#253

Current Good Manufacturing Practice for Animal Cells, Tissues, and Cell- and Tissue-Based Products

Guidance for Industry

Submit comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-2021-D-0399.

For further information regarding this document, contact AskCVM@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or http://www.regulations.gov.

U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

Current Good Manufacturing Practice for Animal Cells, Tissues, and Cell- and Tissue-Based Products

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA's Center for Veterinary Medicine (CVM) is issuing this guidance to provide establishments that manufacture animal cells, tissues, and cell- and tissue-based products (ACTPs) with recommendations for meeting current good manufacturing practice (CGMP) requirements. All new animal drugs, including ACTPs, must be manufactured in accordance with CGMP to ensure that such drugs meet the requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as to safety, and have the identity, strength, quality, and purity characteristics which they purport to or are represented to possess.[1]

There are both statutory and regulatory requirements for CGMP. The CGMP statutory requirements are found in section 501(a)(2)(B) of the FD&C Act. The CGMP regulatory requirements are found in Title 21 of the Code of Federal Regulations, parts 210 and 211 (21 CFR parts 210 and 211).

FDA recognizes that the manufacture of ACTPs presents unique considerations for complying with regulatory CGMP and that these CGMP regulations do not specifically or fully address all aspects of the manufacture of ACTPs, including early stages of the ACTP manufacturing process. This document is specific to ACTPs to help establishments that manufacture ACTPs meet statutory and applicable regulatory CGMP. New animal drugs not manufactured in conformity with statutory and regulatory CGMP are adulterated under the relevant provisions of the FD&C Act.

In this guidance, we address the methods, facilities, and controls used for manufacturing ACTPs, including steps in recovery, processing, storage, labeling, packaging, and distribution. The recommendations in this document should be applied to consistently produce quality ACTPs and to ensure that ACTPs are not contaminated and do not become contaminated during manufacturing. Generally, when we refer to CGMP in this document, we are referring either to statutory CGMP including those ACTP-specific recommendations provided in this document for meeting statutory CGMP, or applicable regulatory CGMP, or both.

[1] See section 501(a)(2)(B) of the FD&C Act [21 U.S.C. § 351(a)(2)(B)]

Each individual manufacturing process may require unique considerations to preserve quality and prevent contamination of an ACTP. For this reason, many of the recommendations provided in this guidance are qualified by "where appropriate." A recommendation or other method is appropriate if it does not result in contamination of the ACTP, in compromised quality of the ACTP, or in the inability to carry out any necessary corrective action(s).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. DEFINITIONS

The following are definitions for terms used in this guidance.

Animal cells, tissues, and cell- and tissue-based products (ACTPs) mean those articles containing, consisting of, or derived from cells or tissues that are intended for implantation, transplantation, infusion, transfer, or other means of administration to an animal recipient. In this guidance, the term ACTP refers only to those products subject to regulation under the FD&C Act. ACTPs include cell-based products and animal stem cell-based products as defined in Guidance for Industry (GFI) #218, "Cell-Based Products for Animal Use" (July 2015).[2]

Establishment means a place of business under one management, and at one general physical location, that engages in the manufacture of ACTPs. This could include large and small animal facilities or veterinary hospitals where tissues are recovered from animals or other tissue recovery facilities, processing facilities, distributors, packaging facilities, contract testing laboratories, etc. The term also includes any individual, partnership, corporation, association, or other legal entity engaged in the manufacture of ACTPs, and facilities that engage in contract manufacturing services for a manufacturer of ACTPs. An establishment may be a facility that manufactures an ACTP. Alternately, an establishment might be the corporate headquarters of an entity that has facilities in multiple locations that perform the manufacturing steps to produce the ACTP.

Facility means the physical location in which manufacturing steps are performed.

In-process control means controls to ensure the identity, strength, quality, and purity of the ACTP during the production process.

Manufacturing step means one of the stages involved in a manufacturing process (e.g., passaging of cells, filling of vials, etc.).

[2] https://www.fda.gov/media/88925/download

Predistribution shipment means the conveyance or shipment of an ACTP within your establishment or between establishments before it has met its product release criteria (i.e., it is not released for distribution).

Process control means controls put in place to address variability and to ensure product quality. Controls can consist of material analysis and equipment monitoring at significant processing points.

Processing means any activity performed on an ACTP, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution. Processing includes activities such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage.

Quarantine of ACTP means the storage or identification of an ACTP, to prevent improper release, in a physically separate area clearly identified for such use or through use of other procedures, such as automated designation.

Recovery means obtaining from a donor (live or deceased) cells or tissues that are intended for use in implantation, transplantation, infusion, transfer, or other means of administration to an animal recipient.

Validation means confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled (e.g., a process consistently produces an ACTP that meets its predetermined specifications).

Validated methods means analytical methods confirmed to be suitable for their intended use through parameters such as accuracy, precision, robustness, linearity, range, specificity, limit of quantitation, and limit of detection.

Verification means confirmation by examination and provision of objective evidence that specific requirements have been fulfilled.

You means the establishment that performs a manufacturing step or the establishment that performs a manufacturing step under contract, agreement, or other arrangement for another establishment.

III. PURPOSE AND SCOPE

This guidance is intended for any establishment that performs a manufacturing step for production of an ACTP, including autologous, allogeneic, and xenogeneic ACTPs. Preserving cellular function and integrity, ensuring consistency of the process and product, and preventing contamination are critical aspects of manufacturing ACTPs. The safety, effectiveness, and quality of an ACTP are dependent on appropriate control of the manufacturing process.

Establishments performing any part of a manufacturing process or any establishment utilized under a contract, agreement, or other arrangement for performing any step in the process must comply with applicable statutory and regulatory CGMP.

We are providing these recommendations to help ensure that establishments are in compliance with statutory and regulatory CGMP. In some cases, regulatory CGMP does not fully or specifically address those aspects of ACTP manufacturing necessary to ensure the safety, identity, strength, quality, and purity of the product. For example, regulatory CGMP does not address critical items that we consider necessary to meet statutory CGMP such as donor eligibility or recovery of ACTPs.

Establishments performing part of a manufacturing process must comply with CGMP that are appropriate for the manufacturing steps they perform with the ACTP. Prior to entering into any contract, agreement, or other arrangement with another establishment, the ACTP sponsor should ensure that the establishment is following the recommendations for meeting CGMP in this document or is otherwise ensuring that the manufacture, processing, packing, or holding of ACTPs complies with CGMP.

A. Category A Establishments

Establishments that manufacture finished ACTPs, other than Type II finished ACTPs,[3] are Category A establishments.

Statutory and regulatory CGMP are applicable to Category A establishments. While regulatory CGMP and the recommendations in this guidance often address similar manufacturing practices, regulatory CGMP does not fully or specifically address all aspects of ACTP manufacturing. The bulleted list below contains aspects of ACTP manufacturing addressed in this and a related guidance[4] that are not partly or fully covered by a corresponding regulatory CGMP and for which an ACTP-specific approach is needed to comply with statutory CGMP:

- Donor eligibility;
- Recovery (see section XII. *Recovery*);
- Prevention of contamination;
- Parts of manufacturing arrangements under a contract, agreement, or other arrangements;

[3] Autologous ACTPs are Type II products if they meet *all* of the following criteria:

a. The ACTP is minimally manipulated;

b. The ACTP is for homologous use;

c. The ACTP is for use in nonfood-producing animals;

d. The manufacture of the ACTP does not involve the combination of the cells with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new safety concerns with respect to the product; and

e. The finished ACTP is not combined with or modified by the addition of any component that is a drug or device. For more information, see GFI #218.

[4] See GFI #254, "Donor Eligibility for Animal Cells, Tissues, and Cell- and Tissue-Based Products," (October 2022)

- Procedures for sharing with other establishments information pertaining to possible contamination;
- Audits;
- Prohibition on pooling (see section XIII. *Processing and Process Controls*);
- Predistribution shipment (see section XVII. *Receipt, Predistribution Shipment, and Distribution of an ACTP*);
- ACTP availability for distribution only after donor eligibility is established;
- Packaging and shipping requirements (see section XVII. *Receipt, Predistribution Shipment, and Distribution of an ACTP*);
- Recordkeeping for 10 years (facility cleaning and sanitation records for 3 years) (see section VIII. *Facilities*); and
- Tracking (see section XIX. *Tracking*).

Category A establishments that follow the recommendations in this document in addition to applicable regulatory CGMP will likely be considered compliant with statutory CGMP. Category A establishments may use an alternative approach to the recommendations in this document if the approach satisfies applicable statutory and regulatory CGMP. Failure to comply with applicable statutory or regulatory CGMP may result in the product being adulterated under the FD&C Act.

B. Category B Establishments

The following establishments are considered Category B establishments:

- Establishments performing steps in the manufacture of an ACTP that do not process cells or tissue for the manufacture of the finished ACTP products, other than Type II finished products; or
- Establishments that only manufacture Type II finished products.

