

Benchmarking GTPs

Lizabeth Cardwell, Compliance
Consulting

Karen Edward, Advanced Cell and
Gene Therapy

Good Tissue Practices

- 21 CFR 1271, The Regulation
- Applies to Human cells, tissues or cellular or tissue-based products (HCT/Ps)
- The guidance documents (last slide)
- Registration – Subpart B
- Donor Eligibility – Subpart C
- cGTP – Subpart D

cGTP Core Requirements 1271.150(b)

- Facilities 1271.190
- Environment
1271.195
- Equipment 1271.200
- Supplies & Reagents
1271.210
- Recovery 1271.215
- Process Controls
1271.220
- Labeling 1271.250
- Storage 1271.260
- Receipt & Distribution
1271.265
- Donor Eligibility
Determinations
1271.50, .75, .80, .85

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- Donor Eligibility (Subpart C)
- Recovery (1271.215)
- Tracking (1271.290)
- HCT/P Receipt and Distribution (1271.265)

Donor Eligibility (DE) - Requirements

- Donor Screen + Test = Donor Eligibility
- “Summary of Records” accompanying the HCT/P from recovery to distribution
- Record reports the donor eligible, ineligible, or eligibility incomplete
- Label product accurately
- Segregate storage in cases of donor ineligibility or when DE incomplete

DE - Implementation

- Requires input from collection and clinical groups to create overarching system
 - DE needs to be well documented “upstream”
 - “Summary of Records” form should be generated at the time of collection; accompanies the HCT/P from collection to manufacturing to distribution to recipient; maintain form in medical record of recipient
- Determine who “responsible person” is in your organization determining eligibility, and “urgent medical need”

DE - Implementation (cont.)

- If manufacturing a variety of products consider having one system to support Auto, Allo, URD, BM, etc.
- Create labels from HCT/Ps where donor ineligible, or eligibility incomplete
- Ensure adequate space to physically quarantine of HCT/Ps

Recovery - Requirements

- States in GTPs to recover HCT/Ps in a way that does not cause contamination or cross-contamination during recovery and core GTPs apply, where appropriate
- This means that systems need to be in place in apheresis collection centers, and other establishments where HCT/P procurement takes place addressing GTPs. These areas are subject to inspection.

Recovery - Implementation

- Recovery and processing activities may be performed in same institution
 - If so, both areas must comply with GTPs, consider sharing SOPs and quality systems
 - Many resources (e.g. QA) can be shared
- If recovery activities are performed by another institution you, as the manufacturer, must ensure they are compliant with GTPs; should be spelled out in contract or quality agreement

Tracking - Requirements

- Unique to GTPs in order to facilitate the investigation of suspected or actual transmission of communicable disease from HCT/Ps
- System for tracking from:
 - Donor to the consignee or final disposition
 - Consignee or final disposition to the donor
- Assign distinct ID code
- Document ID code and disposition

Tracking - Implementation

- Controlled system should be in place for assigning product identifiers (lot numbers)
 - Lot number assignment should be under QA control, or verified by 2nd person, and audited periodically
- Create Tracking form that accompanies product from recovery to distribution, could combine with DE “Summary of Records” form

Receipt and Pre-distribution - Requirements

- Incoming HCT/P evaluated for the presence of microorganisms and inspected for damage and contamination
- Pre-established criteria for receipt and acceptance

Receipt and Pre-distribution - Implementation

- Set up a system for accepting HCT/Ps
 - Establish reasonable criteria: temperature, packaging integrity, appearance, etc.
 - Document in HCT/P production record
- If HCT/P doesn't meet criteria, create process for notification and reporting, rejecting or performing further testing etc.

Availability for Distribution - Requirements

- Manufacturing and tracking records must be reviewed to ensure all release criteria are met
- Responsible person performs record review prior to distribution
- Contaminated HCT/Ps only made available under “urgent medical need”

Availability for Distribution - Implementation

- Establish release criteria - verify labeling, sterility testing, other product characterization not in scope of GTPs, but important for GMP products
- Determine who is “responsible person” who conducts HCT/P release
 - Someone independent from manufacturing operations, QA best choice; be creative in small operations
- Determine “responsible person” who can release an HCT/P under “urgent medical need”

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- Facilities (1271.190)
- Environmental Control (1271.195)
- Equipment (1271.200)
- Supplies & Reagents (1271.210)
- Processing and Process Controls (1271.220)

Facility - Requirements

- Prevent contamination, cross-contamination, mix-ups, exposure to communicable disease agents of HCT/Ps
 - Size, construction, location, state of repair
 - Cleaning and sanitation
 - Segregation of operations
 - Procedural or Temporal
 - Procedures and Records

