

cGMP for Cell Therapy

“It’s not science, it’s manufacturing”

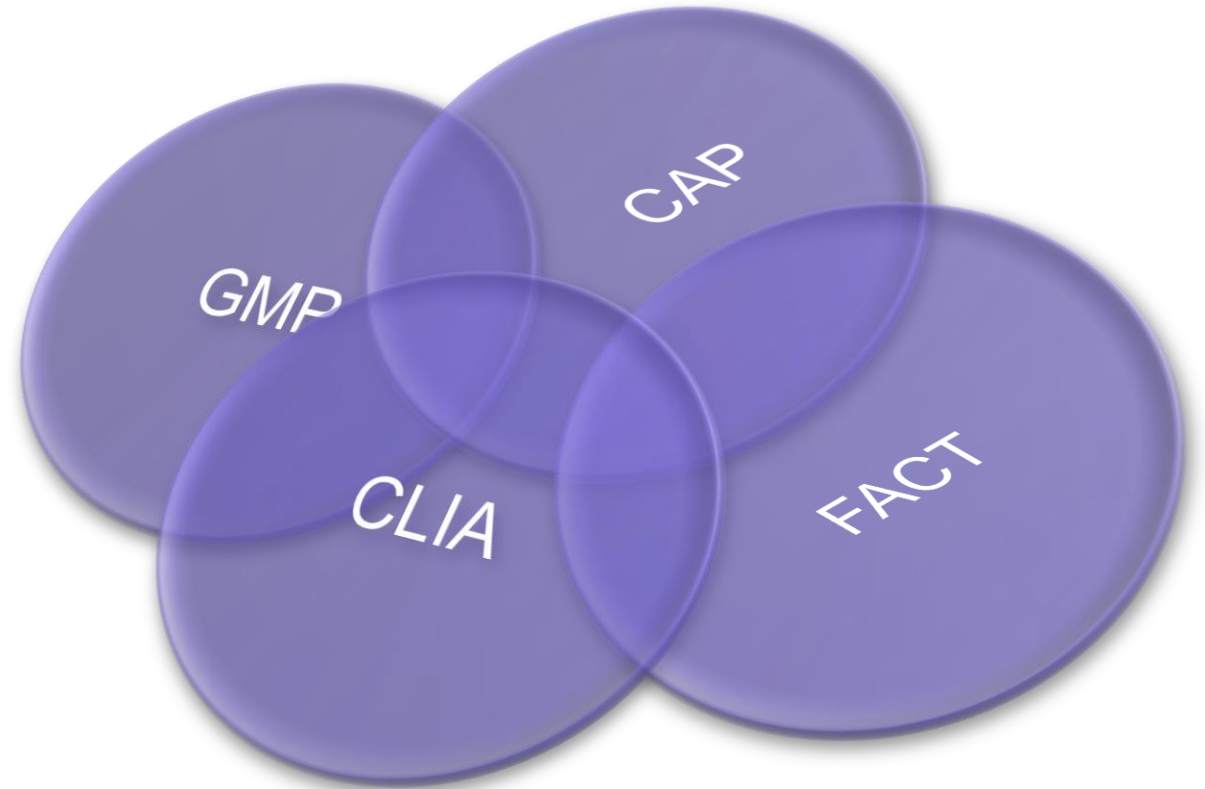
REGULATORY COMPLIANCE AND THE TRANSLATIONAL SCIENTIST

Lisa H. Butterfield, PhD.
Vice President, PICI Research and Development
Adjunct Professor, Microbiology and Immunology, UCSF
Immediate-Past President, SITC



Outline

- Background and history
- Many acronyms, a few central messages
- Academic lab setting examples from this PhD



One Example: Mission and Vision for the IMCPL Hillman Facility

- The Cellular Products Laboratory (CPL) is dedicated to preparation of products for tumor vaccines and for cellular and gene therapy of cancer.
 - cellular product preparation; identity, sterility and safety evaluations
 - assists in the preparation of INDs
 - operates according to FDA criteria for current Good Manufacturing Practice (cGMP)
- The Immunologic Monitoring Laboratory (IML) is responsible for serial monitoring of immunologic functions in patients with cancer.
 - state-of-the-art immunologic assays
 - rigorous quality control program
 - development of new assays
 - advice on test selection and result interpretation
- The Tissue Procurement Facility (TPF) provides tissue and blood banking support under current Good Tissue Practice (cGTP) criteria.

CLIA certified; inspected by CAP and the state of PA; registered with FDA (3004571535)
FDA Master file: BB-MF-12244; FACT accredited



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Services

MANUFACTURING RELATED

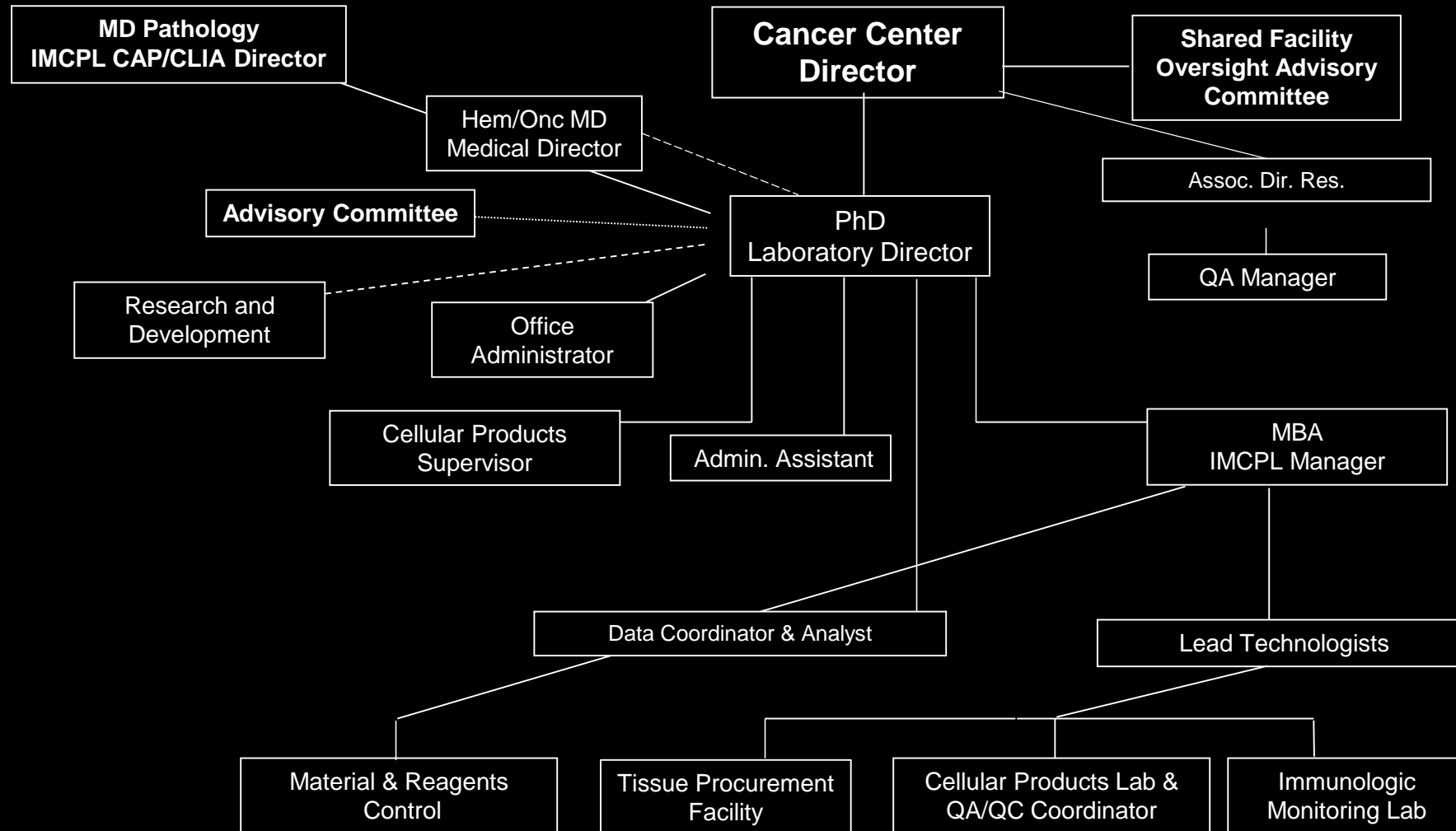
- Specimen intake, processing, banking
- Cell bank preparation
- Culture of peptide-specific T cells
- Culture of tumor infiltrating lymphocytes (TIL)
- DC preparation (peripheral blood, stem cells)
- Gene transfer: any human cells
- Expansion of stem cells
- Vaccine production for intra-tumor,-nodal, -lymphatic or intra-venous administration
- Peptide lyophilization, testing
- Adenovirus and vaccinia production (not fully GMP, with Vector Core)

