Cellular Therapy Compliance Guide

How to ensure that your organization meets CGMP and CGTP requirements

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Introduction

In the last decade, the field of cellular therapy has made significant advancements. While this innovative branch of medicine is poised for major breakthroughs that could revolutionize many types of patient care, sorting through the extensive list of regulations for current good manufacturing practices (CGMP) and current good tissue practices (CGTP) can seem overwhelming. However, failure to meet these requirements could bring progress to a standstill.

To help you avoid problems, we've developed this CGMP and CGTP overview. We've also included with it an introduction to automated solutions that are tailor-made to easily manage these regulations. Browse this resource so you can keep your facilities fully operational and progressing toward your goals.

Safe supplies

Anyone involved in any step of the process of manufacturing human cells, tissues, and cellular and tissue-based products (HCT/Ps) must comply with CGMP and CGTP standards. These requirements were established by the U.S. Food and Drug Administration (FDA), under the direction of the Center for Biologics Evaluation and Research (CBER), to prevent the introduction, transmission or spread of communicable disease.

FDA inspections can occur at any time with no prior notice.

Meeting the CGMP and CGTP standards at all times is obviously critical, in part because of FDA inspections—which can occur at any time with no prior notice.[1] In addition, adherence to these guidelines ensures that the products you provide are safe and effective and, therefore, mitigates risk at all levels.

Minimum manufacturing requirements

The standards for manufacturing processes, as they relate to the preparation of drug therapies, were initially established in the 1938 Food, Drug and Cosmetics Act. With the introduction of biological products for medical treatments, additional regulations established the "minimum current good manufacturing practice for preparation of drug products ... for administration to humans or animals."[2] The details of these requirements are established in Code of Federal Regulations (CFR) Title 21 part 606 for blood and blood components.[3]

Currently, the regulations fall into seven categories—organization and personnel, plant and facilities, equipment, production and process controls, additional labeling standards, lab controls, and records and reports.

Organization and personnel

Everyone who collects, processes, tests, stores and/or distributes blood or blood components must operate in a manner that will ensure that the finished product is safe, pure, potent, correctly identified and effective for its intended purpose. Therefore, current

guidelines require that personnel:

- Be staffed in appropriate numbers to get the job done
- Have sufficient educational background, experience and training, including professional training such as CGMP training, relevant to their functions

1. Plant and facilities

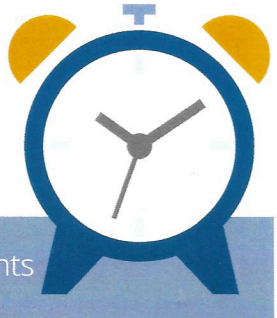
Facility needs vary according to the types of procedures performed within them. However, all facilities must be clean and orderly and must have been designed to facilitate adequate cleaning, maintenance and operations. In addition, facilities must have:

- Specifically defined areas in which to perform procedures
- Sufficient space to perform procedures privately and with minimal risk of contamination
- Adequate lighting and ventilation

2. Equipment, supplies and reagents

All equipment used for blood and blood components must be properly cleaned and maintained, and supplies and reagents must be stored so that they are safe and sanitary. And on a regularly scheduled basis, the timing of which can be monitored by an automated system, be sure to:

- Observe equipment to ensure that it is in good working order
- Standardize and calibrate equipment
- Test samples of reagents and solutions to verify their continued ability to function as intended



Many of these requirements demand action according to a regular, predetermined schedule. A foolproof, automated reminder system will ensure you keep your schedule without fail.

3. Production and process controls

Standard operating procedures (SOP) must be written and must include all the steps to be followed to perform each particular function. SOPs must be updated as necessary and easily accessible to the personnel performing the functions in the specific areas where the work is done. The management and accessibility of these SOPs can be cumbersome, so electronic systems are highly recommended.

