# Production Records & Documentation

**Diane Kadidlo MT(ASCP) SBB**
**University of Minnesota**

**Joanna Stanson, M.S.**
**University of Pittsburgh**

# Production Records

*This Session*:

- Production Records
  - Basic Elements
  - Regulatory Concerns
  - Documentation Practice
- Practical Example of Production Record
- Questions & Discussion

PACT
Production Assistance for Cellular Therapies

# Production Records - Overview

- Common elements
  - Preparation
  - Processing Events
  - Final Review
- Regulatory Concerns
  - AABB, FDA, FACT
- Documentation Practices
- Record Retention

Production Assistance for Cellular Therapies

# Product Manufacturing Records

General Definition

- Detailed, step-by-step instructions of a task that are required to manufacture a product.

*It is all about controlling the process*

Production Assistance for Cellular Therapies

# Production Record Design

*Rules:*

- Be compliant with applicable standards
  - FDA's GMP, GTPs
  - AABB
  - FACT
- Be compliant with regulatory submissions
  - Investigational New Drug (IND) applications
- Facilitate complete and accurate data entry
- Incorporate validation limits & controls

# Production Records Design

Production Records *should*:

- Reduce/minimize redundant or unnecessary data entry
- Reduce/minimize signatures
- Allow records to be completed, logically and chronologically, as work proceeds

# Regulations

- FDA
  - GMPs  Current Good Manufacturing Practice for Finished Pharmaceuticals (21 CFR 211)
  - GTPs 21 CFR 1271
- Process Controls
  - FACT
  - AABB

Production Assistance for Cellular Therapies

# Production Record Outline

- Preparation
  - Bill of Materials
  - Preparation Directives
  - Process Clearance
- Processing Events
  - Compliance with IND
  - Manufacturing Steps
  - Process controls
- Record Review/Close out
  - Role of 2nd Person
  - Reconciliation
  - Expected Yields/Acceptance Criteria
  - Attachments

PACT
Production Assistance for Cellular Therapies

# Preparation – Bill of Materials

- Bill of Materials CFR211.186)
  - A  listing of supplies, materials & equipment used in the process
  - Materials that come in contact with product throughout its shelf life (reagents, bags, vials)
  - Often used as a checklist to ensure all materials acceptable before use

PACT
Production Assistance for Cellular Therapies

# Supplies & Equipment

- Supplies
  - Item
  - Part #
  - Manufacturer
  - Lot #,
  - Expiration Date
- Equipment
  - Name
  - Manufacturer
  - Model
  - Serial Number
  - Last calibration date

PACT
Production Assistance for Cellular Therapies

# Supplies

| Item | Part Number | Manufacturer | Lot Number | Expiration Date | Recorded by/ Date |
|---|---|---|---|---|---|
| Cobe 2991 Triple processing set | MA165283 | | | | |
| Isolymph | CH100081 | | | | |
| 0.9% sodium chloride, injection, 1000 mL | CH100008 | | | | |
| Human serum albumin, 5%, 500 mL | CH100087 | | | | |
| DMSO | CH142790 | | | | |
| Transfer bag, 300 mL | MA191613 | | | | |

PACT
Production Assistance for Cellular Therapies

# Equipment

| EQUIPMENT | MANUFACTURER | MODEL | SERIAL NUMBER | CALIBRATION CURRENT? |
|---|---|---|---|---|
| CliniMACS Cell Separation Device | Miltenyi | 15101 | 12555F | Yes |
| Cell Processor | COBE | 2991 | 385987 | Yes |
| Centrifuge, floor model | Sorvall | RC-3B | BB-6677 | Yes |
| Incubator, 36-38°C 4-6% $CO_2$ | Forma Scientific | 3033 | 35479-12 | Yes |
| Cell Analyzer | Coulter | ACT Diff II | AJ38560 | Yes |
| Fluorescent Microscope | Carl Zeiss, Inc. | 16160 | 3925609004 | Yes |

PACT
Production Assistance for Cellular Therapies

# Preparation Directives

- Brief entries that describe preparation events
- Provides a link to associated preparation record.
  - Ex. Room sanitization, reagent preparation