Facilities - Implementation

- Restrict access and implement gowning procedures
- Segregate HCT/Ps in recovery, process, storage and release areas
- Minimize bench top clutter
- Minimize paper use in processing areas
- Store materials in labeled, cleanable storage bins that can be wiped down
- Write cleaning SOPs, train cleaning personnel
- Maintain records of all activities for 3 years

Environmental Control - Requirements

- Temperature and humidity controls
- Ventilation and air filtration controls
- Ensure aseptic processing operations
 - Clean and sanitize
 - Maintain equipment
 - Inspect environmental control system
 - Monitor environmental conditions (microbial)
- Maintain records of environmental control and monitoring

Environmental Monitoring - Implementation

- Determine environment controls to implement – “where appropriate”
 - How closed is your process?
 - How clean is your laboratory?
 - What processing is occurring?
- Engineered or retrofitted cleanroom

Environmental Monitoring - Implementation

- Perform baseline EM
 - Determine most critical areas to monitor
 - Determine sample period for data set
 - Compile and analyze data
 - Make appropriate changes based on analysis
- Set up reasonable EM program
 - Perform viable counts in BSC
 - Set up action and alert levels
 - Define how data will be used
 - sterility investigation
 - process documentation

Equipment Requirements

- Designed, installed, operated in a manner to prevent introduction, transmission or spread of communicable disease.
- Establish inspections, cleaning and maintenance schedules
- Establish calibration schedules
- Maintain records

Equipment Implementation

- Manufacturing Equipment Files (MEF)
 - Unique identifiers
 - Scheduling and tracking of use/calibrations
 - Use available tools
 - Alarm and monitor as appropriate
 - Equipment logs
 - New equipment acquisition and implementation

Supplies & Reagent Requirements

- Verify to specifications
 - In-house or vendor
 - Sterile
 - Verify/validate in-house production
- Maintain records
 - Receipt
 - Use in product

Supplies & Reagent Implementation

- Create specifications
- Receiving inspection SOPs and forms
- Inventory traceability
 - Bill of Materials
 - Material history form

Processing and Process Controls - Requirements

- Process must not cause contamination or cross-contamination during processing
- Process must prevent introduction of contaminating agents
 - No pooling from 2 or more donors
 - Sampling for release test (representative)
 - Quarantine during testing
- Validate, verify or qualify methods

Process Controls - Implementation

➤ Establish methods

- Processing record or Batch Record
- SOPs for equipment use
- Test methods for sampling, test or outsource
- Gowning/gloving for specific operations

➤ Validate methods if unable to verify

- Prior to implementation
- Change to established methods

Process Controls - Implementation

- Document product changeover activities
 - Remove previously used materials/supplies
 - Clean critical equipment between HCT/Ps
 - Link records to product identifier (lot #)
- Perform sterility testing
 - Fresh product
 - Frozen product

Process Controls - Implementation

- Processing (Batch) Records
- SOPs
 - Reproducibility
 - Training
 - Communication
- Document Control Systems
 - Change control
 - Distribution control & availability

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- Adverse Reactions
- Deviations
- Complaints

Adverse Reaction Reporting Requirements

- Involving communicable disease if,
 - Fatal, or
 - Life-threatening, or
 - Resulting in permanent impairment of a body function, or damage to body structure; or
 - Necessitates medical or surgical intervention, including hospitalization
- Reported to FDA using Form 3500-A within 15 calendar days

HCT/P Deviations - Requirements

- For distributed HCT/Ps related to a manufacturing step
- You must report any such HCT/P deviation relating to the core GTPs
 - Relates the prevention of communicable disease transmission or HCT/P contamination, or
 - Deviation is an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to contamination
- Reported using FDA form 3486 within 45 days

Complaints - Requirements

- Maintain SOPs addressing complaints related to core GTPs
- Maintain a record of complaints
- Review, evaluate, investigate complaints

Reporting and Complaints - Implementation

- Important to set up systems for complaints and reporting
- This is where a good QA unit comes in handy; all activities should be under QA purview
- Determine who in your institution decides what adverse reactions and deviations are reportable; should consult with medical director

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References

- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues and Cellular and Tissue-based Products. February 2007.
- Guidance for Industry: Compliance with 21 CFR Part 1271.150(c)(1) – Manufacturing Arrangements. September 2006.
- 21 CFR Part 1271 Human Cells, Tissues, and Cellular and Tissue-based Products. May 2005.
- Guidance for Reviewers: Instructions and Template for CMC Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications. August 2003
- Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy. March 1998.
- Guidance for the Submission of CMC information and Establishment Description for Autologous Somatic Cell Therapy Products. January 1997.
- www.fda.gov