These are some of the many functions that need to be addressed with SOPs:

- Schedules and procedures for maintaining and calibrating equipment
- Criteria for determining donor suitability
- Methods for ensuring sterile collection
- Methods for relating products to donors
- Procedures for collecting and storing blood
- Procedures for preparing products
- Tests performed during manufacturing
- Methods for labeling, including established safeguards to prevent errors
- Procedures for adverse reactions

4. Additional labeling standards

These guidelines are intended to facilitate uniform container labeling so that contents can be accurately identified. Labels for blood and blood components must include the following information:

- Proper name of the product along with any modifiers and attributes
- Facility information and, when applicable, manufacturer's license number
- Donor numbers, lot numbers or pool numbers

5. Laboratory controls

Manufacturers of blood and blood components must establish procedures to ensure that products are safe, pure and effective. Manufacturers must also follow procedures to monitor the accuracy of lab tests and instruments.

6. Records and reports

The labor-intensive work of documenting every step in the manufacturing process as it happens, as well as reports of product deviations, is required, but a reliable software solution can manage the tasks with ease. Records must:

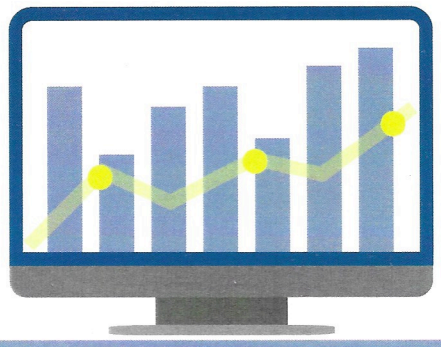
- Be legible and indelible
- Identify the staff members performing the tasks
- Include test results and interpretations of results
- Provide a complete work history
- Include lot numbers and records for donors, processing, storage and distribution, and quality controls

Minimum tissue practices

From a regulatory perspective, HCT/Ps are defined as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient."[4] The use of some of these products was not covered under previous regulations, so CFR Title 21 Part 1271 was established to ensure proper handling, so no infectious materials are obtained and no contamination occurs during processing in order to prevent the introduction, transmission and spread of communicable diseases by HCT/Ps.[5] Current good tissue practices are outlined in Subpart D.[6]

Quality program

Current regulations for tissue practices address every step in the process of manufacturing HCT/Ps. Ten requirements are considered "core" and relate



Periodic quality audits are necessary to verify that your HCT/P manufacturing processes are in compliance and functioning as intended. Therefore, use of a software system with integrated audit features can greatly benefit quality assurance efforts.

to facilities; environmental control and monitoring; equipment; supplies and reagents; recovery; processing and process controls; labeling; storage; receipt, predistribution shipment and distribution; and donor eligibility.

So a first step in complying with CGTP is to establish a quality program—addressing all of these core requirements—that will "prevent, detect and correct deficiencies that may lead to circumstances that increase the risk of introduction, transmission or spread of communicable diseases."[7] The program must be relevant to the specific HCT/Ps manufactured and steps performed in the process and should ensure that organizations have a comprehensive process for manufacturing and tracking HCT/Ps in accordance with CFR Title 21 Part 1271.

Quality programs must:

- Address all procedural functions relevant to the core requirements
- Include periodic quality audits that are documented and independently inspected
- Ensure that computer software, if relied upon to meet core CGTP requirements, is validated for its intended use prior to implementation

Core requirements

Ten core requirements form the foundation of the CGTP regulations, and manufacturers are responsible for adhering to all requirements applicable to the processes performed, including those beyond the scope of the core group.

1. Facilities

Structures used for manufacturing HCT/Ps must be constructed, sized and located so as to ensure that HCT/Ps are not contaminated and that products can be handled in an orderly manner to prevent mix-ups. Facilities must also:

- Be regularly maintained and in good repair
- Have appropriate lighting, ventilation, plumbing, drainage and access to sinks and toilets
- Have separately defined areas for each operation or have other systems to avoid contamination and errors in labeling

2. Environmental control and monitoring

Any environmental condition that could cause or result in contamination must be controlled, and inspections must be performed to verify that controls are functioning as intended. In addition, control systems and inspection activities must be monitored. Where appropriate, you must maintain:

- Temperature and humidity controls
- Ventilation and air filtration
- Clean and disinfected rooms and equipment