ASSAY RELATED (profiling and testing cells)

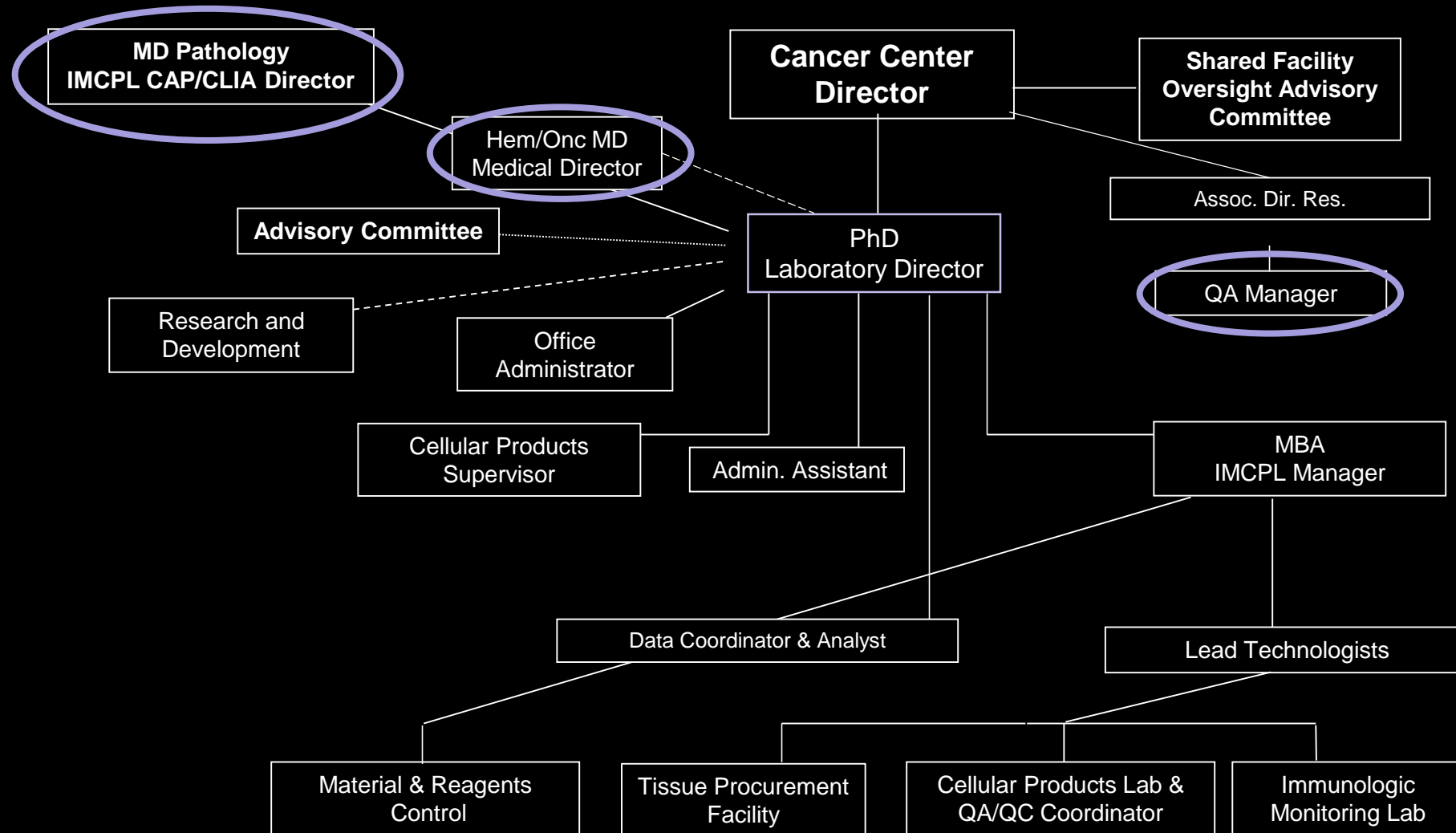
- Assay standardization, normal control ranges
- Mixed lymphocyte-tumor cultures
- Cytotoxicity (^{51}Cr -release, FLOCA, CD107a, Granzyme B ELISPOT)
- Proliferation (^3H -thymidine and CFSE)
- Multiparameter flow cytometry (effectors, regulatory (Treg, MDSC) cells)
- Single-cell assays (ELISPOT (2-color, fluorescence), CFC, and multimer)
- Signaling molecules
- Frequency of apoptotic T cells
- Anti-tumor antibodies
- Cytokine/chemokine analysis (Luminex, ELISA)
- Data entry and analysis

Focus on first-in-human, academic bench-to-bedside trials

Administrative Organizational Chart

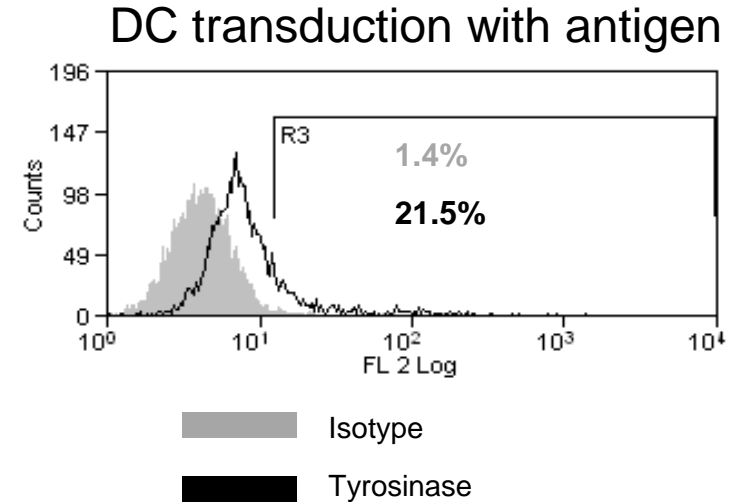
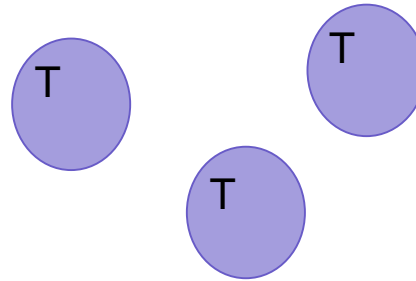
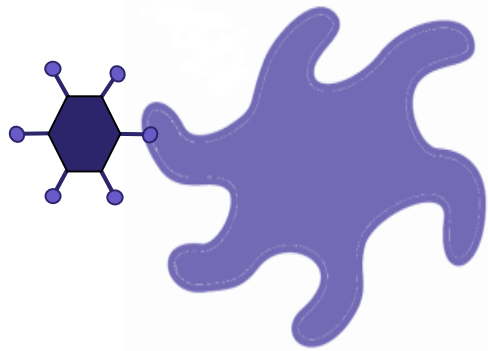


Administrative Organizational Chart



Replication-deficient Adenovirus AdVTMM2 Production for Autologous dendritic cell (DC) vaccines

A novel adenovirus encoding melanoma antigens was prepared by the University Vector Facility and IMCPL. Testing results for virally-transduced DC vaccine scale up studies and vaccines are shown. The clinical trial was RAC-exempt, has IND #15044, is IBC and IRB approved, and 35 patients were vaccinated.



DC identity phenotype

	HLA-DR+	MFI	CD86+	MFI	CD80+	MFI	CD83+	MFI	CCR7+	MFI	CD40+	MFI	CD11c+	MFI
#1	98%	25.6	95%	24	93%	5.45	88%	2.57	28%	1.34	95%	176	96%	23.5
#2	100%	21.4	98%	31.7	95%	4.87	81%	2.49	45%	1.89	98%	184	98%	28

Manufacturing labs in an academic medical center/cancer center: one model

CELL PROCESSING LABORATORY (CPL) IN IMCPL

- Provides cell manufacturing for a variety of clinical trials with internal and external investigators, specializing in **more-than-minimal-manipulation** of cells (both autologous and allogeneic).

HEMATOPOIETIC STEM CELL LABORATORY (HSCLAB)

- Provides cell processing for the stem cell transplant program and other departments, specializing in cell separation and minimally-manipulated autologous and allogeneic cells.