Category B establishments that follow the recommendations in this document will likely be considered compliant with statutory CGMP. Category B establishments may use an alternative approach to the recommendations in this document if the approach satisfies statutory CGMP and applicable regulations. Failure to comply with applicable statutory CGMP may result in the product being adulterated under the FD&C Act.

C. Implementing CGMP

Category A and Category B establishments should implement the recommendations in this document at the time the cells or tissues are recovered from the donor, continue through the early processing steps and throughout the manufacturing process (where appropriate), to ensure product quality and to control contamination.

Category A establishments should follow the regulatory CGMP for finished products as specified in 21 CFR parts 210 and 211 as well as the recommendations in this document. The regulatory CGMP for finished products should be instituted as the manufacturing process progresses (e.g., passaging, harvesting, final formulation, filling, and packaging). The following examples are provided to demonstrate when the implementation of regulatory CGMP should begin for Category A establishments.

Example 1: Allogeneic micronized amniotic membrane: An establishment recovers placental membranes, isolates the amniotic tissue, evaluates the tissue for contamination, and then ships the tissue to other establishments for further processing. This is a Category B establishment. Establishments performing further processing, such as cryofracture, cell isolation, and packaging are Category A establishments.

Example 2: Cultured expanded adipose derived mesenchymal stem cells: An establishment recovers adipose tissue from donor horses, washes the tissue with saline, cools the tissue, and then ships the tissue to another establishment for further processing. This is a Category B establishment. Establishments performing additional processing, such as enzymatic digestion, isolation and culture expansion, cryopreservation, and packaging are Category A establishments.

Example 3: Culture expanded neural stem cells directed to differentiate to a specific neural lineage: An establishment recovers brain tissue from donor dogs, dissects and isolates neural tissue, washes and minces the tissue, cools the tissue, and then sends the tissue to another establishment for further processing. This is a category B establishment. Establishments performing additional processing, such as cell isolation, cell sorting, culture expansion, addition of growth factors, and directed differentiation are Category A establishments.

You should contact CVM with questions regarding what constitutes finished product manufacturing, and whether your establishment is in Category A or Category B.

IV. ESTABLISHMENTS OPERATING UNDER A CONTRACT, AGREEMENT, OR OTHER ARRANGEMENT

Before entering into any contract, agreement, or other arrangement with another establishment to perform any manufacturing step for you, you should verify that the establishment complies with applicable regulatory CGMP in 21 CFR parts 210 and 211. We recommend that you also verify whether the establishment follows the recommended manufacturing practices as discussed in this guidance or otherwise ensures the safety, identity, strength, quality, and purity of the resulting product as required by section 501(a)(2)(B) of the FD&C Act. Some ways that you can ensure the other establishment's compliance with CGMP include the following:

- Ensure that responsibilities are listed and understood as they relate to CGMP;
- Review test kit package inserts that are used by a contract test laboratory;
- Review standard operating procedures (SOPs) applicable to CGMP;
- Review validation reports;

- Review certifications, where appropriate;
- Review previous compliance actions, such as Form FDA 483 and Establishment Inspection Reports (EIRs);
- Perform comparisons of documentation provided by your contractor with source documents from the originator of the material;
- Ensure that the establishment has a quality program that addresses the operations that it performs for you; and/or
- Perform periodic audits of the establishment. We recommend that such an audit include a review of compliance with CGMP that is applicable to the operations the establishment performs for you.

If you become aware that an establishment operating under a contract, agreement, or other arrangement for you may no longer be in compliance with applicable CGMP, you should take reasonable steps to ensure the establishment is in compliance. These reasonable steps may include reviewing the establishment's corrective action plan and verifying that corrective actions have been taken under the establishment's quality program. If you determine that the establishment remains non-compliant, you should immediately terminate your contract, agreement, or other arrangement with the establishment.

Example 1: You are a processor that receives animal tissue from a recovery establishment under contract with you. You have decided to audit the recovery establishment annually to ensure compliance with the recommendations in this document related to recovery, such as donor medical history, obtaining specimens for donor disease agent testing, and shipping ACTPs to you at appropriate temperatures. During the audit, you should consider reviewing a representative sample of the records that were previously provided by the recovery establishment to confirm their accuracy by checking with the source of the information (e.g., the veterinarian, the laboratory testing for disease agents, etc.). You may also want to accompany the recovery team on a recovery to review adherence to procedures and to review the quality program activities.

Example 2: You should ensure that your contract laboratories that perform ACTP donor testing are using validated methods.[5] Such laboratories are considered establishments that must register with FDA because the laboratory performs control activities for a registered drug establishment.[6] These laboratories should have a quality program appropriate for the operations they perform. You should consider including in your contract, agreement, or other arrangement with an establishment a requirement that the establishment provide you with all Form FDA 483s and EIRs that it receives, and copies of its SOPs, and a requirement to be notified of proposed changes to any test kit or testing methodology being used. After your initial assessment to ensure that the establishment performing the manufacturing step for you is in compliance, you should check periodically to ensure its continued operational compliance.

[5] We recommend discussing the suitability of the proposed validation methods with CVM early in the review process.

[6] See 21 CFR 207.1; 207.17(a)

Example 3: You contract out some of your processing steps, such as terminal sterilization and microbial testing. You should ensure that your contractor's processing steps have been verified or validated to be in compliance with CGMP, and that your contractor has a quality program that addresses the SOPs and records.

Example 4: You determine that an ACTP meets all release criteria and you make the ACTP available for distribution; however, you contract out the actual distribution of your product. Even though you are not the actual distributor, you should review manufacturing and tracking records to determine that the ACTP has been manufactured and tracked in compliance with CGMP. As the establishment that makes the ACTP available for distribution, you should ensure that distribution records are kept so that ACTPs can be tracked back to you. You should also review copies of applicable storage SOPs to ensure that your distributed ACTPs are stored per your specifications.

V. ESTABLISHMENT AND MAINTENANCE OF A QUALITY PROGRAM

A. General

A quality program is an establishment's comprehensive system for manufacturing and tracking ACTPs. A quality program is designed to prevent, detect, and correct deficiencies that may lead to circumstances that increase the risk of introduction of contamination or impact product quality.

An establishment that performs any step in the manufacture of ACTPs should establish and maintain a quality program that is appropriate for the manufacturing steps performed and the specific ACTPs manufactured. This can be accomplished by defining, documenting (in writing or electronically), and implementing procedures, then following, reviewing, and as needed, revising procedures on an ongoing basis. For example, the quality program for a recovery establishment could include establishing and maintaining procedures to ensure that a donor's relevant medical records, including the physical assessment, are complete.

B. Functions

1. The quality program should ensure that the establishment complies with procedures appropriate to meet CGMP. The quality program should ensure the review, approval, and revision of CGMP procedures.

2. The quality program should ensure that the establishment has procedures for receiving, investigating, evaluating, and documenting information relating to CGMP, including complaints. You could receive this information before or after distribution of the ACTP (e.g., complaints from the consignee or results of tests detecting contamination performed by other establishments that recovered ACTPs from a shared donor).

   The quality program should ensure that procedures exist to share any information pertaining to the possible contamination of the ACTP with the following:

a. Other establishments that are known to have recovered ACTPs from the same donor;

b. Other establishments that are known to have performed manufacturing steps with respect to the same ACTP; and

c. All entities to whom the affected ACTP was distributed.

When information regarding contamination of an ACTP is received after the ACTP has been made available for distribution, shipped to the consignee, or administered (implanted, transplanted, infused or transferred) to the recipient, procedures should include provisions for assessing risk and appropriate follow-up, evaluating the effect this information has on the ACTP, the notification of all entities to whom the affected ACTP was distributed, the quarantine and recall of the ACTP, and/or reporting to FDA, as necessary.

Example 1: An ACTP establishment receives information from another establishment that a shared donor horse tested positive for Equine Infectious Anemia. The establishment should investigate and evaluate the information received to determine if the ACTP from this donor could potentially result in the transmission of the relevant disease agent. Test results indicating contamination means that the donor is ineligible to donate. In this case, the establishment's quality program should ensure that procedures exist for all of the following:

- The quarantine of any ACTPs in the establishment's inventory from the same donor;
- The notification of all entities to whom the ACTP was distributed. We recommend that this notification include written notification of the facts of the case (i.e., the reactive test results, the other establishment's additional test results, and additional testing that will be or has been performed on archived specimens, and the results when known); and
- The recall of the ACTP, and/or reporting to FDA, as necessary. We recommend that recalls be reported to the FDA District Office's recall coordinator.

In addition, we recommend that establishments instruct all consignees on procedures for return of unused ACTPs.

Example 2: A recovery establishment has contracts with multiple processing establishments to recover ACTPs for them. When the recovery establishment receives information from one processing establishment that a recipient of an ACTP from a shared donor experienced an adverse drug event, the recovery establishment should share this information with the other processing establishments that received ACTPs from the same donor. We recommend that these procedures be defined in your contracts, agreements, and other arrangements with other establishments.

