN THE PLANNING

- Engage the head of institutional space planner
  - Educate about the type of work, tour the current facility.
  - Provide a hand-drawn space diagram along with approximate square footage of each space needed.
  - Communicate the ideal space will be an existing shell space if the facility will be housed within the medical center/university (an external site is possible).
- University of Chicago Facility
  - Constructed in an existing empty shell space within 5 min walk from the previous facility.
  - Shell space occupies approximately 10,000 square feet.
  - In a isolated area away from patient traffic.

PLANNING

ENGAGE AN EXTERNAL ARCHITECT FIRM

-For cost estimation and feasibility purposes only – predesign phase

- Select final space together with internal space planner, external architect and the owner (stake holder).
- Architect drawing using owner hand-drawn plan.
- Secure an initial cost estimate from a consultant architect firm.
- Obtain final approval of budget from the leadership.
- Begin recruitment/solicit bids of a qualified company for design and engineering.

PLANNING

MAJOR ELEMENTS OF PROJECT BUDGET

- Not necessarily the highest cost items

- Design and engineering drawings.
- Costs associated with HVAC systems.
- Costs associated with cGMP consultants, permits and regulatory compliance.
- Costs associated with construction and interior finishes.
- Costs associated with commissioning, validation, IQ/OQ.
- Central monitoring systems (ie Johnson control and REES).
- Medical Equipment.

(Note: Medical equipment costs will depend on complete new purchase or using existing equipment **)**

PLANNING

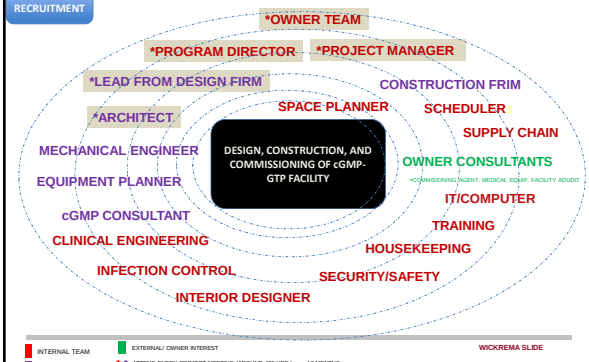
BUDGET/COST CONTINUED…….

(based on build out of an empty shell space of 10,000 square feet)

- Typical costs of major items: (**Total budget 7.6 million US**)
  - Design, architectural and engineering firm **($750K).**
  - Construction/HAVC **($ 4.4 million).**
  - Commissioning agent –owner hired **($ 80K).**
  - Medical equipment **($ 1.1 million).**
  - Contingency **($450K).**

TEAM RECRUITMENT

PROJECT TEAM

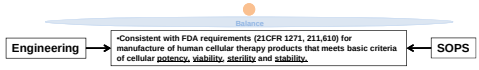


INTERNAL TEAM
EXTERNAL TEAM
EXTERNAL/ OWNER INTEREST
* ATTEND EVERY PROJECT MEETING (AROUND 400 HRS.) —— 17 MONTHS

DESIGN

PRINCIPLES GUIDING DESIGN METRICS

- A hybrid facility that is multifunctional.
- Consistent with FDA guidelines (21CFR parts1271, 211, 610).
- Manufacture covers steps of recovery, processing, storage, labeling, packaging, distribution and testing/screening (361 & 351 prod).
- Adequate space and segregated areas capable of processing multiple human cell or tissue based products (HCT/Ps).
- Physical facility design aimed at minimizing introduction of microbial contamination (Uni-directional flow, medical grade finishes, workflow segregation).



DESIGN

HVAC AND ENGINEERING METRICS

- 100% redundant two air handlers servicing work spaces. A third handler servicing office area (ISO7-30/50 ACH; ISO8-20 ACH).
- A single air pass setup. 0.05 pressure gradient. No phoenix valves.
- Equipped with HEPA filters both at source and terminal spaces.
- ISO7 spaces have positive and negative pressured suites.
- Piped-in gasses, vacuum and liq N2.
- Redundant remote monitoring and UPS systems for power.
- Connected to building back-up power system.

DESIGN

FACILITY SPACES

- ISO8 GTP cell processing area (4 work stations)---height adjustable BSCs.
- ISO8 QC/product development space.
- ISO7 cGMP cell processing suites (2 +1).
- Uni directional gown-in and gown-out spaces.
- Material storage, Material pass, cGMP cleaning supply room, Locker room.
- Material receipt area, non-cGMP cleaning supply room, Biowaste room.
- Mechanical space, gases and Liquid N2 storage space (within the shell space).
- Offices and document storage, private bathroom, kitchen and conference room, private internal corridors.

