

**DUKE****DOCUMENT NUMBER:** COMM-QA-078**DOCUMENT TITLE:**

Good Tissue Practice (GTP)

DOCUMENT NOTES:**Document Information****Revision:** 03**Vault:** COMM-QA-rel**Status:** Release**Document Type:** COMM-QA**Date Information****Creation Date:** 20 Feb 2024**Release Date:** 31 Jan 2025**Effective Date:** 31 Jan 2025**Expiration Date:****Control Information****Author:** CAC220**Owner:** RB232**Previous Number:** COMM-QA-078 Rev 02**Change Number:** COMM-CCR-246

Good Tissue Practice (GTP)

21 CFR 1271: PART 1271— HUMAN CELLS, TISSUES, AND
CELLULAR AND TISSUE-BASED PRODUCTS (HCT/PS)

What is Good Tissue Practice?

- GTP refers to the Good Tissue Practice regulations enforced by the US Food and Drug Administration (FDA) & effective 5/25/2005.
- Written to be compatible with GMP (Good Manufacturing Practices) while adding additional requirements specific to transmission of communicable disease and contamination of tissue during processing.

What is Good Tissue Practice? (Continue)

- GTP rules are specific to tissue which has not been significantly modified. Such as stem cells for transplantation.
- Significant modification of tissue function or characteristics will be considered either a medical device or drug product.

A Few Differences / Similarities

Between cGMP and cGTP?

	cGMP	cGTP
Must have a quality unit/program	✓	✓
Personnel must be adequate, trained, sufficient	✓	✓
Facilities must be of adequate: size, location, construction	✓	✓
Equipment must be of appropriate design and maintenance for intended use	✓	✓
Governs the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps		✓
Governs the methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to ensure that such drug meets the requirements of the FD&C Act.	✓	

Who interprets and enforces GTP?

- The FDA, Specifically CBER (Center for Biologics Evaluation and Research).
- Inspections generally occur every 2 years but may occur at any time.
- Inspections are unannounced, with exception of pre-approval inspection.

Core cGTP Requirements

- Defined in 21 CFR 1271.150(b)-Guidelines that aim to prevent the introduction, transmission or spread of communicable diseases.
 - facilities (§ 1271.190(a) and (b))
 - environmental control (§ 1271.195(a))
 - equipment (§ 1271.200(a))
 - supplies and reagents (§ 1271.210(a) and (b))
 - recovery (§ 1271.215)
 - processing and process controls (§ 1271.220)
 - labeling controls (§ 1271.250(a) and (b))
 - storage (§1271.260(a) through (d))
 - receipt, predistribution shipment, and distribution of an HCT/P (§ 1271.265(a) through (d)); and
 - donor eligibility determinations, donor screening, and donor testing (§§ 1271.50, 1271.75, 1271.80, and 1271.85)

Other cGTP Requirements

- Include but are not limited to (21 CFR 127.145-.320):
 - Personnel (§1271.170)
 - Procedures (§1271.180)
 - Quality program
 - Labeling controls (§1271.250)
 - Process validation (§1271.230)
 - Tracking (§1271.290)
 - Complaints (§1271.320)
 - Records (§1271.270)

Personnel

- §1271.170 (a) General: Must have sufficient, competent and appropriately trained personnel to ensure compliance.
- §1271.170 (b) Competent performance of functions: Must determine the qualifications needed to perform manufacturing functions in your establishment(s) and should reflect these qualifications in a job/position description.
- §1271.170 (c) Training: Must train all personnel, and re-train as necessary, to perform their assigned responsibilities adequately.

Procedures

- Must have procedures appropriate to meet cGTP requirements for all manufacturing steps and design these procedures to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable diseases.
- Procedures must be readily available to personnel in the area where operations are performed. However, procedures do not have to be physically maintained in the area of operation if such availability is impractical.

Procedures (Continues)

- §1271.180 (a) General: Must establish and maintain procedures appropriate to meet cGTP requirements for all steps that are performed during manufacture of HCT/Ps.
- §1271.180 (a) General: Must design procedures to prevent introduction, transmission, or spread of communicable diseases.
- §12.71.180 (b) Review and approval: Procedures must be reviewed by a responsible person prior to implementation.
- §1271.180 (c) Availability: Procedures must be readily available to staff/employees.