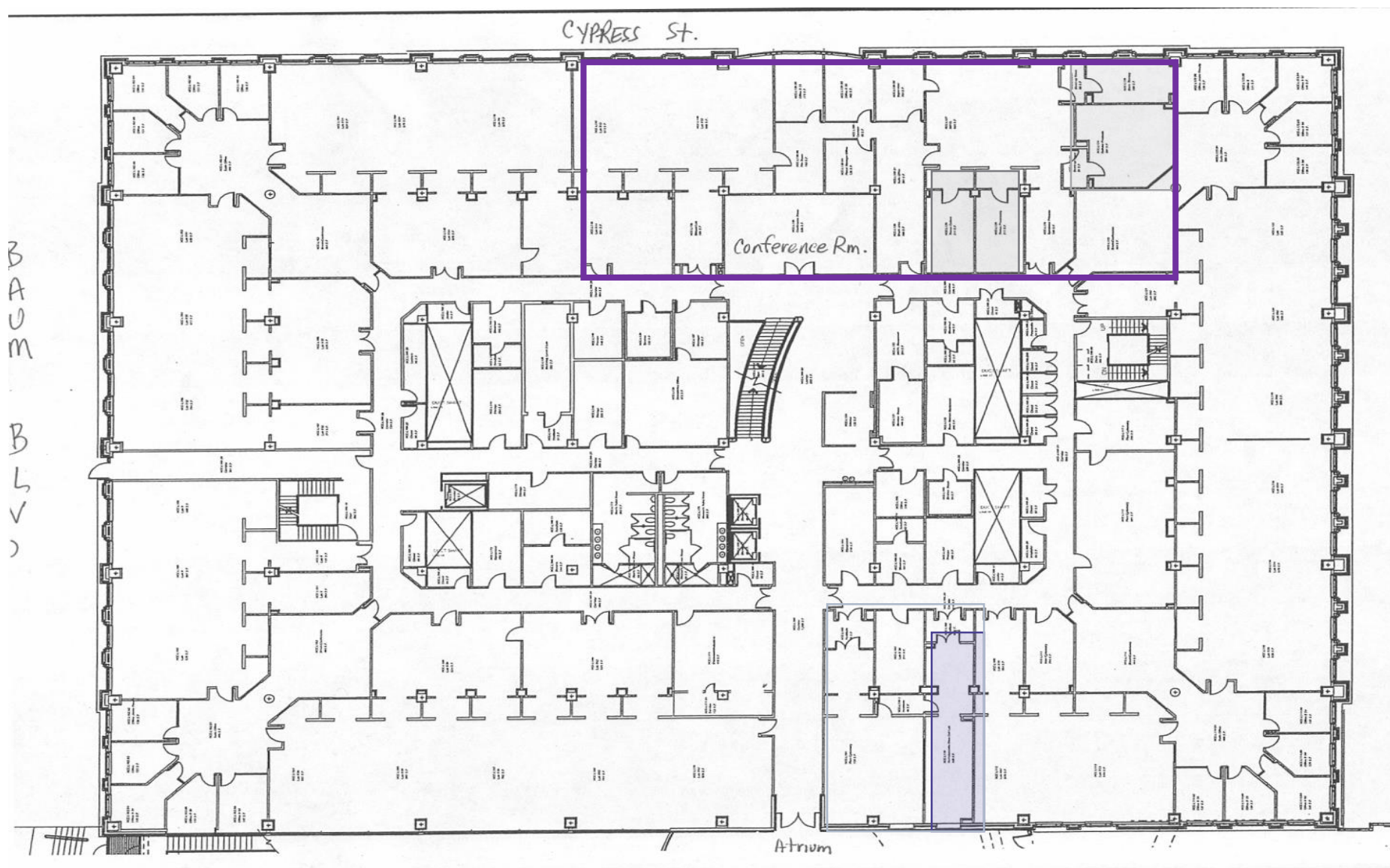
Physical Environment

- Designed after discussions with the FDA
- Stainless steel casework
- Coved epoxy terrazzo floors with a seamless join with the wall
- Solid ceilings
- Water-resistant epoxy paint
- Preliminary and terminal HEPA filtration
- Positive and negative air pressure areas
- Temperature and humidity controlled
- Secured area with restricted access

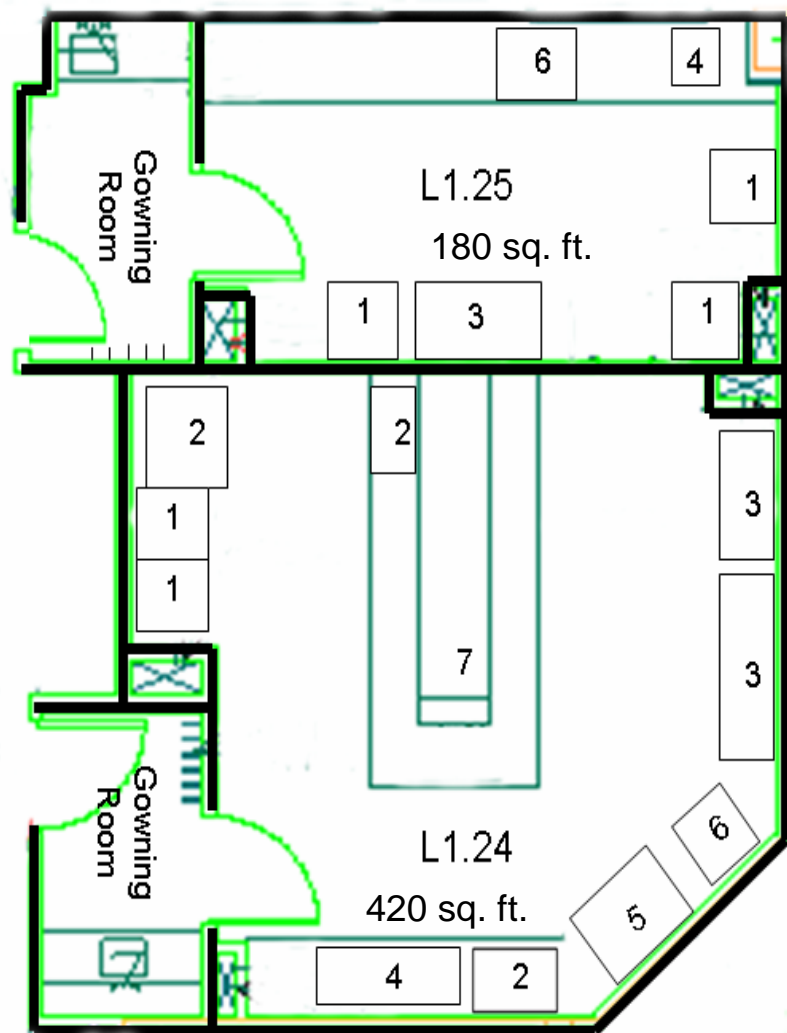
Facility Design

- Planning, design and documentation are keys to building a cGMP facility
- Separate, defined areas for each operation of the laboratories:
 - Accessioning of products
 - Product labeling
 - Processing
 - Storage of products, short-term and long-term
 - Waste disposal
 - Supply and reagent storage
 - Testing
- Interlocked anterooms between outer labs and cleanrooms
- Surfaces are non-shedding and non-porous
- Card-key access to authorized-user areas

Blueprint



Floor Plan



The floor plans and equipment in two of the three cleanrooms

LEGEND:

*	Indicates the pass-through
1	CO ₂ Incubators
2	CliniMACS magentic bead purification
3	Biosafety cabinets
4	Centrifuges
5	ELUTRA system
6	Refrigerators
7	Microscopes

Cellular Products

- CPL consists one large testing laboratory with several smaller attached labs and three cleanrooms
- Main laboratory
- contains
 - Flow Cytometer
 - Centrifuges
 - Incubators
 - Microscopes
 - Refrigerators &
 - Freezers
 - Controlled-rate Freezers





- Cleanrooms contain
 - Biological safety cabinets
 - Centrifuges
 - Incubators
 - Microscopes
 - Elutra
 - CliniMACS

Autologous Products from Cancer Patients

- Cell Quality – often from heavily treated patients
 - May not grow or function as expected
- Uniform collection procedures
 - Training and competency, donor screening
- Transportation
 - Carrier/Packaging/Monitoring
- Processing
 - Regulated by FDA
- Cryopreservation
 - Effects?
 -

Regulatory compliance and quality measures can eliminate as many variables as possible, and provide a plan for unexpected issues