PACT
Production Assistance for Cellular Therapies

# Process Clearance

- Also known as "Line Clearance"
- A check to ensure that the processing area is ready for production and all requirements have been met.
  - Ex. Documenting the Biological Safety Cabinet is free of potential cross contaminants before initiating work.
  - Ex. Labeling

# Production Record Outline

- Preparation
  - Bill of Materials
  - Preparation Directives
  - Process Clearance
- **Processing Events**
  - Compliance with IND
  - Manufacturing Steps
  - Process controls
  - Role of 2nd Person
- Record Review/Close out
  - Reconciliation
  - Expected Yields/Acceptance Criteria
  - Attachments

PACT
Production Assistance for Cellular Therapies

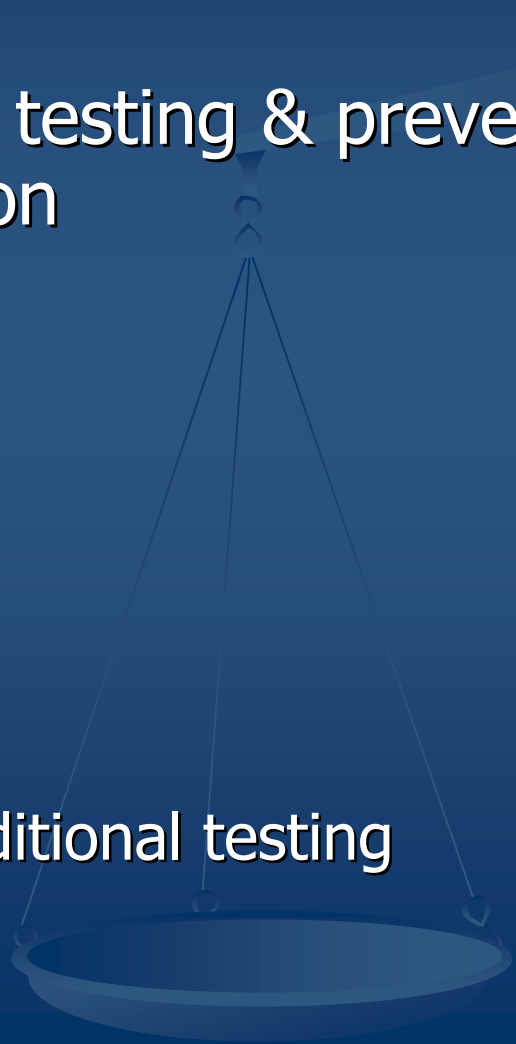
# Production Record & CMC

- Must be compliant with regulation submissions – eg. INDs
- Section 7 of the IND
- Critical component in the trial/IND submission
  - Product manufacturing & characterization information
  - Product testing (including lot release testing) information
  - Product stability information
  - Other
    - Product labeling, tracking, etc.

Production Assistance for Cellular Therapies

# CMC Elements

- Procurement
- Infectious disease testing & preventation of cross contamination
- Process
  - Description
  - Flow diagram
- Reagents
- Product Testing
  - Lot release
  - Post release & additional testing



PACT
Production Assistance for Cellular Therapies

# FDA Guidances

- Guidance for Reviewers- Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs). August 2003.
- Guidance for Industry: INDs-Approaches to Complying with CGMP During Phase I

PACT
Production Assistance for Cellular Therapies

# Processing Events

Production Records *shall* include:

- Documentation that each significant step in manufacturing was accomplished including:
  - Dates
  - Equipment used
  - Materials used
  - Weights & measures of components used
  - In-process & laboratory controls

21 CFR 211.188

Production Assistance for Cellular Therapies

# 21CFR 211.188 cont'd

- Batch Record *shall* include:
  - Inspection of packaging & labeling area before and after use
  - Calculations of Yields
  - Labeling records
  - Drug container & closures
  - Samples taken
  - ID of person performing & reviewing
  - Any investigations
  - Results of packaging & label examinations

PACT
Production Assistance for Cellular Therapies

# Responsibility of the Operator

- Document observations as they occur
- Signature or initials of operator implies the data
  - Accurately describes what is observed
  - Authentic – person signing is the person who observed or performed
  - Meets all expectations, no unfinished work