DESIGN

OTHER DESIGN FEATURES

- **Comfort, esthetic and non-essential features:**
  - Custom lighting throughout, height adjustable BSCs.
  - See-through glass panels throughout the facility.
  - State of the art automatic doors that slide as well as swing.
  - Unobstructed island work spaces with ceiling plug-ins.
  - 10 feet high ceiling in non-cGMP spaces.
  - Staff amenity space, staff office space, private bathroom, conference room.

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CONSTRUCTION

ASPECTS DURING CONSTRUCTION

- Construction phase required very little input of the owner team compared to all other phases (Supervision by design firm and internal project manager).
- Aspects to pay attention:
  - All changes and substitutions of materials and any changes to the layout and HVAC should be pre-approved by owner team.
  - Periodic tour/inspection of the construction space.
  - Opportunity for owner team to try out finishes/materials (flooring, lighting etc.).

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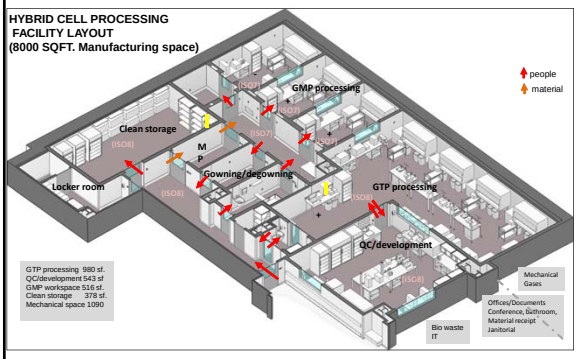

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CONSTRUCTION

FULL-SCALE MOCK UP

- 100% Scale mock-up of GTP, QC, and cGMP spaces (extremely valuable)
- An opportunity to adjust layout and design of work spaces and personnel

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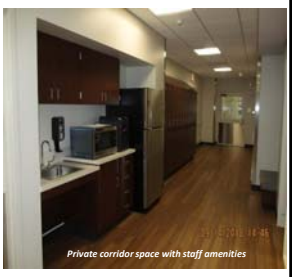
COMPLETED FACILITY SPACES

ISO8 GTP space



Private corridor space with staff amenities

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COMPLETED ISO7 SPACE

ISO7 negative pressured suite

vestibule to the clean room suites

Mechanical space

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TO AVOID SECOND GUESSING AT THE END OF THE PROJECT

- Visit similar facilities that has been commissioned recently.
- Retain and engage an experienced advisor in the field (outside of the design firm) outside of relying on recommendations of the design firm only.
- Entertain multiple bids from design firms. Face-to-face interview prior to hiring. The lowest bid should not be a criterion for selecting a firm.
- Be engaged in all decisions from start to finish as the "owner" (minimize delegation).
- The "owner" or his/her staff member must attend all project meetings (around 400 hrs).
- Do not compromise on HVAC and other engineering features to save money for equipment and/or esthetic aspects.

COMMISIONING

Validation & Move-in

SUMMARY OF ITEMS POST CONSTRUCTION

- **Initiate commissioning activities end of substantial completion**
  - Independent commissioning agent certify all HVAC and other mechanical metrics as stated in the design plans.
  - Perform IQ/OQ functions for medical and non-medical equipment.
  - Comprehensive walk through by owner and project manager.
  - **Initiate pre- move-in validation activities**
    - Follow owner designed *master validation plan*:
      - Include process validations (budgeted US $50K)
      - Include equipment and space validations.

performed by cell processing staff

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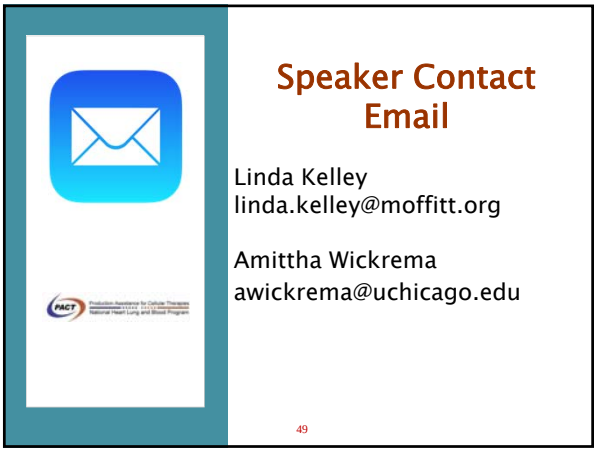

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