3. The quality program should ensure that appropriate corrective actions relating to manufacturing practices are taken and documented and verify that such corrective actions are effective and in accordance with CGMP. The corrective action should not adversely affect other operations. Where appropriate, corrective actions should include both short-term action to address the immediate problem and long-term action to prevent the problem's recurrence.

   You should document (where appropriate) the following:

   a. Identification of the ACTP affected and a description of its disposition;
   b. The nature of the problem requiring corrective action;
   c. A description of the corrective action taken; and
   d. The date(s) of the corrective action.

4. The quality program should ensure that personnel involved in activities related to CGMP have proper training, education, and experience to perform those activities, and that personnel perform only those activities for which they are qualified and authorized.

   Example: The quality program could ensure that personnel are properly trained and educated by establishing training and education criteria for specific positions. This might be accomplished by ensuring that the content of training is relevant for an individual performing specific activities related to CGMP and by requiring a certain level of education and/or certification, as appropriate. For example, you may want to establish that personnel performing recovery operations on live animals are licensed veterinarians.

5. The quality program should establish and maintain appropriate monitoring systems.

   Example: You might develop systems within the facility for environmental control (e.g., systems to monitor temperature and humidity), environmental monitoring (e.g., viable particulate monitoring in a clean room), and storage (e.g., systems that monitor the temperature of ACTP storage units and alarm when out of range).

6. The quality program should investigate and document CGMP deviations and trends of CGMP deviations related to CGMP and make reports as recommended in this document. Each investigation should include a review and evaluation of the CGMP deviation, the efforts made to determine the cause, and the implementation of corrective action(s) to address the CGMP deviation and prevent recurrence.

   Example: ACTPs are recovered, but later review of donor records indicate that the donor did not meet certain donor criteria stated in your establishment's SOPs. The recovered ACTPs are destroyed after processing and before distribution. This event is a deviation from CGMP that should be investigated and documented for ACTPs,

but as long as no other reporting requirements apply, it is not necessary to report the deviation to FDA because the ACTPs were not distributed.[7]

C. Audits

You should periodically perform, for management review, a quality audit of activities related to CGMP. We recommend that a quality audit be conducted at least annually, and more frequently, if necessary. A quality audit is a documented, independent assessment and review of the establishment's activities related to CGMP. The audit verifies compliance with CGMP by examining and evaluating objective evidence. An assessment and review is considered to be independent when it is performed by an individual who does not have direct responsibility for the matter being audited or is external to the audited establishment.

It is not FDA's current policy to review or copy your actual quality audit reports during routine inspections by FDA. However, you should have a mechanism to demonstrate to the FDA investigator that quality audits are performed.

D. Computers

If you rely upon computer software to comply with CGMP, and if the software either is custom software or is commercially available software that has been customized or programmed (including software programmed to perform a user-defined calculation or table), you should validate the software for its intended use. You should verify the performance of all other software for the intended use if you rely upon it to comply with CGMP. You should approve and document these activities and results before implementation.

VI. PERSONNEL

A. General

You should have personnel sufficient to ensure compliance with CGMP and to ensure that the ACTP is manufactured in a way that does not compromise product quality or increase the risk of contamination.

B. Competent Performance of Functions

Personnel should have the necessary education, experience, and training to ensure competent performance of their assigned functions. Personnel should perform only those activities for which they are qualified and authorized.

[7] See 21 CFR 514.80

C. Training

You should train all personnel, and retrain as necessary, to perform their assigned responsibilities adequately. You should establish criteria for each position and periodically review the qualifications, training, and professional development of your personnel to ensure competency for their assigned functions.

VII. PROCEDURES

A. General

You should establish and maintain procedures appropriate to meet CGMP for all steps that you perform in the manufacture of ACTPs. You should design these procedures to prevent circumstances that compromise product quality or increase the risk of contamination.

B. Review and Approval

Before implementation, you should have a responsible individual review and approve new procedures. You should also ensure the periodic review and approval of procedures and ensure compliance with the recommended procedures with respect to such procedures as a function of your quality program.

C. Availability

Procedures should 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.

Example 1: Copies (e.g., on paper, or electronic media) of recovery SOPs could travel to recovery sites with personnel or could be accessed electronically from a separate location, as long as they are easily accessible to all employees performing recovery.

Example 2: It may not be feasible to physically keep SOPs in clean rooms where processing operations occur, because the SOPs could cause contamination of ACTPs. In that case, you could keep the SOPs in an adjacent area outside the clean rooms. As long as a paper and/or electronic copy of the SOPs are physically available, additional methods of obtaining information, such as an immediate communication method using wired or wireless technologies from personnel with questions to personnel who have access to current procedures, could be used to resolve, answer, or clarify questions that arise during operations.

D. Standard Procedures

If you adopt current standard procedures from another organization, you should verify that the procedures meet CGMP and are appropriate for your operations.

VIII. FACILITIES

A. General

Any facility used in the manufacture of ACTPs should be of suitable size, construction, and location to preserve quality and prevent contamination of ACTPs and to ensure orderly handling of ACTPs without mix-ups. You should maintain the facility in a good state of repair. You should provide lighting, ventilation, plumbing, drainage, and access to sinks and toilets that are adequate to maintain product quality and prevent the introduction of contamination.

All facilities manufacturing or distributing ACTPs must register with FDA and drug list their products prior to marketing.[8]

B. Facility Cleaning and Sanitation

You should maintain any facility used in the manufacture of ACTPs in a clean, sanitary, and orderly manner to prevent the introduction of contamination. You also should dispose of sewage, trash, and other refuse in a timely, safe, and sanitary manner.

You should have a cleaning program supported by environmental monitoring, where appropriate. You should determine the appropriate frequency, method, and concentration of disinfectants to ensure prevention of contamination and cross-contamination in your facility.

Example: You use a broad-spectrum disinfectant that has been demonstrated to inactivate bacteria and fungi on surfaces. You should follow the manufacturer's instructions for proper dilution and adequate contact time and document that all parameters were met.

C. Operations

You should divide a facility used in the manufacture of ACTPs into separate or defined areas of adequate size for each operation that takes place in the facility, or you should establish and maintain other control systems to prevent improper labeling, mix-ups, contamination, cross-contamination, and accidental exposure of ACTPs to prevent contamination.

It is not necessary that there be a separate designated room for each task performed during the manufacture of an ACTP. You should evaluate the type of area that a task would require to prevent contamination or cross-contamination of ACTPs and designate an appropriate area for those tasks.

[8] See 21 CFR part 207; https://www.fda.gov/drugs/electronic-drug-registration-and-listing-system-edrls/electronic-drug-registration-and-listing-instructions

Example: A clean room used for processing ACTPs could have defined areas designated for:

- Initial tissue processing;
- Cell or tissue culturing;
- Preparation of media; or
- Filling of vials.

It would not be appropriate to utilize a clean room normally used for processing ACTPs to perform the following activities:

- Preparing packaged, recently recovered ACTPs for shipment to another facility;
- Prepackaging freshly recovered ACTPs for subsequent quarantine;
- Handling (e.g., centrifugation, serum/plasma separation) of blood specimens to be used for relevant disease agent testing; or
- Decontaminating instruments used for recovery or processing.

D. Procedures and Records

You should establish and maintain procedures for facility cleaning and sanitation for the purpose of preventing the introduction of contamination. These procedures should assign responsibility for sanitation and should describe in sufficient detail the cleaning methods to be used and the schedule for cleaning the facility. You should document and maintain records of all cleaning and sanitation activities performed to prevent contamination of ACTPs. You should create these records concurrently with cleaning and sanitation activities. We recommend that you retain such records for 3 years after their creation.

E. Recovery

The facility-related recommendations apply to recovery of ACTPs. You should determine how to evaluate an area used for recovery to prevent contamination and cross-contamination, per the general facilities recommendations. As these recovery facilities may not be under your day-to-day control, you should establish and maintain procedures to prevent the introduction of contamination that may occur during each recovery.

You should consider the following issues when evaluating an area used for recovery:

- Facility size, location, and construction for aseptic recovery;
- Access to recovery site during the recovery procedure/period;
- State of repair of facility;
- Lighting and space;
- Ventilation and airflow;
- Access to a sink;

- Cleanliness of working spaces used for recovery operations with verified cleaning agents and proper cleaning documentation; and
- Capability to perform aseptic techniques.

A description, checklist, and/or other means could be used to document that the recovery site meets established, desired parameters each time a recovery is performed. The site of the recovery should be documented. Before entering into a contract with a recovery establishment, you should examine the facilities where recoveries take place.

Example: A tissue recovery facility may be a barn in which bone marrow or adipose tissue is extracted from animals such as horses. A facility such as this may not have a heating and cooling system or specific air filtration. However, the facility may comply with CGMP for facilities by having recovery, handling, and storage procedures in place to prevent contamination of the ACTP.