# Role of 2nd Person

- Review critical processes (calculations, label checks)
  - 2nd person does not necessarily have to watch the work performed, but must be able to audit and edit the data collection.
- Verification
  - Generally refers to a 2nd person actually observing the work being done.
    - Weighing a product
    - Addition of critical reagent

PACT
Production Assistance for Cellular Therapies

# 2nd Person's Role

- Knowing the process
- Accuracy
  - Verifying calculations
  - Ensuring that the data is recorded properly
- Completeness
  - Data legible, logical
- Complies with Standards & institutional policies
  - Often a QA function
  - Confirming specifications met or not met
  - Ensuring that the document complies with cross-outs, signatures, sig-fig, averaging policies.

PACT
Production Assistance for Cellular Therapies

# Production Record Outline

- Preparation
  - Bill of Materials
  - Preparation Directives
  - Process Clearance
- Processing Events
  - Manufacturing Steps
  - Process controls
  - Role of 2nd Person
- **Record Review/Close out**
  - Reconciliation
  - Expected Yields/Acceptance Criteria
  - Attachments

# Reconciliation

- What was used and how much
- Reconciliation/accountability of components used for production. 21CFR 211.184
  - Ex. Labels, vials, product #'s
- Does not include product and its container as that is controlled through product inventory.
- Suggest establishing limits (± %)

PACT
Production Assistance for Cellular Therapies

# Expected Yields

- Expected yields, objective end points, accepted ranges…
  - Requirement for GMPs, FACT & AABB
  - Investigate when not met
- Based upon
  - Manufacturer
  - Literature
  - Standards
  - Your historical data

PACT
Production Assistance for Cellular Therapies

# Acceptance Criteria

- List of information that must fulfilled to consider a production record acceptable.
  - Lot Release

PACT
Production Assistance for Cellular Therapies

# Attachments

- Labels
- Source documents (printouts, charts)
- Contract testing
- Deviations & Investigations

# Documentation Practices

- Printouts
  - Identify and sign all printouts, charts, source data
- Making changes afterwards
  - Any changes to original data must be signed & dated
  - Do not obscure original entry
  - Determine if changes warrant procedural change or investigation

PACT
Production Assistance for Cellular Therapies

# Record Control

- Controlled document and comply with institution's document control policies
- Maintain indefinitely

Production Assistance for Cellular Therapies

# Next….

## *Practical Applications*

# Production Records and Documentation

Joanna Stanson, M.S.
Senior Specialist Cellular Products Laboratory
University of Pittsburgh Cancer Institute

# Topics

- Cellular Products Laboratory (CPL)
- General requirements for production and documentation
- Flow Chart for the implementation of a production process (somatic cell culture)
- Steps associated with the DC generation
- Production Records and Control
- Release Criteria
- Product acceptance and Accessioning

PACT
Production Assistance for Cellular Therapies

# Cellular Products cGMP/GTP Laboratory (CPL)

- The CPL handles somatic cells from leukapheresis or smaller volumes of body fluids and human tissues for processing to single cell suspensions
- The recovered cells are variously manipulated: purified, activated, cultured etc
- Most of the products are for autologous use