3. Equipment

All equipment must be used according to its intended purpose and must be located to facilitate proper functioning, cleaning and maintenance. It must also be able to produce valid results. To care for your equipment according to CGTP specifications, you must:

- Maintain usage records for each piece of equipment, including the identification of each HCT/P manufactured with that equipment
- Establish and adhere to schedules for cleaning, sanitizing, calibrating and maintenance
- Routinely inspect equipment to ensure that it meets cleanliness, sanitation, calibration and maintenance requirements
- Document your equipment care activities, and post near—or make readily available—recent equipment inspection, maintenance and cleaning actions

4. Supplies and reagents

Only supplies and reagents that have been verified—either by your staff or by the vendor—to meet specifications can be used, and reagents must be sterile when appropriate. In addition, accurate records (ideally those that are quickly searchable via an electronic system) are required for:

- Your receipt of supplies and reagents—include type, quantity, manufacturer, lot number, date of receipt, and expiration date

- The verification of each supply or reagent—either test results or certificates of analysis from vendors
- The lots of supplies or reagents used in the process of manufacturing each HCT/P

5. Recovery

If your business recovers HCT/Ps, you must do so in a way that does not cause contamination of any kind.

6. Processing and process controls

If your business processes HCT/Ps, you must do so in a way that does not cause contamination. And you must keep cells and tissues from each donor separate during the manufacturing process. Moreover, you must:

- Ensure that in-process controls are met and that each HCT/P in process is controlled until inspection and/or testing is complete
- Ensure that sampling of the in-process HCT/Ps is representative
- Verify processes in your establishment, including those that are published and validated

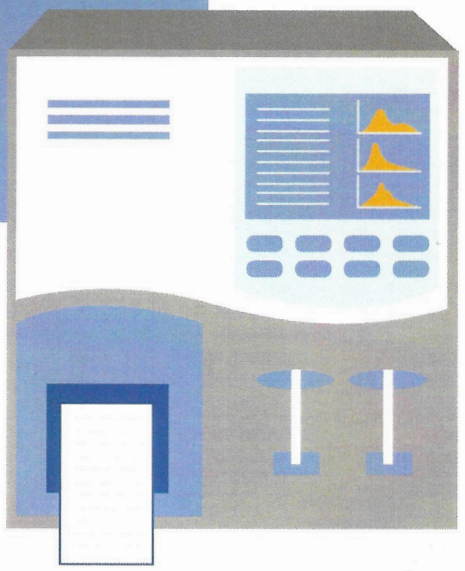
7. Labeling controls

Proper identification of HCT/Ps is critical, so this core CGTP requirement means that manufacturers must establish and maintain systems to guarantee that labels are always accurate. In addition:

- The established systems must include verification of accuracy, legibility and integrity
- HCT/Ps made available for distribution must be accompanied by documentation of donor eligibility determinations

Due to the critical nature of this good tissue practice, automation of this process is recommended because it allows manufacturers to reliably generate labels and track histories. Therefore, patient safety is enhanced, labeling compliance is proven and risk is mitigated.

If your critical equipment, such as hematology analyzers and flow cytometers, can communicate with you via your software application, manual data entry (along with potential for error) is significantly reduced.



8. Storage

All storage areas and supply rooms must be controlled to prevent mix-ups, contamination and improper distribution. Corrective actions must be taken and documented if conditions fail to be met.

HCT/Ps must be stored at appropriate temperatures and within established temperature limits at every step of the manufacturing process. Storage temperatures must be recorded, maintained and periodically reviewed to ensure that they have been, at all times, within acceptable limits.

Expiration dates, when relevant, must be assigned to each HCT/P according to:

- Type of HCT/P
- Method of preservation and other processing
- Storage conditions
- Packaging

9. Receipt, predistribution shipment, and distribution

This core good tissue practice requires that HCT/P manufacturers manage the chain of custody from receipt to implantation. At every step in the process, documentation is necessary to ensure that all products are safe and able to be utilized in patient care.