Quality Unit

- The Quality Unit is responsible for ensuring adherence to cGTP requirements by:
 - Ensuring procedures exist for receiving, investigating, evaluating, and documenting information relating to cGTP requirements, complaints and contamination.
 - Performing audits to ensure compliance with cGTP and associated appropriate corrective actions relating to cGTP regulations.
 - Investigating and documenting HCT/P deviations (e.g., CAPA audits, re-audits, deviations from procedure, monitoring).
 - Relating to the consignee recall and quarantine information, and FDA reporting.
 - Provisions on risk assessment and appropriate follow-up (recall, FDA reporting).
 - Training and education.
 - Validation of computer software for performance.

Buildings and Facilities

- §1271.190 – (a) General: Must be of suitable size, construction, and location to prevent contamination and to ensure orderly handling of HCT/Ps without mix-ups.
- §1271.190 (a) General: Must maintain the facility in a good state of repair with suitable lighting, ventilation, plumbing, drainage, and sanitation to prevent the introduction, transmission, or spread of disease.
- §1271.190 (c) Operations: Must divide a facility used in the manufacture of HCT/Ps into separate or defined areas of adequate size for each operation to prevent improper labeling, mix-ups, contamination, cross-contamination, and accidental exposure to communicable disease agents.
- §1271.160 (b5) Must have specific environmental control and monitoring requirements.
- §1271.190 – (d2) Procedures and records: Must document, and maintain records of, all cleaning and sanitation activities.

Environmental Control

- Temperature and humidity controlled via ventilation and air filtration.
- Cleaning and disinfecting of rooms and equipment to ensure aseptic operations.
- Maintenance of equipment used to control aseptic conditions.

Equipment

- §1271.200 (a) General: Equipment must be of appropriate design for its use and must be suitably located and installed to facilitate operations, including cleaning and maintenance.
- §1271.200 (a) General: Any automated, mechanical, electronic, or other equipment used for inspection, measuring, or testing must be capable of producing valid results.
- §1271.200 (b) Procedures and Schedules: Must establish and maintain procedures for cleaning, sanitizing, and maintaining equipment to prevent malfunctions, contamination or cross-contamination.

Equipment (Continue)

- §1271.200 (c) Calibration of Equipment: Must routinely calibrate all automated, mechanical, electronic, or other equipment used for inspection, measuring, and testing.
- §1271.200 (e) Records: You must document and maintain records of all equipment maintenance, cleaning, sanitizing, calibration, and other activities performed.

Supplies & Reagents

- §1271.210 (a) Verification: Must not use supplies and reagents until they have been verified to meet specifications.
- §1271.210 (b) Reagents: Reagents used in processing and preservation of HCT/PS must be sterile.
- §1271.210 (c) In-house reagents: Must validate and/or verify the processes used for production of in-house reagents.
- §1271.210 (d1) Records: Must maintain records of the receipt, including the type, quantity, manufacturer, lot number, date of receipt, and expiration dates.
- §1271.210 (d2) Records: Must keep records certificates of analysis and records supplies & reagents used in the manufacture.

Recovery

- § 1271.215 Establishment that recover HCT/Ps, must do so in a way that does not cause contamination or cross-contamination during recovery.

Processing/Process Control

- §1271.220 (a) General: Must recover and process each HCT/P in a way that does not cause contamination or cross-contamination.
- §1271.220 (b) Pooling: Human cells or tissue from two or more donors must not be pooled during manufacturing (cannot be combined from more than one donor).
- Any change to a process must be verified or validated and approved before implementation by a responsible person.
- Any changes to a process must be communicated to employees.

Labeling Controls

- §1271.250 (a): Must establish and maintain procedures to control the labeling of HCT/Ps and must design these procedures to ensure proper HCT/P identification and to prevent mix-ups.
- §1271.250 (b): Must verify label accuracy, legibility, and integrity.
- §1271.50 (c): Labeling must include:
 - Expiration Date
 - Storage temperature
 - Type of HCT/P
 - Any applicable Warnings
 - Name & Address of Manufacturer/Establishment
 - Instructions for use

Storage

- §1271.260 (a) Control of storage areas: Storage areas/stock rooms must be controlled to prevent mix-ups, contamination, and cross-contamination of HCT/Ps, supplies, and reagents.
- §1271.260 (b) Appropriate temperature should be sufficient to prevent conditions that could increase the risk of contamination of each HCT/P stored.
- §1271.260 (c) Expiration dates based on HCT/P type, processing, including the method of preservation, storage conditions, and packaging.
- §1271.260 (e) Acceptable temperature limits: Manufacturer / Establishment must establish acceptable storage conditions of HCT/Ps at each step of the manufacturing process to inhibit the growth of infectious agents and must document storage conditions.