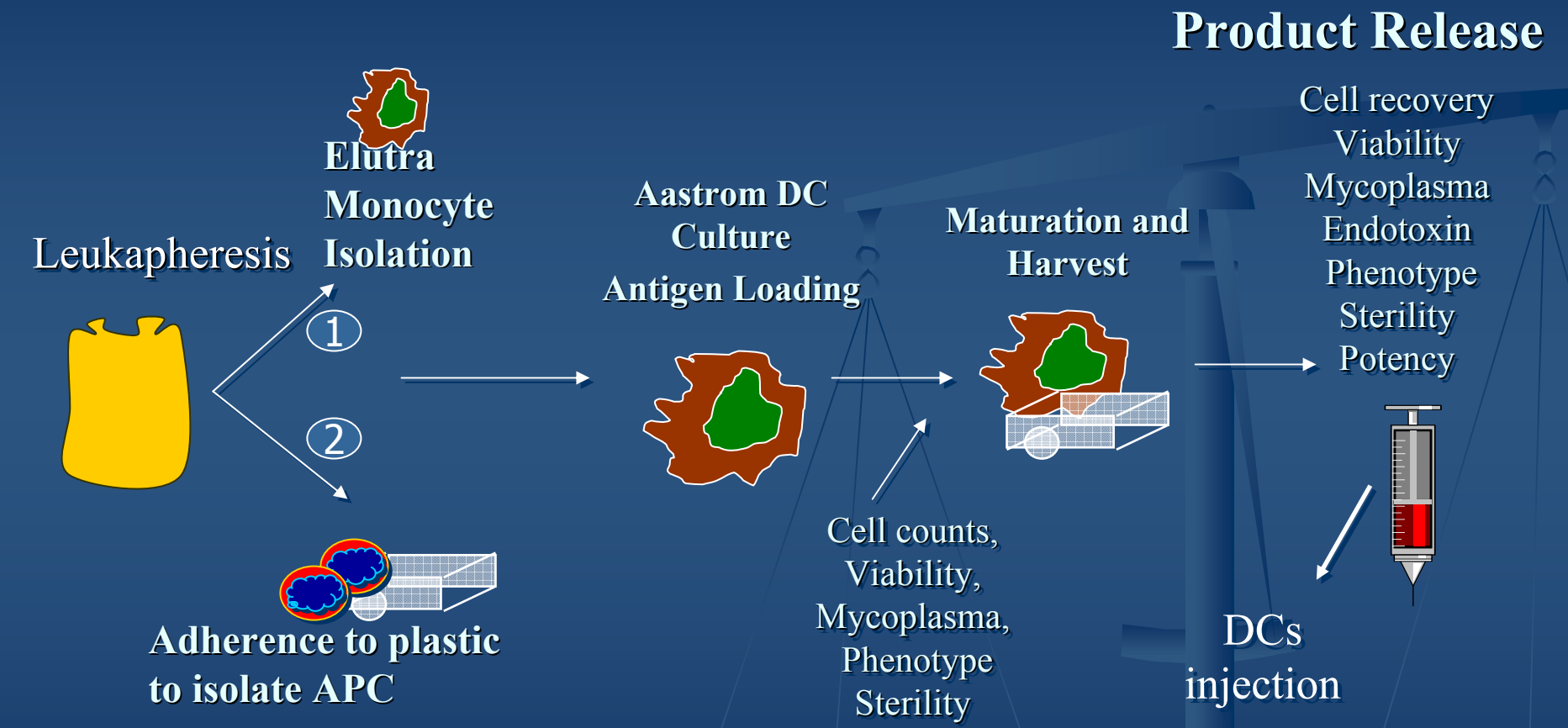
Production Assistance for Cellular Therapies

# Steps associated with the human dendritic cell (DC) production

- Leukapheresis
- Monocyte separation by elutriation (ELUTRA ™ System)
- Culture of monocytes in Aastrom Replicelle closed system in the presence of IL-4 and GM-CSF
- iDC recovery and testing
- DC maturation in cytokines
- Testing of the vaccine (the generated product)
- Release of the vaccine

PACT
Production Assistance for Cellular Therapies

# The production process : human DC




**CLINICAL OUTCOME**

PACT
Production Assistance for Cellular Therapies

# Flow Chart for the implementation of a production process

- IND Approval on file
- Initiate Manufacturing
- Maintain batch records throughout manufacture
- In-process Testing
- Release Testing
- QA/QC Review
- Batch record completed
- Product release for clinical use & shipment to investigator
- Receipt documentation from the investigator (clinical coordinator)
- Infusion Reactions & adverse reactions reported by Investigator to FDA

PACT
Production Assistance for Cellular Therapies

# Product acceptance and Accessioning

Leukapack is the primary source of patient cells.