Other Labs

SITE A

- One hood shared with blood bank
- 1.5 FTE for 70 transplants/year
- LN₂ tanks in office area, no O₂ monitors
- No secure facility in which to process products
- Bloodbank refrigerators in processing area, constant traffic in front of processing area
- No cleanrooms

SITE B

- Office area/eating area from accessioning and testing area by tape on the floor
- Carpet
- Old equipment, standard lab cabinets, cramped space

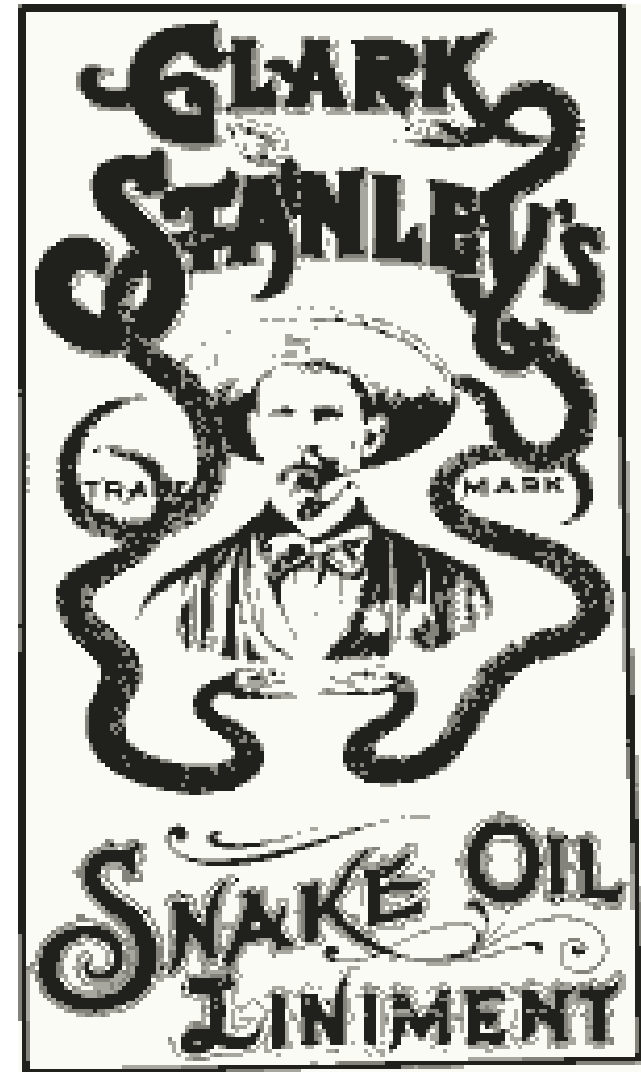
GxP

Where the X stands for any of several FDA regulations and the c stands for “current”:

- GCP – Good Clinical Practise
21 CFR 50, 54, 56
- GLP – Good Laboratory Practise
21 CFR 58
- GTP – Good Tissue Practise
21 CFR 1271
- cGMP – Good Manufacturing Practise
21 CFR 210, 211

History of the FDA (1880s)


- 1880s Snake oil salesmen
- “Patent” medicines being sold
- Adulterated food
- “Medical” devices
- Grassroots “pure food” movement



DR. BONNORE'S

CURES

MEASLES
FEMALE COMPLAINTS
NECROSIS
CHRONIC ABSCESS
MERCURIAL ERUPTIONS
EPILEPSY
SCARLET FEVER
HIP
DYSPEPSIA
PARALYSIS
RHEUMATISM
CHOLERA
NEURALGIA



ELECTRO MAGNETIC BATHING FLUID.

TRADE MARK

J. MOSES'



Electro Galvanic, Pat. 2 June, '68.

Startling and Beautiful Invention!

A continuous stream of Electricity conveyed to the Optic Nerve!!

The organ of SIGHT restored to its original strength!!!

Eye employment, however continuous, rendered free from discomfort!!!!

BY J. MOSES'S Patent Electro Gal- vanic Spectacles.

WHOLESALE DEPOTS,
10 CORTLANDT ST.,
NEW YORK,

AND

398 MAIN STREET,
HARTFORD, CONN.

Jim the Horse

- 1901
- Used Jim's serum to produce diphtheria vaccine
- Jim contracted tetanus
- Children contracted tetanus from the vaccine
- Led to the passage of the Biologics Control Act of 1902



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- Food preparation
- Medical devices
- Ingredients in medicines

[illegible]

Patent medicines are poisoning people throughout America to-day. Babies who cry are fed liniment under the name of Syrup. Women are led to injure themselves for life by reading in the papers about the meaning of backache. Young men and boys are robbed and contaminated by vicious criminals who lure them to their dens through seductive advertisements.

◎ 俗文化語彙 · 俗文化語彙 · 俗文化語彙 · 俗文化語彙 · 俗文化語彙

FDA (1927)

Became a law enforcement agency but receives funding and direction from Congress.

Permitted to

- Ban product
- Control distribution
- Control marketing

CBER, formed in 1902 by the Biologics Control Act to control vaccine manufacture, predates the FDA and was incorporated into the Agency in 1972.

History of the FDA (1930s)

- Elixir Sulfanamide - Antibiotic 1937
- Unpalatable as a pill
- Massengill decided to make soluble formulation
- Added pink color and cherry flavor
- Soon after its release, people started dying
- Testing performed by EMK Geiling, and assisted by Frances Oldham Kelsey, it turned out the solvent was diethylene glycol (*i.e.*, antifreeze)
- 107 deaths attributed, Massengill not held accountable due to FDA not requiring safety data. Fined for “misbranding” product.



History of the FDA (1938)

- Federal Food Drug and Cosmetic Act
- Required pharmaceutical companies to provide
 - Evidence of SAFETY of products
 - Warnings of potential hazards
- Covers:
 - Drugs
 - Cosmetics
 - Food additives including colorings

History of the FDA (1932-1972)

TUSKEGEE SYPHILIS TRIAL

- 399 infected/200 uninfected poor, illiterate, African-American sharecroppers
- Purpose: study natural history of disease
- Participants:
 - Not informed of diagnosis
 - Told they had 'bad blood' and could receive
 - Free treatment
 - Free ride to clinic
 - One hot meal/day
 - \$50 for their funeral



History of the FDA (1932-1972)

Participants (continued)

- Not given antibiotics when it became available (SOC) in 1940s
 - Prevented from participating in syphilis treatment programs
 - Received lumbar punctures under the guise of a special free treatment
 - Hundreds of men died of syphilis, many wives infected and many children born with congenital syphilis
- Investigator goal: how the disease spreads and kills, but trial ended due to whistle-blower
 - 1974 National Research Act
 - Commission to study and write regulations governing studies involving human participants

History of the FDA (1932-1972)



In 1966 Peter Buxtun, a venereal disease investigator, reported his concerns to the national director of the Division of Venereal Diseases, who ignored it. Two years later, Buxtun went to the press and that is what finally closed the study.

History of the FDA (1932-1972)

On May 16, 1997, President [Bill Clinton](#) formally apologized and held a ceremony for the Tuskegee study participants: "What was done cannot be undone. But we can end the silence. We can stop turning our heads away. We can look at you in the eye and finally say on behalf of the American people, what the United States government did was shameful, and I am sorry ... To our African American citizens, I am sorry that your federal government orchestrated a study so clearly racist." Five of the eight remaining study survivors attended the White House Ceremony.

[Wikipedia.org/wiki/Tuskegee_syphilis_experiment](https://en.wikipedia.org/wiki/Tuskegee_syphilis_experiment)

History of the FDA review

- 1906 Food and Drug Act
What's in it? (IDENTITY/PURITY)
- 1938 Federal Food, Drug & Cosmetic Act
Is it safe? (SAFETY)
- 1962 Kefauver-Harris amendment
- Does it work as you say it does? (POTENCY)
- 1974 National Research Act
Do people know what you're doing to them? (CONSENT)

GCP

GOOD CLINICAL PRACTISE

- Not directly applicable to the laboratory
- PI, Physicians and Nurses are responsible for meeting GCP
- 21 CFR 50 Informed Consent
- 21 CFR 54 Financial Disclosure by Clinical Investigators
- 21 CFR 56 IRB
 - How clinical trials should be conducted, roles and responsibilities of staff

GLP

GOOD LABORATORY PRACTISE

- NON-CLINICAL laboratory testing
 - 21 CFR 58
- Ensures consistency and reliability
 - Results
 - Resources
 - Knowledge transfer
 - Well-defined audit trail