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Receipt & Pre-Distribution

- §1271.265 (a) Receipt: Must evaluate each incoming HCT/P for the presence and significance of microorganisms and inspect for damage and contamination.
- §1271.265 (a) Receipt: Must determine whether to accept, reject, or place in quarantine each incoming HCT/P, based upon pre-established criteria designed to prevent communicable disease transmission.
- §1271.265 (b) Predistribution shipment: Shipments prior to distribution must ensure prevention of disease transmission.

Distribution

- §1271.265 (e) Procedures: Must establish and maintain procedures for distribution and associated release criteria.
- §1271.265 (c1) Availability for distribution: Prior to distribution must review HCT/P manufacturing/batch records to verify and document that release criteria have been met.
- §1271.265 (c2) Availability for distribution: Must not distribute HCT/P that is quarantined, contaminated, or recovered from a donor who has been determined to be ineligible.
- §1271.265 (d) Packaging and shipping: Packaging and shipping containers must be designed and constructed to protect the HCT/P from contamination.

Records

- §1271.270 (a) General: Must maintain records concurrently with the performance of each step required by the cGTPs.
- §1271.270 (a) General: All records must be accurate, indelible, and legible and must identify the person performing the work and the dates of the various entries, and must be as detailed as necessary to provide a complete history of the work performed.
- §1271.270 (b) Records management system: Must establish and maintain a records management system that allows for review of the HCT/Ps manufacturing history before making it available for distribution.

Records (Continue)

- §1271.270 (c) Method of retention: May maintain required records electronically, as original paper records, or as true copies. Electronic records must be backed up.
- §1271.270 (d) Length of retention: Must retain all records for 10 years after their creation, unless stated otherwise and retain the records pertaining to a particular HCT/P at least 10 years after the date of its administration.
- §1271.270 (d) Contract and Agreements: Contracts and agreements must be kept.

Tracking

- §1271.290 (b) Records management system: Must establish and maintain a system that enables the tracking of all HCT/Ps from donor to the consignee or final disposition and from consignee or final disposition to the donor.
- §1271.290 (c) Distinct identification code: Must ensure that each HCT/P is assigned and labeled with a distinct identification code.

Complaints

- §1271.320 (a) Procedures: Must establish and maintain procedures for the review, evaluation, and documentation of complaints relating to cGTP.
- A complaint is any written, oral, or electronic communication about a distributed HCT/P that alleges the following:
 - That the HCT/P has transmitted or may have transmitted a communicable disease to the recipient of the HCT/P.
 - Any other problem with an HCT/P relating to the potential for transmission of communicable disease, such as the failure to comply with CGTP requirements.

Complaints (Continue)

- §1271.320 (b) Complaint file: Must maintain a record of complaints that you receive in a file designated for complaints that is available for review and copying upon request from FDA.
- §1271.320 (c) Review and revaluation of complaints: Must determine if the complaint is related to an HCT/P deviation or to an adverse reaction, and whether an Adverse Reaction Report to the FDA is required.
- §1271.320 (c) Review and revaluation of complaints: If not reportable to FDA, must still perform a review and evaluation to determine whether an investigation is necessary.
- §1271.320 (c) Review and revaluation of complaints: If no investigation is made, must maintain a record that includes the reason no investigation was made, and the name of the individual(s) responsible for the decision not to investigate.

Return to Inventory

- Must establish and maintain procedures to determine if an HCT/P that is returned to your establishment is suitable to be returned to inventory.
- It is acceptable not to permit return to inventory but this should be made clear to the consignee (person/established that received the HCT/P).

QA Contacts

- Please feel free to reach out to QSU if you have any questions about this presentation.
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Signature Manifest

Document Number: COMM-QA-078**Revision:** 03**Title:** Good Tissue Practice (GTP)**Effective Date:** 31 Jan 2025

All dates and times are in Eastern Time.

COMM-QA-078 Good Tissue Practice (GTP)

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