- Visual inspection of each raw material, check for damage, cells clotting etc.
- Assign CPL unique identification number (UIN)
- Cerner Database assigned ID based on Julian calendar: 06-094-000001
- UIN ID labeling on each container throughout the product tenure at the CPL

# Production and Documentation General Requirements

- Manufacture of all cellular products: in the facility operated as cGMP and based on INDs
- Components: All are specified in the SOPs; COAs on file
- Equipment: Production equipment description and ID are included in the SOP and specified on worksheets
- Procedure: Production steps are specified in the SOPs
- Batch Records: Maintained through all production steps on forms unique to each product
- Documentation of all production steps: retained in a subjects folders
- Folders: Placed and maintained in a secure location within the CPL

Production Assistance for Cellular Therapies

# Production and Documentation cont.

Batch Records

- Records concurrent with performance of each significant step. Accurate, indelible, legible, operator identified. Detailed.
  - In CPL: Patient folders/files are created for each specimen received, entered in log book and assigned a UIN consisting of the access # with a prefix indicating study protocol. Example: EG-06-0011

Production Assistance for Cellular Therapies

# Production and Documentation cont.

Changes / Deviations during production

- Changes in procedure and production process: approved in writing by the director
- Record all departures from the SOP
- Not completed batch products: include explanation of early termination
- Disruptions, difficulties, problems: record and explain
- Records should be maintained in a way that allows the complete history of a product batch to be reviewed before distribution

PACT
Production Assistance for Cellular Therapies

# Production records

- Critical steps recorded on the daily worksheet
- Calculations; data integrity verified by a second technologist
- Signature of the observer/ verifying person

<u>Traceability to primary records of the facility:</u>

Support services: Sterility assays performed by Microbiology lab, Myco/ Endo tests performed by CPL

- Environmental monitoring: particle counts, viable count, humidity, temperature recorded
- Supply and Reagents
- QC results: Viability, Phenotypic characterization prior to release
- All assembled into a file which is unique for each product

# Production control

- All flasks/containers labeled with CPL assigned UIN, batch number and color coded
- QC check on volume; documentation of cell count & record
- Intermediate & final product check & prohibited product release until discrepancy resolved (if any detected)
- Sample (at least 10% of a cell product) & test product before release
- Cross-contamination control: isolation (use one hood per product), scheduling (one patient per room), cleaning (hood and incubator between different products),

PACT
Production Assistance for Cellular Therapies

# Quality Control / Criteria for release

Product qualification: Defined in the IND for human DC

- Recovery: Variable (depends on the donor)
- Viability: normal range (70-95%)
- Product purity: ≥70%
- Endotoxin level: below 5EU/kg of body weight
- Mycoplasma: negative
- Gram Stain negative
- Phenotype/Maturation: CD86+, CD80+, CD83+, CCR7+
- Sterility: free of microbial contamination (available after 14 days)
- Test for potency (not required but recommended)

PACT
Production Assistance for Cellular Therapies

# Cellular Product Release / Delivery Form

Patient Name: _____ Product: _____
CPL No: _____ Date: _____
Protocol: _____ Course/Vaccine: _____
**Cell #:** _____ **Cell viability:** _____

**CAUTION: New Drug Limited by Federal Law to Investigational Use.**
**For Autologous Use Only.**

**Product preparation/labeling by:**_____ **Verification by**_____

initials/date

**Product meets all specified release criteria, release authorized by:**

_____ _____
signature/title date/time

**Product delivered by:**_____ _____
Signature date/time

**Product received by:**_____ _____
Signature date/time

**Product administered by:**

_____ _____
Signature/title date/time

**Warning: Product expires _____ hours from release time.**
**Warning: Advise patient of communicable disease risks. Product final sterility pending.**
**Please fax completed form to CPL 412-624-0264.**

PACT
Production Assistance for Cellular Therapies

# PRODUCT REVIEW FORM

UPCI-CPL
HCC, Suite 1.27, Pittsburgh, PA 15213
Ph: (412) 624-0080

**PRODUCT REVIEW FORM**

CPL Batch # _____ Protocol # _____
Patient Name_____ Vaccine # _____
Sample Received_____
Date/Time Sample Rec'd _____
Comments:
Date for Product Release: _____

I certify that this product has met the release criteria as per the IND filed for the above listed Protocol and the product is acceptable to be released for its intended use.

_____ _____
Director Release Signature Date

PACT
Production Assistance for Cellular Therapies

# Overall Objectives

- **Objective of the regulated production process**
  - Clearly defined and documented production and control procedures to prevent cross-contamination and to ensure that the finished product meets specifications as they are defined I the IND

PACT
Production Assistance for Cellular Therapies