Often related to animal toxicology studies for new therapeutics

GTP

GOOD TISSUE PRACTISE

- Clinical laboratory testing
- Processing of tissue and cellular products intended to treat a disease or condition
- 21 CFR 1271
- Prevention of spread of communicable disease due to cellular and tissue based products
 - SAFETY of product being manufactured
 - Reporting mechanisms
 - Donor Eligibility

cGMP

CURRENT GOOD MANUFACTURING PRACTISE

- Only the US uses the little “c” to emphasize that this is the current thinking of the Agency and is a dynamic interpretation
- Intended primarily for pharmaceutical manufacturing processes
- 21 CFR 210, 211
- Worldwide: regulations from the World Health Organization are in use in over 100 countries
- Document every aspect of the processing, activities and operations

CBER Products

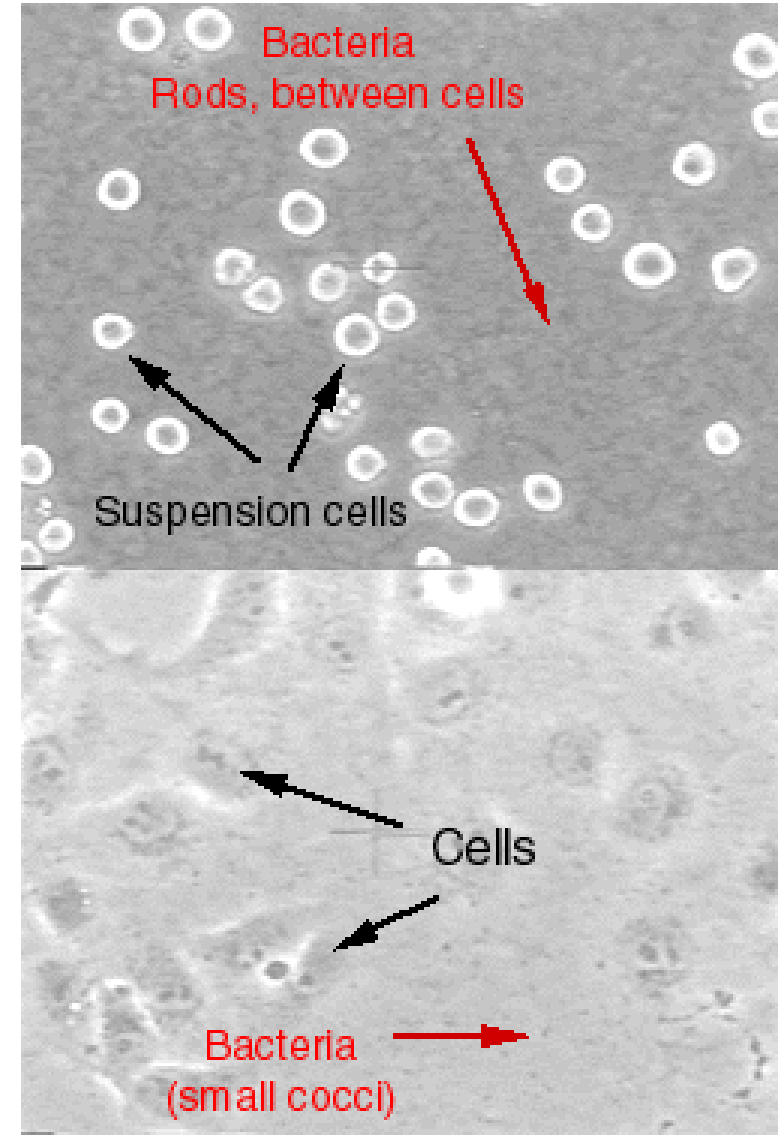
- Tissue & Tissue Products
 - Bone, Skin, Corneas, Ligaments, Tendons, Stem Cells, Sperm, Heart Valves
- Vaccines
 - Vaccines for Use in Children and Adults, Tuberculin Testing
- Xenotransplantation
 - Transplantation of Non-Human Cells, Tissues or Organs Into a Human

CBER is who regulates Cellular Therapy Labs

Aseptic Technique

GOOD ASEPTIC TECHNIQUE

- Prevents cross-contamination of cells from both cellular and microbial sources
- Prevents misidentification of cell line
- Saves money and time: experiments are performed using the correct, uncompromised cells, thereby eliminating a variable.
- Repeats of the experiment cost time (tech time, supervisor time, director time) and money (tech costs, reagents, supplies, facility resources)
- Allows for good science!



Accountability and Deviation Management

- Report errors that you discover
- Deviation management is not something to fear – it's an opportunity to make improvements, and shows that issues that are identified are addressed
- If you don't document it, it didn't happen

UNIVERSITY OF PITTSBURGH CANCER INSTITUTE
IMMUNOLOGIC MONITORING AND CELLULAR PRODUCTS LABORATORY

DEVIATION MANAGEMENT RECORD DM # 14-006

Report Date: 2/7/14 Staff: M. DeRiggi Section: TPF ☐ CPL ☒ IML ☐

Event Dates: 11/25/13-1/30/14 Protocol: 10-052/13-106 Specimen ID: See below

Description: ☒ Internal ☐ External

UVB lamps were used past their calibration due date of 10/29/13 to irradiate tumor cells for 13-106 and 10-052.

Date: 2/7/14 Tech: MD

Director Notified: ☐ Yes ☒ No Date/Time: ----- Tech: MD

QA Manager Notified: ☐ Yes ☒ No Date/Time: ----- Tech: MD

QA Analysis: ☒ Regular DM Process ☐ CAPA Process/Possible Reportable event QA 2/26/14

Category: ☐ Facilities ☐ Environmental control ☒ Equipment ☐ Supplies & reagents ☐ Recovery
☐ Processing ☐ SOPs ☐ Labeling ☐ Storage ☐ Receipt, shipment & distribution ☐ Records & database
☐ Personnel ☐ Sterility/testing ☐ Donor eligibility, screening/testing ☐ Complaints ☐ Other

Investigation:

On 1/30/14 while preparing tumor lysate for patient DC on 10-052, technologist KK discovered the UVB lamp she was going to use had a sticker reading "calibration due: 10/29/13." All 5 UV lamps are sent at the same time for calibration to Spectronics Corporation where the lamps' intensities are measured and bulbs replaced if necessary. The past-calibration lamps were used for the following products:

- 11/19/13- TPF-13-472 Patient PW 10-052 tumor lysate UVB irradiation, lysate used for DTHs
 - Sterility result- No growth 14 days
- 11/25/13- CPL-13-24 Patient RS 13-106 tumor UVB irradiation, irradiated cells were used for co-culture
 - ApTu sterility result- No growth 14 days
 - 84% PI, 33% Annexin
- 01/23/14- TPF-14-9 Patient GH 10-052 tumor lysate UVB irradiation, lysate used for DTHs
 - Sterility result- No growth 14 days
- 01/30/14- TPF-14-32 Patient DC 10-052 tumor lysate UVB irradiation, lysate used for DTHs
 - Sterility result- No growth 14 days

Certificate of Conformance from Spectronics Corporation received and approved by Materials Management on 2/13/14.

Materials Manager confirmed that the devices contained the same bulbs before and after testing.

The procedures above use gamma irradiation to stop proliferation and UVB for sterilization (bacterial). All products tested NO GROWTH 14 days.

Date: 2/13/14 Tech: MD

Corrective Action, Short Term: ☐ Not applicable

All 5 UV lamps were immediately sent for calibration on 1/30/14.

Date: 2/7/14 Tech: MD

Corrective Action, Long Term: ☐ Not applicable

A preventive maintenance spreadsheet was made to include due dates for all equipment.

I:\CPL schedules

Date: 2/7/14 Tech: MD

Review by Supervisor/Lead Tech:

Problem resolved? ☒ Yes ☐ No Comment

Follow up required? ☐ Yes ☒ No Comment

Date: 2/26/14 Tech: VS

Additional/follow up comments and Final Review:

Supervisor/Designer Review/Date:

Veronica Sutherland 2/24/14

Staff Review of finalized DM/Date:

M. DeRiggi 2/27/14

*Attach additional pages if necessary, including documentation.

QA documented in database: MD 2/7/14 Tech/date

Original filed in: patient folders

DM finalized/PDF made: MD 2/27/14 Initial/date

DEVIATION REPORT:

1. What happened
2. What it might have impacted
3. Information gathered, additional testing performed
4. Steps taken to fix problem
5. Confirmation that problem was fixed
6. Review and sign off

The Foundation for the Accreditation of Cellular Therapy

(FACT) is a non-profit corporation co-founded in 1996 by the International Society for Cellular Therapy (ISCT) and the American Society of Blood and Marrow Transplantation (ASBMT) to provide a peer network of experts committed to improving stem cell transplantation and cellular therapy practices by formulating and disseminating evidence-based guidelines.