IX. ENVIRONMENTAL CONTROL AND MONITORING

A. General

Where environmental conditions could reasonably be expected to cause contamination or cross-contamination of ACTPs or equipment, or impact the quality of the ACTP, you should adequately control environmental conditions.

B. Environmental Control

To adequately control environmental conditions, where appropriate, you should provide for the following control activities or systems:

- Temperature and humidity controls;
- Ventilation and air filtration;
- Cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations; and
- Maintaining equipment used to control conditions necessary for aseptic processing operations.

We are not recommending clean room classification requirements for particular facilities or manufacturing steps; instead, you should determine the appropriate level of control. The appropriate level of control may depend on such factors as which manufacturing steps are involved, whether they are performed in an open or closed system, whether they are performed in a laminar flow hood (LFH) or biological safety cabinet (BSC), and other factors as described in FDA GFI, "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice" (September 2004).[9] This guidance provides useful information for an ACTP establishment that is developing procedures on

[9] https://www.fda.gov/media/71026/download

environmental control and monitoring. Also, United States Pharmacopoeia Chapter <1116> *Microbiological Evaluation of Clean Rooms and Other Controlled Environments*[10] contains information on environmental monitoring.

We recommend that you determine the types of microorganisms that could exist in your facility and design your cleaning and environmental control and monitoring programs accordingly. You should select the types of disinfectant/cleaning agents to use that are effective against microorganisms you have identified.

Example: Adipose tissue is extracted from a horse in a barn. The tissue is shipped to a processing facility where mesenchymal stem cells (MSCs) are isolated from the tissue. Processing (i.e., treatment of the cells with collagenase and extraction of the MSCs) should be performed in an LFH or BSC because this equipment provides a controlled environment and can be adequately cleaned and monitored.

C. Inspections

You should inspect each environmental control system periodically to verify that the system, including necessary equipment, is adequate and functioning properly. You should take appropriate corrective action as necessary.

D. Environmental Monitoring

You should monitor environmental conditions where environmental conditions could reasonably be expected to impact quality of the ACTP, cause contamination or cross-contamination of ACTPs or equipment, or cause accidental exposure of ACTPs to contaminating agents. Where appropriate, you should provide environmental monitoring for microorganisms. You should design your environmental monitoring system based on the type of operations performed in your facility.

You should establish and maintain procedures for environmental control and monitoring. We recommend that you define the type and frequency of environmental monitoring to be performed, including the monitoring used to verify that cleaning procedures are adequate, and that the environmental control systems are capable of maintaining the degree of control specified.

You should define alert and action levels for test results and specify potential corrective actions when alert and/or action levels are exceeded.

The following types of environmental monitoring should be considered in clean rooms, LFHs, and BSCs used for processing:

- Non-viable particulate air monitoring;
- Viable particulate air monitoring;

[10] http://ftp.uspbpep.com/v29240/usp29nf24s0_c1116.html

- Clean area positive pressure levels;
- Surface monitoring (taking into account all different surfaces in the manufacturing environment); and
- Personnel monitoring (e.g., gloves).

Example: We recommend that you perform periodic monitoring of non-viable and viable particulates, work surfaces, and personnel. This monitoring should be performed in clean rooms using LFHs and BSCs for processing in order to evaluate environmental changes that may impact quality of the ACTP or increase the likelihood of contamination or cross-contamination of ACTPs.

E. Temperature and Humidity

Each establishment should determine what temperature ranges and humidity levels could reasonably be expected to have an adverse effect on the ACTPs it manufactures.

Example: If steps in the manufacture of ACTPs have identifiable parameters for maintaining a certain temperature and/or humidity, or the performance of the reagents used in the manufacturing of ACTPs could be adversely affected by temperature and/or humidity over the length of storage of the reagent or product, you should adequately control and monitor environmental conditions and provide proper conditions for operations.

F. Records

You should document and maintain records of environmental control and monitoring activities. In addition, you should retain records concurrently with the performance of each step included in the environmental control and monitoring activities.

G. Recovery

Environmental control and monitoring considerations during recovery operations are similar to those of other manufacturing steps. You should consider the need for environmental control and monitoring of facilities used for ACTP recovery. You should establish and maintain procedures to prevent contamination or cross-contamination during recovery, or circumstances that otherwise increase the risk contamination with use of the ACTP. While environmental monitoring might not have to be performed at each recovery site, you should have controls in place to provide assurance that the recovery site does not increase the potential for contamination and cross-contamination of ACTPs. You should set specific parameters for recovery site suitability and verify for each recovery that these parameters have been met. A controlled environment with adequate temperature and humidity controls and adequate ventilation should be used for recovery. We recommend an operating room or similar type of facility.

Recovery establishments should have the following, where appropriate:

- Air filtration;
- Temperature and humidity controls;
- Non-porous surfaces for handling donor specimens;
- Washable walls;
- Refrigeration for donor storage; and
- Appropriately cleaned and sterilized surgical instruments.

X. EQUIPMENT

A. General

Equipment used in the manufacture of ACTPs should be of the appropriate design for its use and suitably located and installed to facilitate operations, including cleaning and maintenance, to control contamination and ensure product quality. Any automated, mechanical, electronic, or other equipment used for inspection, measuring, or testing should be capable of producing valid results. Equipment should be cleaned, sanitized, and maintained per established schedules. The equipment's potential to contaminate the ACTP should be considered during use. It is recommended that an installation plan for equipment be developed and executed, if applicable, to ensure that the equipment is suitably located, installed properly (per the manufacturer's specified requirements), and operates properly.

B. Procedures and Schedules

You should establish and maintain procedures for cleaning, sanitizing, and maintaining equipment to prevent malfunctions or contamination of ACTPs.

There are no required schedules for cleaning equipment. Each establishment should determine and justify cleaning procedures to prevent the contamination of ACTPs. Manufacturer's instructions for cleaning materials and equipment could provide useful information for determining appropriate cleaning schedules.

Example: Apheresis machines or bioreactors using disposable tubing may not require cleaning between each ACTP recovery if new sterile tubing is used with each recovery. However, if there is a spill, there should be special cleaning procedures in place.

C. Calibrations and Equipment

Where appropriate, you should routinely calibrate, per established procedures and schedules, all automated, mechanical, electronic, or other equipment used for inspection, measuring, and testing.

Example: An instrument used to monitor the temperature of an ACTP storage unit should be regularly calibrated.

To determine an appropriate calibration schedule, you should consult the equipment's operations manual or contact the manufacturer of the equipment to determine and establish appropriate intervals for calibrating each piece of equipment. You should also take into consideration the specific use of the equipment within the manufacturing facility to determine if special conditions could warrant more frequent calibration than is recommended by the equipment manufacturer. Calibration accuracy should be traceable to accepted/known standards, for example, those from the National Institute of Standards and Technology,[11] or the manufacturer's supplied or recommended standard.

D. Inspections

You should routinely inspect equipment for cleanliness, sanitation, and calibration and to ensure adherence to applicable equipment maintenance schedules.

E. Records

Records of all equipment maintenance, cleaning, sanitizing, calibration, and other activities should be documented and maintained. These records should also be displayed on or near each piece of equipment or should be made readily available to the individuals responsible for performing these activities and to the personnel using the equipment. Records should be maintained of the use of each piece of equipment, including the identification of the ACTP manufactured with that equipment. Records for cleaning and maintenance of equipment (including simple instruments that are regularly washed and disinfected), tools, and other equipment used or reused in the manufacturing of ACTPs should be kept to document that the items were adequately cleaned and maintained to prevent contamination.

Example: For single-use instruments, you should maintain records of the use of that equipment, including the identification of each ACTP manufactured with that equipment. Maintaining records for the use of single-use instruments would be helpful, for example, to the ACTP manufacturer in the event that the single-use devices are recalled because the manufacturer discovered that the distributed devices were not sterile.

If it is necessary to implement an alternate method of identifying the current maintenance, cleaning, sanitizing, and/or calibration status of each piece of equipment, the alternate method should permit the operator to easily check, prior to each use, that the equipment's maintenance, cleaning, sanitizing, and/or calibration have been properly performed.

You may have another establishment perform equipment maintenance, cleaning, sanitizing, and/or calibration for you, under a contract, agreement, or other arrangement. You may use the other establishment's records to demonstrate compliance with the recommendations for equipment. However, you should ensure that the services provided are adequate and in compliance with CGMP.

[11] http://www.nist.gov/

See section XVIII. *Records* for further information about general recordkeeping.

F. Qualification and Certification

It is recommended that equipment be qualified and certified to ensure consistent operation and the production of desired results. This is consistent with the recommendations outlined in FDA's GFI titled "Process Validation: General Principles and Practices" (January 2011).[12] Routine certification for certain equipment, such as LFHs and BSCs, should be performed per the manufacturer's specifications.