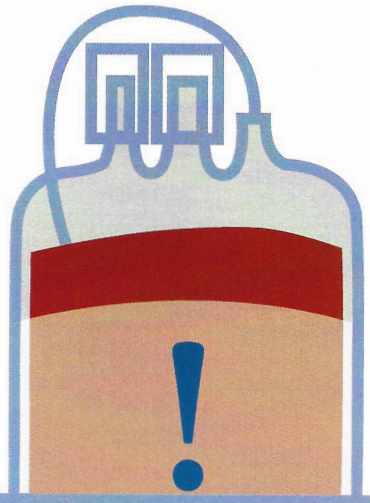
The first step in the process is to evaluate and inspect every incoming HCT/P to determine if it should be accepted, rejected or placed in quarantine. The process is based on predetermined criteria to prevent the transmission of communicable disease.

Before accepted HCT/Ps can be distributed, manufacturing and tracking records must be reviewed. Based on that review, manufacturers must verify and document that the HCT/Ps are suitable for distribution. If items are to be shipped prior to this determination, the items may need to be shipped in quarantine. And products shipped must be protected from contamination in transit.

For all of these actions, including the suitability to return to inventory when applicable, procedures must be established, maintained and documented. Documentation must include:

- Identification of every HCT/P and the establishments that supplied them
- Actions taken and the results of each
- Dates of actions
- Quantity of HCT/Ps on which actions were performed
- Final disposition of HCT/Ps

Managing this process without the reliable assistance of automation is incredibly challenging and has significant potential for risk. However, powerful software applications are available to monitor and report on the entire chain of custody, including post-procedure outcomes.



Errors in labeling could be disastrous, but an electronic system can manage the details and enable you to reliably track your products at all times.

10. Donor eligibility determinations

Potential donors of cells and tissues must be screened and tested for communicable diseases and disease agents to ensure that donated products are safe. Once donors are confirmed, each donated HCT/P must, at all times, be accompanied by:

- A distinct identification code attached to the container that relates the product to the donor and to all related records
- A statement of eligibility
- A summary of the records used to determine eligibility along with test results and a statement that the testing was performed by an appropriately certified lab

Manufacturers must also maintain, for at least 10 years, accurate records that are indelible and legible and can be made available for authorized inspection. These records must include:

- Results and interpretations of tests performed as well as the testing labs' contact information
- Donor-eligibility determinations along with the dates of determination and the names of those who made the determinations

Management tools

Comprehending all of the CGMP and CGTP guidelines, not to mention adhering to them, can be overwhelming. Following established schedules, documenting actions, reliably maintaining records and tracking everything is a chore of monumental proportions, and errors at any point in the system could be disastrous.

Therefore, software applications that manage these functions for you are wise investments. Look for comprehensive systems that can maintain patient, product, clinician and donor information all in one place, so your data is accessible, and your inventory is easily tracked and managed. In addition, seek solutions that can easily generate the reports and other documentation you'll need on an ongoing basis.

With automated solutions in place, your cellular therapy program can stay on the cutting edge and continue to provide revolutionary treatments to patients in need.

References

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2. Code of Federal Regulations Title 21 Part 211 www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=211&showFR=1

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4. Code of Federal Regulations Title 21 Part 1271.3 www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=1271.3

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7. Code of Federal Regulations Title 21 Part 1271.160 www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=1271.160

About Mediware®

Mediware is the leading expert in software solutions for cellular therapy organizations.

Our Transtem™ system was designed by industry professionals to provide a comprehensive solution for cell therapy labs, cord blood banks, transplant centers and academic medical centers. It provides complete chain of custody management, so your facility can easily conform to federal requirements for CGMP and CGTP while also increasing quality and efficiency.

For more information about customized solutions for cellular therapy, go to www.mediware.com/CT.

Our thanks to Jonathan Wofford, product manager for Transtem, for his help in developing this white paper. Jonathan spent more than a decade as bioinformatics lead for a major cord blood bank and blood and marrow transplant program in St. Louis and has extensive experience in hematopoietic stem cell transplant and cellular therapy.

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