These guidelines have until recently been formulated in 3 documents: 1) FACT Common Standards for Cellular Therapies, 2) FACT-JACIE Hematopoietic Cell Therapy Standards, and 3) NetCord-FACT Cord Blood Banking Standards.

FACT also offers a voluntary accreditation program for hematopoietic progenitor cell (HPC) therapy programs and UCB banks, with over 90% of eligible US HPC facilities and programs holding accreditation.

Achieving FACT accreditation after a comprehensive inspection performed every 3 years demonstrates to patients, physicians, commercial manufacturers, regulatory agencies, and insurance payers that a given program/laboratory is committed to quality measures and oversight in cell therapy practices and downstream patient care.

The why, what, and how of the new FACT standards for immune effector cells, M. Maus and S. Nikiforow, Journal for ImmunoTherapy of Cancer 2017

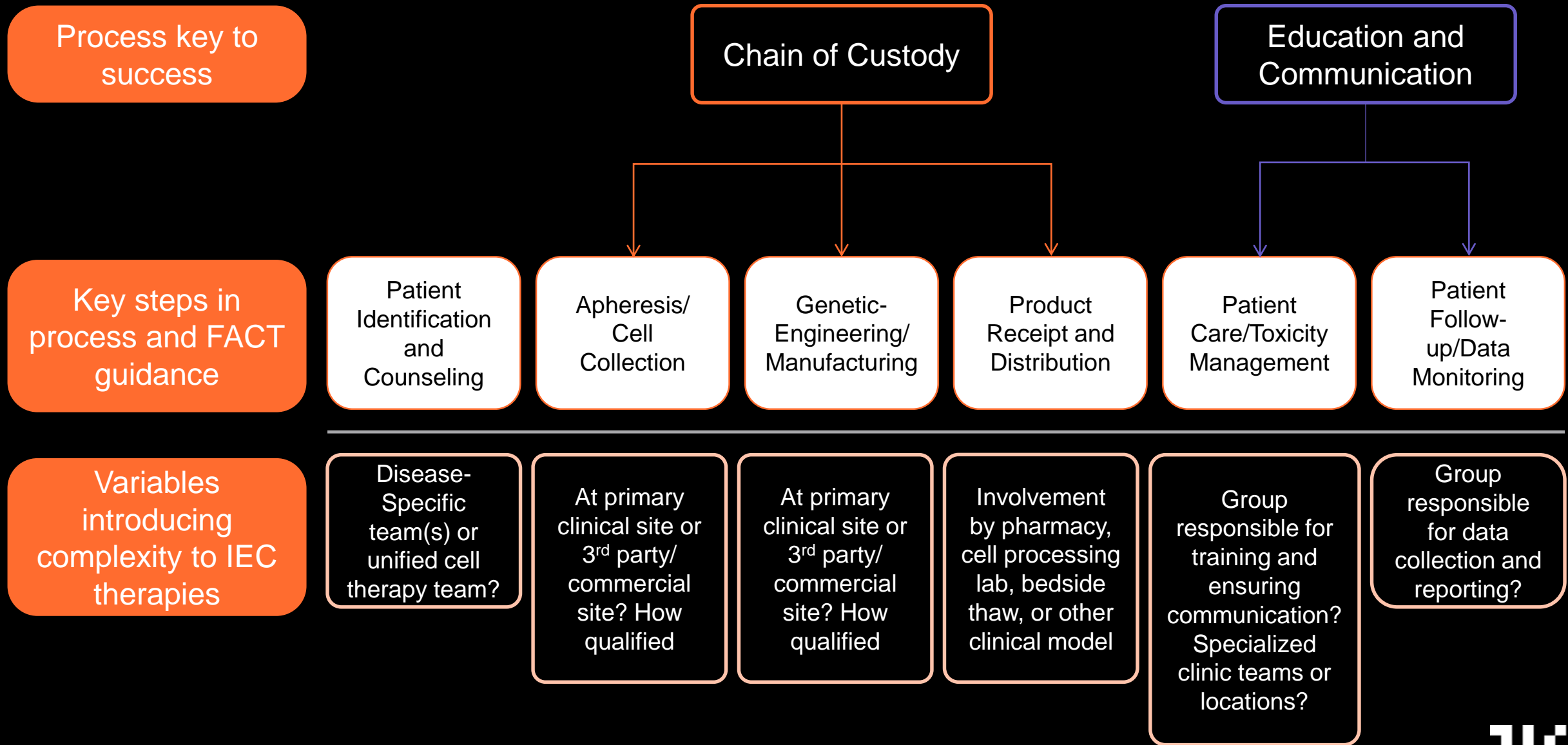
Current Cellular Products

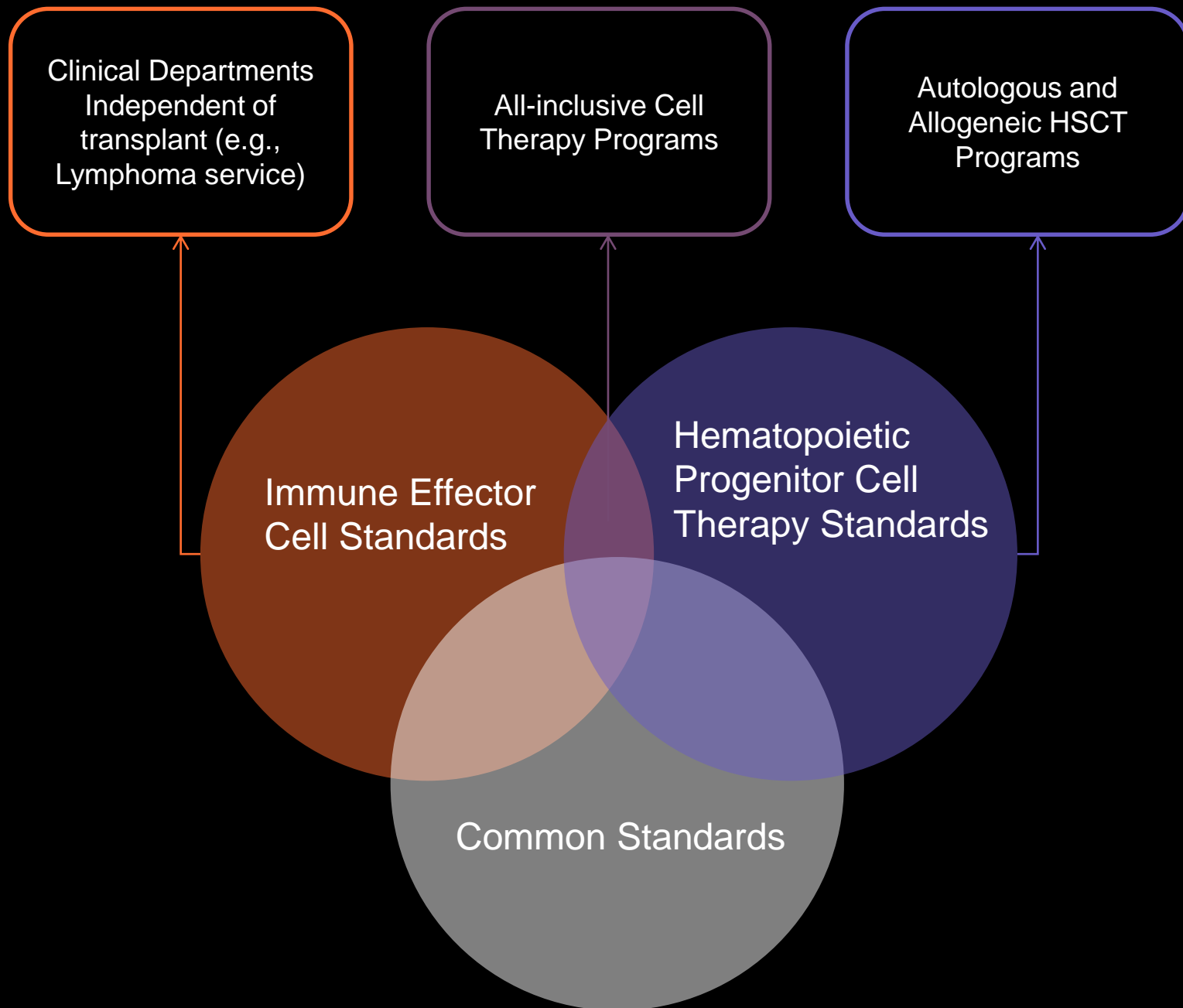
The administration of CAR-T cells can consume significant effort from: transfusion medicine, the cell-processing laboratory, pharmacy, outpatient and inpatient clinical teams, and consultants.