Example: Periodic recertification of an LFH could include measuring the air flow and velocity, ensuring proper operation of the HEPA filter (e.g., particle testing), and/or making sure that the exhaust is properly directed. An event or activity that warrants recertification of the LFH would include, but is not limited to, repair or replacement of parts.

G. Recovery

Recovery equipment should be cleaned to remove dirt, debris, and biological material prior to sterilization or high-level disinfection. Cleaning should involve the use of water with detergents or enzymatic products. Cleaning and disinfection solutions should be used per the manufacturer's instructions. Containers used to clean recovery equipment should be cleaned and sanitized after each use.

If equipment is cleaned manually, you should have a cleaning procedure in place that ensures removal of dirt, debris, and biological material. Manual cleaning procedures should include segregation of instruments from donors at risk of infection with relevant disease agents. If you use an automatic washer, you should ensure that the washer operates consistently and is properly cleaned after each use, per established procedures. There is no requirement to segregate recovery equipment (e.g., instruments) used for different donors prior to cleaning in an automated washer. It is acceptable to place multiple instrument trays into the same automated washers. If possible, it would be preferable to clean instruments used on the same type of tissue together in such loads.

To demonstrate that cleaning and sterilization of recovery instruments performed by a contract facility are appropriate, the recovery establishment should:

- Obtain and approve the procedures, and review the records of cleaning and sterilization;
- Establish and maintain verification procedures for any instruments cleaned and sterilized for you by a facility under contract, agreement, or other arrangement; and

[12] https://www.fda.gov/media/71021/download

- Have the procedures and records available for review on inspection.

Establishments that only clean and sterilize recovery equipment (e.g., instruments) under contract, agreement, or other arrangement to a registered recovery establishment are not required to register, because this function is not considered a manufacturing step. However, the sponsor should be able to verify that the recovery instruments are clean and sterile at the time of use.

XI. SUPPLIES AND REAGENTS

A. General

Supplies and reagents include all materials that are used during manufacture, not just those coming into direct contact with ACTPs. Examples of supplies include sterile drapes, gauze, cleaning swabs, gloves, alcohol pads, and equipment (e.g., instruments). Examples of reagents include cleaning agents, saline, dimethyl sulfoxide, anticoagulants, and chemical and antibiotic solutions used in processing.

Control of supplies and reagents is critical to preventing contamination and ensuring the quality of your ACTP.

B. Verification

You should not use supplies and reagents until they have been verified to meet specifications designed to ensure product quality and prevent circumstances that increase the risk of contamination. Verification may be accomplished by the establishment that uses the supply or reagent, or by the vendor of the supply or reagent. Use of a contaminated or otherwise defective supply or reagent in the manufacture of an ACTP could lead to such problems as the introduction of a relevant disease agent or the failure to properly preserve the ACTP.

You should verify that those supplies and reagents used in all steps of the manufacture of ACTPs (not only those that come in contact with an ACTP), including recovery, meet specifications designed to ensure product quality and prevent circumstances that increase the risk of introduction of contamination. You should store and use supplies and reagents per the manufacturer's instructions. We recommend that you keep product information data sheets for all supplies and reagents used, update these sheets as products change, and keep an archive of previously used products. Verification that reagents meet specifications may be accomplished either by reviewing the Certificate of Analysis (COA) or by performing relevant testing. For supplies, such as sterile drapes or gloves, that are not expected to have a COA, we recommend that you obtain information from the vendor on the relevant specifications and the manufacturing of the supply. You should maintain records of the verification of each supply or reagent, which may include test results and vendor COAs. If you receive supplies and/or reagents from a vendor or another establishment, you should verify that the vendor or other establishment has a system in place to certify that the supplies and/or reagents meet established specifications.

Example 1: You could reference specification sheets, COAs, or manufacturer's package inserts describing the reagent and/or supply to verify suitability.

If you require that specific supplies and reagents be used by recovery establishments, then you should verify the supplies and reagents, and should include this information in any contract, agreement, or other arrangement with the recovery establishment.

Example 2: Supplies used to wrap or package the individual ACTPs at recovery should be designed to prevent leakage that could cause contamination or cross-contamination and should be able to perform in this capacity when subjected to expected storage temperatures for that ACTP type.

C. Reagents

Reagents used in processing and preserving ACTPs should be sterile, where appropriate.

Example 1: It may be appropriate to use non-sterile water during processing for an ACTP that will be terminally sterilized, if the water meets specifications for use determined during process validation. However, only sterile reagents should be used in the processing of an ACTP that is not terminally sterilized.

Reagents of human or animal origin that are used in the manufacture of an ACTP should be assessed for their potential to contribute possible contaminating adventitious agents. Risk mitigation or testing strategies should be implemented, as appropriate.

Example 2: Fetal bovine serum utilized in the manufacture of an ACTP may require an evaluation of the source animal and collection procedures as it relates to prion contamination, in addition to other adventitious agent testing. As part of the risk mitigation strategy to control possible adventitious agents, such as bacteria and viruses, filtration and irradiation may be employed.

D. In-House Reagents

You should validate and/or verify the processes used for production of in-house reagents.

Example: In the case of reagents produced for disinfecting recovery processes, the recovery establishment should verify that these reagents meet specifications designed to prevent circumstances that increase the risk of the introduction of contamination (e.g., solutions are sterile (where appropriate), have the proper concentrations, and fall within a specific pH range).

E. Records

You should maintain the following records pertaining to supplies and reagents:

- Records of receipt for each supply or reagent, including the type, quantity, manufacturer, lot number, date of receipt, and expiration date;

- Records of verification for each supply or reagent, including test results or, in the case of vendor verification, a COA from the vendor; and

- Records of the supply or reagent lot used in the manufacture of each ACTP.

You should establish a system under which specific supply and reagent lots can be linked to individual ACTPs. This does not necessarily require an individual record for each supply used in preparing every ACTP (e.g., sterile drapes and gloves). For instance, you may track those supplies by recording dates between which certain lot numbers were used, rather than individually recording each supply as it is used during the manufacture of each ACTP. Maintaining such records will enable you to determine which supply and reagent lots were used at a particular time and which ACTPs were manufactured during that same time period. This would facilitate a recall of ACTPs if the supplies or reagents used in their manufacture are later found to increase the risk of introduction of contamination.

XII. RECOVERY

A. General

Recovery means obtaining from a donor, cells or tissues that are intended for implantation, transplantation, infusion, transfer, or other means of administration to an animal recipient. You should recover each ACTP in a way that maintains quality of the tissue or cells and does not cause contamination or cross-contamination during recovery, or otherwise increase the risk of the introduction of contaminating agents with use of the ACTP.

Establishments that recover ACTPs must register with FDA because the establishment is engaging in the manufacture, preparation, or processing of a drug.[13] However, if you are a person (e.g., an individual veterinarian, veterinary practice) under contract, agreement, or other arrangement with a registered establishment and you are engaged solely in recovering cells or tissues (e.g., cord blood, adipose tissue) and sending the recovered cells or tissues to the registered establishment, we do not expect you to register or list your ACTPs independently. You should comply with all other applicable CGMP. When operations are conducted at more than one establishment and common ownership and control among all the establishments exists, the parent subsidiary or affiliate company may submit registration information for all establishments.

[13] See 21 CFR 207.17(a)

B. Procedures and Records

You should establish and maintain procedures for CGMP related to recovery operations where appropriate, such as:

- Facilities;
- Environmental control;
- Equipment;
- Supplies and reagents;
- Labeling controls;
- Storage; and
- Receipt, predistribution shipment, and distribution of an ACTP.

Your quality program should address all of these aspects of CGMP. Maintenance of records and a record management system should adhere to the CGMP in section XVIII. *Records* of this document.

C. Controlling Contamination

You should evaluate all recovery-related operations to determine how these activities can be performed to control contamination and cross-contamination, including the following:

- Technical procedures used;
- Personnel involved;
- Equipment, supplies, and reagents that are used during recovery; and
- Facilities where recoveries take place (see section VIII. *Facilities*).

Specific examples of such activities include:

- Staff should have the experience, education, and training necessary to perform recovery operations;
- Recovery site suitability parameters should be established and documented, including facility cleaning and maintenance, and environmental controls;
- Recovery should be performed using aseptic technique;
- Recognized published industry practices appropriate to controlling contamination (e.g., zone recovery, isolation draping, and sequencing) should be utilized;
- ACTPs should not be recovered from an area of the body where there is localized infection;
- Equipment, including instruments used in the manufacture of ACTPs, should be of appropriate design for its use. You should clean, sanitize, and maintain equipment per established schedules. You should document and maintain records

of all equipment maintenance, cleaning, sanitizing, calibration, and other activities performed; and

- Supplies and reagents used during recovery should be of the appropriate quality and standard and records should be maintained.

Recovery activities and problems related to microbial contamination should be evaluated. For example, technical errors should be assessed and pre-processing culture results should be tracked and trended.

D. Donor Identification

Verifying and documenting the donor identity is the first step in ACTP tracking and is critical for preventing contamination with relevant disease agents by ensuring that donor eligibility information corresponds to the actual donor of the ACTPs.

Prior to recovering ACTPs from a donor, you should compare the potential donor by a permanent identification method with the donor's information as indicated on donor eligibility documentation.

You should document the methods used to verify the donor identity and should include the source of the verification information, the date and time at which the identification was made, and the name of the recovery staff member(s) who made the identification.

Example: Methods of documenting a donor animal's identification include photographing the donor's unique markings or permanent identification tag or tattoo, documenting a microchip number, verifying age, sex, weight, markings, and breed of the animal.

E. Audits

A processor should periodically audit the records provided by the recovery establishment by comparing them to other available information related to the donors and could contact the responsible person referenced in the donor records. Before entering into a contract with a recovery establishment, a processor should examine the facilities where recoveries take place and verify that they are adequate.

XIII. PROCESSING AND PROCESSING CONTROLS

A. General

You should process each ACTP in a way that maintains quality of the ACTP and does not cause contamination or cross-contamination during processing.

Processing is defined as any activity performed on an ACTP, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as:

- Testing for microorganisms;

- Preparation;
- Sterilization;
- Steps to inactivate or remove adventitious agents;
- Preservation for storage; and
- Removal from storage.

In the context of this guidance, the set of manufacturing activities that an establishment performs on an ACTP taken together would be considered a process.

Example: In the manufacture of an MSC, a process may consist of activities such as treatment of the stromal vascular fraction (SVF) with collagenase, isolation of the MSCs from the SVF, growth and passaging, filling into drug product containers, and cryopreservation.

Processing also includes obtaining specimens from an ACTP that are subsequently sent for microbiological testing (e.g., collection of swab specimens or representative ACTPs for destructive cultures), and the actual microbiological testing, including speciation of microorganisms that are detected.

When manufacturing an ACTP that cannot be terminally or filter sterilized, aseptic technique should be implemented throughout each step of the manufacturing process, including recovery and processing of tissue, to prevent contamination and cross-contamination. In situations where results of final sterility testing are not available before the product is administered, additional controls and testing should be considered.

Example: Additional sterility tests can be performed at intermediate stages of manufacture, such as after the last manipulation of the product prior to harvest in combination with other tests that may indicate microbial contamination, such as rapid microbial tests, microscopic examination, Gram stain (or other bacterial and fungal stain), endotoxin testing, etc. These tests should be performed and meet acceptance criteria prior to product release.

B. Pooling

1. Pooling ACTPs from two or more donors

   Cells or tissue from two or more donors should not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing. For example, commingling MSCs from different donors during processing would be considered pooling. In the event that you determine that pooling of ACTPs from two or more donors is necessary to obtain a therapeutic dose, we recommend that you discuss this with CVM early in product development. Pooling does not include the sequential administration of ACTPs from different donors to an individual recipient.

2. Pooling ACTPs recovered at different times from one donor

In general, we discourage the practice of pooling ACTPs that were recovered from a single donor at different points in time during processing or post-thaw because of the increased risk that one product could be contaminated and could cross-contaminate the other. However, the practice of pooling ACTPs that were recovered from a single donor may be acceptable if the processing otherwise complies with the applicable recommendations and the tracking/labeling systems are well-controlled to prevent mix-ups.

C. In-Process Control and Testing

Your procedures for processing and process controls should ensure that specified requirements, for in-process controls are met, and that each in-process ACTP is controlled until the required inspection and tests or other verification activities have been completed, or until necessary approvals per the quality program are received and documented. Sampling of in-process ACTPs should be representative of the material to be evaluated.

You should establish appropriate, objective mechanisms to control and monitor each process to ensure that you are processing ACTPs in a way that maintains quality and does not cause contamination or cross-contamination during processing. You could use a variety of methods for controlling and monitoring your processes, including statistical process-control methods and review of product acceptance criteria and results, as well as a meaningful quality audit.

For in-process control and testing you should check the results of testing at various steps during processing (e.g., by sampling in-process ACTPs and testing for parameters such as viability, cell count, performing a microbiological culture, etc.). The sample selected for testing (e.g., culture) should be representative of the ACTP to be evaluated. This may not be the case if a small portion of a large musculoskeletal ACTP or companion ACTP (i.e., ACTPs adjacent to the ACTP that is processed along with the ACTP) is cultured.

D. Pre-Processing Controls and Testing

To evaluate each incoming ACTP for the presence of microorganisms or contamination, you could utilize practices such as culturing the ACTP prior to processing. This culture is known as the pre-processing culture. Recovery establishments may perform the culture and send the results to the processor. Alternatively, using pre-established criteria, the processor may perform the culture, and based upon the results determine whether to reject or accept the ACTP for processing.

For instance, some processors may irradiate the ACTP to reduce the bioburden prior to additional processing, depending upon the amount and/or type of microorganisms detected.

It may not be possible to culture some ACTPs prior to processing, such as tissues that are immediately placed into an antibiotic solution after recovery. Under these circumstances, alternative approaches may be utilized.

Example: You could use storage or transport solutions that contain a pH indicator where a color change could indicate contamination. Additional testing may also be needed to confirm these results.

XIV. PROCESS CHANGES AND PROCESS VALIDATION

A. General

Any change to a process should be verified or validated to ensure that the change does not create an adverse impact elsewhere in the operation and does not affect the quality of the ACTP.

Example 1: If you develop software to store information used to make donor eligibility determinations, you should validate the software for this intended use.

Example 2: If you use a commercial electronic spreadsheet to record donor testing results which are used to make a donor eligibility determination, you should verify that the unmodified software performs this activity correctly.

B. Approval and Implementation of a Process Change

Any change should be approved by a responsible individual with appropriate knowledge and background, before implementation. You should communicate approved changes to the appropriate personnel in a timely manner. This provision does not apply to manufacturing steps other than processing.

Changes to verified processes may require either verification or validation.

Example: A switch from one brand of a solution used in processing to another brand of solution would be a process change. In this situation, the establishment should verify that the new solution performs as intended, in a manner that maintains quality, and does not introduce contamination.

C. Process Validation

Where the results of processing described under section XIII. *Processing and Processing Controls* cannot be fully verified by subsequent inspection and tests, you should validate and approve the process per established procedures. The validation activities and results should be documented, including the date and signature of the individual(s) approving the validation.

D. Written Representation

Any written representation that your processing methods reduce the risk of contamination of an ACTP, including but not limited to a representation of sterility or pathogen inactivation of an ACTP, should be based on a fully verified or validated process.

E. Changes

When changes to a validated process such as described above occur, you should review and evaluate the process, and perform revalidation where appropriate. You should document these activities.

XV. LABELING

A. General

All labeling must be truthful and not misleading.[14] You must follow the applicable labeling requirements for all animal drugs.[15] Labeling information provides important information regarding the safety and quality of the ACTP. It should ensure proper ACTP identification and prevent mix-ups.

B. Controls

You should establish and maintain procedures to control the labeling of ACTPs.

Your procedures should ensure that each ACTP is labeled in accordance with CGMP, including those in the following sections of this guidance and GFI #254, "Donor Eligibility for ACTPs"[16]:

- Section XVIII. *Records*;
- Section XIX. *Tracking*;
- Section XV. *Labeling*;
- GFI #254, section VII. *Records*;
- GFI #254, section VIII. *Quarantine of ACTPs*; and
- GFI #254, section IX. *ACTPs From Ineligible Donors*.

Examples of procedures that you could use to prevent labeling errors include the following:

- Identifying dedicated work areas and controlling separation of activities;
- Enclosing an additional copy of the label in the processing record as evidence of the actual label used (or if using electronic systems, you could retain an electronic copy);
- Labeling the ACTPs from one donor at a time; and

[14] See sections 502(a) and 201(n) of the FD&C Act [21 U.S.C. § 352(a) and 321(n)]

[15] See section 502 of the FD&C Act and 21 CFR part 201; See also footnote 2 on p. 2.

[16] See footnote 4 on p. 4.

- Confirming that all additional copies of labels or pre-labeled containers issued for ACTPs obtained from a specific donor have been reconciled and removed from the work area.

Example: Two distinct lots of the same culture expanded cell-based product are ready for formulation and filling. However, only one room in the manufacturing facility is designed to support aseptic processing and filling operations. Therefore, processing and filling operations are time-staggered to ensure that the products are not intermixed and mislabeled. The first lot of culture expanded cells are processed and filled in the biosafety cabinet while labeling for just this lot is prepared. Sealed and crimped vials are then moved to a dedicated work area for controlled labeling. Processing and filling operations of the second lot are now executed while labeling for the second lot is prepared. Sealed and crimped vials of the second lot can be moved to the dedicated work area for controlled labeling only once it is verified that all documentation from the first lot has been removed.