A robust clinical infrastructure is required to handle the complex **scheduling logistics**, maintain the **chain-of-custody** and chain-of-identity of the cellular product, and facilitate communication to manage potentially severe **toxicities**.

Cells are not stored in vials, nor are they mixed and re-labeled in the pharmacy. These products must be **temperature-controlled** at all times during preparation, shipping, and administration, and can only be manipulated under aseptic conditions.

The importance of the chain-of-custody and absolute certainty regarding identity of the cellular product, along with its label and attendant paperwork, cannot be overstated, as administration of the wrong product can have lethal consequences.





Relationship between different FACT standards. Individual programs will reference standards and seek accreditation as best suits their needs.

While all cellular therapy manufacturing and distribution should comply with the guidelines in the Common Standards, clinical teams may operate and apply for accreditation within an HSCT program, an IEC program or one that involves both types of cell therapies.

Maus, JITC 2017

Scope of FACT Immune Effector Cell Standards

- Cells used to **modulate an immune response** for therapeutic intent
- May elicit a response or mitigate a response
- Cell types **include DC, NK, T, and B** (does not include MSCs)
- Common products
- Chimeric antigen receptor T cells (**CAR-T cells**)
- Therapeutic vaccines using dendritic cells

PROCESSES –NOT SCIENCE

- Donor selection and management, collection, preparation for administration, administration of cells, management of adverse events, and evaluation of clinical outcomes
- Quality Management (QM) program that establishes, maintains, monitors, and implements improvements
- Education

FDA Cell Therapy Lab Registration

See Instructions for OMB Statement. FORM APPROVED: OMB No.0910-0543. Expiration Date: 6/30/2020

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION ESTABLISHMENT REGISTRATION AND LISTING FOR HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS (HCT/PS) (See reverse side for instructions)		1. REGISTRATION NUMBER (FDA Establishment Identifier) FEI: 3004571535		2. REASON FOR SUBMISSION a. <input type="checkbox"/> INITIAL REGISTRATION / LISTING b. <input checked="" type="checkbox"/> ANNUAL REGISTRATION / LISTING c. <input type="checkbox"/> CHANGE IN INFORMATION d. <input type="checkbox"/> INACTIVE		VALIDATION--FOR FDA USE ONLY 1 VALIDATED BY FDA: 19-NOV-2016 DISTRICT: Philadelphia PRINTED BY FDA: 15-NOV-2017											
PART I - ESTABLISHMENT INFORMATION 3. OTHER FDA REGISTRATIONS a. BLOOD FDA 2830 NO. _____ b. DEVICES FDA 2891 NO. _____ c. DRUG FDA 2656 NO. _____		PART II - PRODUCT INFORMATION 10. ESTABLISHMENT FUNCTIONS AND TYPES OF HCT / Ps								11. HCT/PS DESCRIBED IN 21 CFR 1271.10		12. HCT/PS REGULATED AS MEDICAL DEVICES		13. HCT/PS REGULATED AS DRUGS OR BIOLOGICAL DRUGS		14. PROPRIETARY NAME(S)	
4. PHYSICAL LOCATION (Include legal name, number and street, city, state, country, and post office code) University of Pittsburgh Cancer Institute Hillman Cancer Center 5117 Centre Avenue Suite 1.27 Pittsburgh, Pennsylvania 15213-1863 a. PHONE 412-623-1418 EXT _____ b. <input type="checkbox"/> SATELLITE RECOVERY ESTABLISHMENT (MANUFACTURING ESTABLISHMENT FEI NO. _____) c. <input type="checkbox"/> TESTING FOR MICRO-ORGANISMS ONLY		Types of HCT / Ps		Establishment Functions Recover Screen Test Package Process Store Label Distribute													
5. ENTER CORRECTIONS TO ITEM 4		a. Bone															
		b. Cartilage															
		c. Cornea															
		d. Dura Mater															
		e. Embryo		<input type="checkbox"/> SIP <input type="checkbox"/> Directed <input type="checkbox"/> Anonymous													
		f. Fascia															
		g. Heart Valve															
		h. Ligament															
		i. Oocyte		<input type="checkbox"/> SIP <input type="checkbox"/> Directed <input type="checkbox"/> Anonymous													
		j. Pericardium															
		k. Peripheral Blood Stem		<input type="checkbox"/> Autologous <input type="checkbox"/> Family Related <input type="checkbox"/> Allogeneic													
		l. Sclera															
		m. Semen		<input type="checkbox"/> SIP <input type="checkbox"/> Directed <input type="checkbox"/> Anonymous													
		n. Skin															
		o. Somatic Cell Therapy Products		<input checked="" type="checkbox"/> Autologous <input checked="" type="checkbox"/> Family Related <input checked="" type="checkbox"/> Allogeneic			X	X	X	X	X	X	X		X		
		p. Tendon															
		q. Umbilical Cord Blood		<input type="checkbox"/> Autologous <input type="checkbox"/> Family Related <input type="checkbox"/> Allogeneic													
		r. Vascular Graft															
		s. Parathyroid						X	X	X	X	X					
		t.															
		u.															
		v.															
6. MAILING ADDRESS OF REPORTING OFFICIAL (Include institution name if applicable, number and street, city, state, country, and post office code) University of Pittsburgh Cancer Institute Hillman Cancer Center Attn: Lisa H. Butterfield, Ph.D. 5117 Centre Avenue Suite L1.27 Pittsburgh, Pennsylvania 15213-1863 a. PHONE 412-623-1418 EXT _____																	
7. ENTER CORRECTIONS TO ITEM 6		b. PHONE _____															
8. U.S. AGENT a. E-MAIL _____																	
9. REPORTING OFFICIAL'S SIGNATURE a. TYPED NAME Lisa H. Butterfield, Ph.D. b. E-MAIL butterfieldl@upmc.edu c. TITLE Director, IMCPL d. DATE 18-NOV-2016																	

Lab Director definitions: overlapping and non-overlapping regulations

CAP definition of Lab Director: The individual who is responsible for the overall operation and administration of the laboratory, including provision of timely, reliable and clinically relevant test results and compliance with applicable regulations and accreditation requirements. This individual is listed on the laboratory's CAP and CLIA certificate

CAP TLC11425 Defines the Directors delegation of functions, including what can and cannot be delegated. If delegated, the Lab Directory still remains the responsible party for ensuring the task is done properly and carried out by the designee. All Lab Director

Oversight and Responsibilities are clearly defined in the Team Leader Assessment Checklist (TLC).

1. Functions that may be delegated include review of QC data, proficiency testing performance, and test methodology performance studies. The laboratory director remains responsible [A] that all persons performing delegated functions are qualified to do so; and [B] that the delegated functions are properly carried out.

2. Functions that may not be delegated include provision of appropriately trained supervisory and technical staff and the identification of their responsibilities. The laboratory director must document personal, on- site assessment of physical and environmental conditions and the adequacy of staffing.

3. The responsibilities and duties of supervisors, consultants, and testing personnel involved in pre-analytic, analytic, and post-analytic phases of testing must be defined in writing, with records of authorization to perform testing, and the level of supervision required, as applicable.

FACT: D3.1.1 There shall be a Processing Facility Director with a medical degree, doctoral degree, or equivalent degree...

FACT 3.1.2 Defines: The Processing Facility Director shall be responsible for all procedures, administrative operations, and the Quality Management Program. This also discusses what can be delegated and is in agreeance with CAP. The Lab Director is the overall responsible party for ensuring any designated task is carried out by the designee as defined.

cGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities.

Adherence to the [cGMP regulations](#) assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations.

This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories.

This formal system of controls, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. This assures that drug products meet their quality standards.

The cGMP requirements were established to be **flexible** in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures.

The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. Accordingly, the "C" in CGMP stands for "current," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations.

Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards.

It is important to note that CGMPs are minimum requirements. Many manufacturers are already implementing comprehensive, modern quality systems and risk management approaches that exceed these minimum standards.

21 CFR Part 210.

Current Good Manufacturing Practice in Manufacturing Processing, packing, or Holding of Drugs.



CFR - Code of Federal Regulations Title 21

FDA Home Medical Devices Databases



The information on this page is current as of April 1 2018.

For the most up-to-date version of CFR Title 21, go to the [Electronic Code of Federal Regulations \(eCFR\)](#).

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[Title 21, Volume 4]
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TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER C--DRUGS: GENERAL

PART 210 -- CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

Sec. 210.1 Status of current good manufacturing practice regulations.