C. Verification

To ensure proper identification of ACTPs at every step of manufacturing, your procedures should include verification of label accuracy, legibility, and integrity.

Example: One way to verify identification of donors and ACTPs at recovery would be to have multiple personnel examine the labels. If a recovery establishment uses hand-generated labels, one method to verify the accuracy and legibility is to use indelible ink and fixative to ensure label integrity.

D. Information on the ACTP Finished Product Label and Labeling to Ensure Product Quality and Prevent Contamination or Mix Ups

1. You should label each ACTP made available for distribution clearly and accurately. Note that a label can include the affixed container label or an attached tie-tag.

2. You should place the following information on the ACTP label:
    - Distinct identification code affixed to the ACTP container;
        - Your labeling procedures should be designed to ensure that consignees can readily link the product to all required labeling and accompanying records, such as instructions for use.
    - Description of the type of ACTP;
    - For ACTPs from eligible donors, a statement that the donor has been determined to be eligible and a summary of information used to make the donor eligibility determination; and

- For ACTPs in quarantine and ACTPs from ineligible donors, warnings related to donor eligibility.[17] For ineligible donors, the reason for ineligibility should be stated. If it is not physically possible to include these warnings on the label, the warnings should accompany the ACTP.

3. You must include an expiration date on the product label, as appropriate for the ACTP.[18]

4. The following information should either appear on the ACTP label or accompany the ACTP:

    - Name and address of the establishment that determines that the ACTP meets release criteria and makes the ACTP available for distribution;
    - Name and address of the establishment that made the donor eligibility determination;
        - The name and address of the establishment that made the donor-eligibility determination should appear in the summary of records that accompanies the ACTP. However, if the establishment that makes the donor-eligibility determination is not the same establishment that makes the ACTP available for distribution, the labeling or accompanying information should contain the name and address of both establishments and specify which establishment performed which function; and
    - Storage temperature.[19]

XVI. STORAGE

A. General

ACTPs should be stored in an appropriate manner to prevent mix-ups, contamination, and cross-contamination, and in a manner that does not compromise the quality of the ACTP.

B. Control of Storage Areas

You should control your storage areas and stock rooms to prevent the following:

- Mix-ups, contamination, and cross-contamination of ACTPs, supplies, and reagents; and
- An ACTP being improperly made available for distribution.

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[17] See GFI #254, sections VIII. *Quarantine of ACTPs* and IX. *ACTPs From Ineligible Donors*

[18] See 21 CFR 201.17. The format of the expiration date should be appropriate for the product. See section XVI.D. *Expiration Date*.

[19] See section XVI.C. *Temperature*

You should identify and design areas used for storage of ACTPs to facilitate monitoring of temperature and locating in-process ACTPs, quarantined ACTPs, and ACTPs that have been made available for distribution. Each storage area should have signs indicating the types of supplies, reagents, and ACTPs contained in that area, and should be organized to prevent mix-ups, cross-contamination, and improper release of ACTPs.

Before completing the donor-eligibility determination, you should keep an ACTP in quarantine and clearly identify it as in quarantine. The quarantined ACTP should be easily distinguishable from ACTPs that are available for release and distribution. Quarantine means the storage or identification of an ACTP, to prevent improper release, in a physically separate area clearly identified for such use, or through use of other procedures, such as automated designation.

C. Temperature

You should store ACTPs at an appropriate temperature. The storage temperature should be sufficient to prevent conditions that could increase the risk of contamination of each ACTP stored, taking into consideration the types of packaging and preservatives used, and the expected duration of storage. You should establish criteria for storage temperature(s) and storage period(s) for specific ACTPs stored in your facility. These criteria may be based on established industry standards issued by professional organizations, if applicable.

D. Expiration Date

Where appropriate, you should assign an expiration date to each ACTP based on the following factors:

- ACTP type;
- Processing, including the method of preservation;
- Storage conditions; and
- Packaging.

An expiration date based on the factors listed above would be considered appropriate for your ACTP if the absence of a defined expiration date could reasonably be expected to negatively impact product quality or result in the product becoming contaminated. We consider it appropriate to assign expiration dates for fresh (i.e., non-cryopreserved) ACTPs, and for ACTPs that are thawed or reconstituted prior to administration. If such applicable expiration dates have been established by industry or veterinary practice and meet the recommendations of this section, you may be able to use those dates for your ACTPs, whether fresh or preserved. If scientific data do not exist for establishing expiration dates, then an expiration date may not be applicable.

Example: Where appropriate, you should assign expiration dates to final products, both fresh and cryopreserved, as needed to ensure that they maintain quality and remain free from microbial contamination. It may not be necessary to assign expiration dates to

ACTPs that are cryopreserved, because there is a low risk of contamination so long as they remain immersed in the liquid phase or retained in the vapor phase of liquid nitrogen in containers that maintain their integrity and barrier properties throughout the storage period. Data may be needed to support storage even if an expiry is not specified (retesting). You should assign an expiration time for a cryopreserved product once it is thawed to ensure product quality.

E. Corrective Actions

You should take and document corrective action whenever proper storage conditions are not met.

Example: In response to an alert from your temperature monitoring system indicating temperatures outside acceptable limits, you may need to transfer your ACTPs to an alternative storage area. If the temperature excursion was of sufficient duration to increase the risk of contamination or impact quality, you may need to discard or otherwise dispose of the affected products. After taking the appropriate corrective action(s), you should document the transfer or other disposition of each affected product.

F. Acceptable Temperature Limits

You should establish acceptable temperature limits for storage of ACTPs at each step of the manufacturing process to prevent contamination. You should maintain and record storage temperatures for ACTPs. You should periodically review recorded temperatures to ensure that temperatures have been within acceptable limits.

Example: If you determine that your ACTP can be stored at room temperature, you should define the temperature limits (e.g., 20-25 degrees centigrade), and document and maintain records of environmental control and monitoring activities. These records should be reviewed periodically to ensure that the temperatures have been within acceptable limits.

XVII. RECEIPT, PREDISTRIBUTION SHIPMENT, AND DISTRIBUTION OF AN ACTP

A. General

You should evaluate incoming and outgoing ACTPs to confirm the absence of contamination and to ensure the ACTP meets the defined release criteria.

B. Receipt

You should evaluate each incoming ACTP for the presence and significance of microorganisms and inspect for damage, quality, and contamination. You should determine whether to accept, reject, or place in quarantine each incoming ACTP, based upon pre-established criteria designed to prevent contamination. When you receive an ACTP, you should visually inspect the shipping carton, packaging, ACTP container, and

ACTP for damage and contamination. If there are indications that the quality of the product has been compromised or that contamination or cross-contamination of the ACTP could have occurred, you should quarantine the ACTP until your investigation is complete.

C. Predistribution Shipment

Predistribution shipment is the conveyance or shipment of an ACTP within your establishment or between establishments before it has met its release criteria (i.e., it is not available for distribution). The sender should determine and document whether the ACTP has met pre-established criteria designed to maintain quality and prevent contamination before shipping. The ACTP should be kept in quarantine during predistribution shipment and upon receipt.

Example 1: An ACTP is being shipped from the recovery facility to another facility for processing. The ACTP should be transported in a shipping container that is capable of maintaining the desired temperature during transport, and that is capable of withstanding physical stress.

Example 2: Predistribution shipment can also occur within one establishment (e.g., transported between buildings or transported between floors in the same building before the ACTP is available for distribution). Transferring ACTPs from one room to the next during processing (between steps) within the manufacturing suite is not considered a predistribution shipment.

D. Availability for Distribution

Available for distribution means that the ACTP has been determined to meet all release criteria. Distribution means any conveyance or shipment (including importation and exportation) of an ACTP that has been determined to meet all release criteria, whether or not such conveyance or shipment is entirely intrastate. Before making an ACTP available for distribution, you should review manufacturing records (such as records from the donor eligibility determination, recovery, processing, and storage) and tracking records pertaining to the ACTP, and, on the basis of that record review, verify and document that the release criteria have been met. A responsible individual should document and date the determination that the ACTP is available for distribution.

You should not make available for distribution an ACTP that:

- Is in quarantine;
- Is contaminated;
- Is improperly stored or transported;
- Is from a donor who has been determined to be ineligible or a donor with an incomplete donor eligibility determination; or
- Otherwise does not meet release criteria.

If you maintain CGMP records in more than one location, you may fax or email records for review prior to release for distribution, provided that the records can be adequately evaluated (e.g., legible and accurate).

If you deviate from a procedure (e.g., a deviation from an SOP) that is relevant to maintaining quality and preventing contamination, you should not make an ACTP manufactured under the deviated procedure available for distribution unless a responsible individual has determined that the deviation does not decrease the quality of the product or increase the risk of introducing contamination through use of the ACTP. You should record and justify any deviation from a procedure at the time of its occurrence.