(a) The regulations set forth in this part and in parts 211, 225, and 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in parts 211, 225, and 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

(c) Owners and operators of establishments engaged in the recovery, donor screening, testing (including donor testing), processing, storage, labeling, packaging, or distribution of human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined in



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Related Resources

Electronic Code of Federal Regulations

e-CFR data is current as of **December 20, 2018**

Title	Volume	Chapter	Browse Parts	Regulatory Entity
Title 21 Food and Drugs	1	I	1-99	FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES
	2		100-169	
	3		170-199	
	4		200-299	
	5		300-499	
	6		500-599	
	7		600-799	
	8		800-1299	
	9	II	1300-1399	DRUG ENFORCEMENT ADMINISTRATION, DEPARTMENT OF JUSTICE
		III	1400-1499	OFFICE OF NATIONAL DRUG CONTROL POLICY

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Example of a Manufacturing SOP

Pg. 1 of 8

One of the major steps in preparing the vaccine product

PROCEDURE FOR ADENOVIRAL TRANSDUCTION OF DC FOR UPCI 09-021 PROTOCOL

1. Purpose and Scope

- 1.1. The purpose of this procedure is to describe the methodology for transfecting DNA into Dendritic Cells (DC) using the adenoviral vector AdVTMM2 (Tyrosinase, MART-1, and MAGE-A6; melanoma associated antigens, MAA).
- 1.2. Dendritic cells (DC) have been a major focus of basic and clinical research for several years. Their putative therapeutic value is related to the fact that DC are potent antigen presenting cells. As such, they are often used for immunotherapy. Transfection is a frequently used method to achieve in vitro antigen expression in DC. With adenoviral vectors, gene transfer into human DC can be achieved with up to >90% efficiency.
- 1.3. Transduced DCs maintain antigen expression for at least 7 days. Before or after transduction, they can be matured or used directly as antigen presenting cells in order to achieve anti-tumor CD4+ and CD8+ T cell responses.

2. Responsibility

- 2.1. Technologist: Responsible for the following this procedure and for documenting results.
- 2.2. Lab Manager: Responsible for review of results for accuracy, completeness and acceptability.
- 2.3. QA Manager: Responsible for reviewing and approving this procedure.
- 2.4. Laboratory Director: responsible for final review and approval of this procedure when originated, revised and on a biannual basis.

3. Safety and Precautions

- 3.1. **ALL HUMAN SAMPLES ARE POTENTIAL BIOHAZARDOUS!** All equipment, supplies and reagents in contact with human blood, body fluids, and/or tissues should be handled and disposed of as biohazardous. **HANDLE ALL MATERIALS AS IF CAPABLE OF TRANSMITTING INFECTIOUS AGENTS!** When performing this procedure, follow the UPCI IMCPL Biohazard Precautions as outlined in the IMCPL.
- 3.2. AdV particle measurements (by OD) include both infectious (plaque-forming units, PFU) and non-infectious, defective virions. Particle: PFU ratios can be up to 100:1. Therefore, a viral titer (concentration measurement) of "particles per ml" is of interest (and FDA-required, as toxicity can be from total particles used), but use is based on infectious pfu measurement, which is performed by plaque assay on permissive 293 cells, or by hexon titer kit (immunohistochemistry assay for AdV hexon protein-producing cells, which means cells which are successfully infected and making hexon protein). It is customary to derive the MOI for a batch of GMP virus, then maintain that number of *particles*, even if infectious titer changes over time, at annual re-certifications of virus. The decision to modify the amount of virus after an annual recertification will depend on the protocol and IND.

Example of Facilities Master File for the FDA

Table of Contents.....		5.13 Materials management.....	48
1. Name and Address of Site.....	6	5.13.1 Raw Materials Management.....	48
2. Overview of the Facility.....	6	5.13.2 In-Process Materials.....	49
3. Overview of Products Manufactured.....	10	5.13.3 Final Products.....	49
4. Detailed description of the Cell Production Facility.....		5.14 Quality control of the final product.....	51
5. CPL (located within IMCPL).....	11	5.14.1 Testing performed by the QC laboratory.....	51
5.1. Short description of the site.....	11	5.14.2 Additional required testing contracted to commercial testing Laboratories.....	51
5.1.1. Figure 1a: IMCPL facility architectural plan.....		5.14.3 Selection of commercial contract laboratories by Laboratory Director.....	51
5.1.2. Figure 1b: Detailed architectural drawing of PPC1, PPC2 and NPC.....	1	5.14.4 Testing protocols are kept on file in the IMCPL office.....	51
5.1.3. Figure 2a: Traffic patterns for Products.....		5.14.5 Vendor Qualification.....	51
5.1.4. Figure 2b: Traffic Patterns for Supplies.....		5.14.6 Customer Satisfaction Survey.....	51
5.1.5. Figure 2c: Traffic Patterns for Waste.....		5.14.7 QC responsibilities.....	51
5.2. Labs/Services.....	16	5.15 Distribution, complaints and product recall.....	
5.3. Types of products manufactured.....	16	5.15.1 Storage and distribution.....	
5.3.1. Autologous dendritic cell (DC) based vaccines.....	17	5.15.2 Complaint files.....	
5.3.2. Nucleofected Fibroblasts genetically modified.....	17	5.15.3 Quality indicator and audits.....	
5.3.3. Autologous tumor.....		APPENDIX A. Map of IMCPL at the Hillman Cancer Center.....	
5.3.4. Autologous Lymphocytes.....	17	APPENDIX B. Listing of Policies and SOPs.....	
5.3.5. Autologous Leukaphersis donor leukocytes.....	17		
5.3.6. Primary Autologous leukocyte subsets.....			
5.3.7. Autologous donor leukocytes transduced with viral vectors.....	17		
5.3.8. Lymph node lymphocytes (LNL).....	17		
5.3.9. Tumor Infiltrating Lymphocytes (TIL).....			

Good and less good issues with GMP

GOOD NEWS:

- Flexibility allows for the possibility that you can make the product you want to make the way you want it to be.
- Phase I trials have extra flexibility in GMP regulations.

#1 is safety

LESS GOOD NEWS:

- The lack of strict rules allows for reviewers to disallow what you propose.
- It is challenging to know exactly what to propose to guarantee it can be approved.

A Solution: PICI-FOCR “Future of cell therapy”



Meeting in Washington DC on May 17, 2019




Efficiencies Gained Through Early Stage Manufacturing

CMC Activity	Typical Time ¹ Investment	Areas of Proposed Flexibility	Potential Time ² Savings	Potential Cost Savings ³
Use of R&D Reagents	3-6 months	Increasing options for use of R&D reagents and reducing cost and time to either enable or negotiate GMP manufacture of reagents	1-3 months	\$ to \$\$\$
Plasmid Manufacturing	4 months (+ 3 to 6 months in queue)	Reduced plasmid characterization & infrastructure requirements	5-7 months	\$\$
Viral Manufacturing	6 months (+ 9 to 12 months in queue)	Waive RCL testing in lieu of surrogate testing; reduced cGMP requirements for ancillary reagents	4 months	\$
Cell Product Engineering Runs (3 runs)	3 months	Use representative pilot virus for parallel cell product engineering runs	2 months*	N/A

Strategies to Facilitate Development of Cellular Therapies

	Description/Process
Early Phase	
Parent-Child IND	Parent IND would contain common sections providing all relevant information for the candidates or manufacturing alterations. Each child IND would cross-reference common sections while providing only the candidate or process specific information
Exploratory IND paradigm	Enrollment in trials with exploratory cellular therapy INDs would be limited to patients with advanced cancers and limited or no treatment alternatives. Early planned safety reporting would support an open regulatory dialog. This pathway would facilitate the efficient generation of clinical data and inform whether more formal trials should be pursued.
Late Phase	
Adaptive Manufacturing Process	An adaptive manufacturing process with the goal of generating a highly similar drug product from the patient-specific starting material is needed. A regulatory strategy that adjusts a process as product and process knowledge increases and based on patient or patient-specific raw material information to maximize product quality for all patients will permit the avoidance of extensive costly and lengthy clinical studies.
Post-marketing Product Optimization and Modifications	...modifications to manufacturing processes could be managed via a pre-negotiated plan with health authorities (e.g., Post-Approval Lifecycle Management or Comparability Protocol). Filing requirements for the change may include a combination of an analytical comparability assessment, and/or a small clinical study, analogous to a bioequivalence study for a new process.



cGMP for Cell Therapy

“It’s not science, it’s manufacturing”