Example: You arrive at a recovery site to recover ACTPs from a donor and you discover that the cleaning solution that you routinely use to disinfect the work surface is not available. You clean the surface with an alternative cleaning solution and proceed to recover ACTPs. The ACTPs are sent to a processing establishment. The ACTPs should not be made available for distribution until a responsible individual determines that the alternate cleaning solution is as effective as the routine cleaning solution and does not increase the risk of ACTP contamination.

E. Packaging and Shipping

The packaging and shipping containers should be designed and constructed to protect the ACTP from contamination and to maintain quality. For each type of ACTP, you should establish appropriate shipping conditions to be maintained during transit. You could use industry standards, if available, or establish for yourself appropriate shipping conditions to be maintained during transit. It is also important to ensure that appropriate shipping conditions are maintained throughout distribution. If you have a contract, agreement, or other arrangement with distributors, sub-distributors, and/or sales agents who distribute, you should ensure that appropriate shipping conditions will be maintained before entering into such contracts, agreements, or other arrangements.

F. Procedures

You should establish and maintain procedures, including release criteria, for receipt, predistribution shipment, availability for distribution, and packaging and shipping. For example, you could accomplish this with a checklist or a packing list. Documentation should include the following:

- Identification of the ACTP;
- Identification of the sender (i.e., the establishment that supplied the ACTP);
- Activities that you performed on the ACTP (e.g., inspection, acceptance, or rejection of the ACTP) and the results of each activity;
- Date(s) of activity;
- Quantity of ACTP subject to the activity (e.g., received or distributed); and

- Disposition of the ACTP (e.g., identity of the consignee to whom the ACTP was sent).

G. Return to Inventory

You should establish and maintain procedures to determine if an ACTP that is returned to your establishment is suitable to be returned to inventory. If return is not permitted, this should be made clear to the consignee. If return is permitted, you should specify the conditions under which the return could be accepted.

XVIII. RECORDS

A. General

Records contain important information, such as donor testing and release criteria, and confirm the identity, purity, potency, and safety of ACTPs. You should maintain records concurrently with the performance of each manufacturing step. Documenting an action involves the creation of a record, which is subject to the CGMP in this section. All records should be accurate, indelible, and legible. The records should identify the individual performing the work and the dates of the various entries and should be as detailed as necessary to provide a complete history of the work performed and to relate the records to the specific ACTP involved.

To help ensure the accuracy of records retained, we recommend that establishments that make an ACTP available for distribution obtain records directly from the creator of such documents whenever possible (e.g., serology/microbiology results should be obtained directly from the testing laboratory). All records should be in English or, if in another language, should be retained and translated to English and accompanied by a statement of authenticity by the translator that specifically identifies the translated document so that compliance with CGMP can be more easily determined by FDA.

B. Records Management System

You should establish and maintain a records management system relating to CGMP. Under this system, you should maintain records pertaining to a specific ACTP in such a way as to facilitate review of the ACTP's history before making it available for distribution and, if necessary, after the ACTP's release, as part of a follow-up evaluation or investigation. You should also maintain and organize records pertinent to the manufacture of the ACTP (e.g., labeling and packaging procedures, and equipment logs). If you maintain records in more than one location, you should design the records management system to ensure prompt identification, location, and retrieval of all records. You should organize your records in a useful manner in accordance with this section.

Example: A recovery establishment under contract with a processor sends ACTPs to the processor. The recovery establishment should send all relevant records, including donor records and records relating to recovery site suitability, as described in section XII.B.

Procedures and Records, to the processor. The recovery establishment should maintain copies of all transferred records and organize them in its records management system.

C. Methods of Retention

You may maintain records electronically, as original paper records, or as true copies such as photocopies, microfiche, or microfilm. Equipment that is necessary to make the records available and legible, such as computer and reader equipment, should be readily available. You should back up records stored in electronic systems.

Example: You are a processor that receives paper records of the donor's medical history from the recovery establishment. You review the medical history as part of the donor eligibility determination. Later, you scan the paper records and save them as a .pdf file on a computer that is backed up. The electronic records are true copies of the paper records. Therefore, you may destroy the paper records. However, if instead of scanning, you were to re-type (transfer) the information into the computer, you would be creating a new record, not making a true copy. Errors may have been introduced while re-typing the information into the new record. In this scenario, you should keep the original paper (hardcopy) records as proof of concurrent recordkeeping.

D. Length of Retention

To ensure the identity, purity, potency, and safety of ACTPs, we recommend that records be kept for 10 years after their creation, unless stated otherwise in this document.[20] You should retain the records pertaining to a specific ACTP at least 10 years after the date of its administration, or if the date of administration is not known, then at least 10 years after the date of the ACTP's distribution, disposition, or expiration, whichever is the latest date.

Laboratories that perform relevant disease agent testing of donor specimens and/or microbiological testing of ACTPs that do not know the date of administration, distribution, disposition, or expiration, should keep donor testing information for 10 years after the creation of the record.

E. Contracts and Agreements

You should maintain the name and address and a list of the responsibilities of any establishment that performs a manufacturing step for you. You should have this information available during inspections conducted by the FDA. We recommend that contracts, agreements, or other arrangements describe the responsibilities of all parties.

[20] The regulations in 21 CFR 211.180 require that records be kept for at least 1 year after expiration. However, we recognize that expiration of ACTPs varies from hours to an indefinite period of time for some cryopreserved ACTPs. Additionally, some forms of contamination or safety concerns may not be evident until years after the product is manufactured. For these reasons, we recommend a record retention period of at least 10 years.

Example 1: A contract, agreement, or other arrangement with an individual or establishment who obtains the donor's medical records should describe the information that you want that individual or establishment to obtain.

Example 2: When donor eligibility is determined following a review of records obtained by another establishment, the contract, agreement, or other arrangement might specifically identify what records will be obtained, in what format they will be provided, responsibilities for record retention and access, and if the reviewing firm will convey donor eligibility conclusions back to the establishment that collected the information.

XIX. TRACKING

A. General

Each ACTP should be tracked throughout manufacturing, from recovery to final disposition, to ensure that the ACTP is free from contamination and to ensure the quality of the ACTP. If you perform any step in the manufacture of an ACTP during which you handle the ACTP, you should track the ACTP. You should perform tracking to facilitate the investigation of an actual or suspected incidence of contamination, or impact on product quality, and take appropriate and timely corrective action. If you do not handle the ACTP (e.g., the testing laboratory that receives a specimen but does not actually handle the ACTP), you would not participate in tracking the ACTP.

B. System of ACTP Tracking

You should establish and maintain a tracking system that enables the ACTP to be tracked from:

- The donor to the consignee or final disposition; and
- The consignee or final disposition to the donor.

Alternatively, if you perform some, but not all, of the steps in the manufacture of an ACTP during which you handle the ACTP, you may participate in a system of ACTP tracking established and maintained by another establishment responsible for other steps in the manufacture of the same ACTP. You should verify that the tracking system is effective, especially if you participate in a tracking system maintained by another establishment.

C. Distinct Identification Code

You should ensure that each ACTP that you manufacture is assigned and labeled with a distinct identification code that relates the ACTP to the donor and to all records pertaining to the ACTP. You should also ensure that labeling includes information needed to facilitate effective tracking from the donor to the recipient and from the recipient to the donor. The distinct identification code should be created specifically for tracking purposes.

You may adopt the distinct identification code assigned by another establishment engaged in manufacturing or assign a new code. You should verify and/or validate that your tracking system is effective. The distinct identification code should be able to track to the donor but does not necessarily have to be on all records concerning the donor or on the package insert. However, the distinct identification code should be affixed to the ACTP container.

D. Tracking from Consignee to Donor

As part of your tracking system, you should establish and maintain a method for recording the distinct identification code and type of each ACTP distributed to a consignee to enable tracking from the consignee to the donor.

E. Tracking from Donor to Consignee or Final Disposition

As part of your tracking system, you should establish and maintain a method for documenting the disposition of each of your ACTPs, to enable tracking from the donor to the consignee or final disposition. This information should permit the prompt identification of the consignee of the ACTP, if any.

F. Consignees

As part of the tracking system, you should inform the consignee that the consignee should enter the distinct identification code for the ACTP in the recipient animal's veterinary medical record. This will help to identify affected recipients in the event you become aware of ACTP contamination or a product defect (e.g., contamination with a disease agent or improper storage conditions). Also, you should request that the consignee notify you of the distinct identification code for the ACTP if an ACTP is associated with any adverse drug experiences or product defects.

Example: You distribute an ACTP to a veterinary hospital. As part of your tracking system, the ACTP label contains a distinct identification code that relates the ACTP to the donor, the donation event, and the records pertaining to that ACTP. The ACTP label also includes a sticker with the distinct identification code and directions for the veterinarian to maintain the sticker in the recipient animal's veterinary medical record. After distribution of the ACTP you become aware that the donor of the ACTP was infected with a relevant disease agent at the time of donation. Using your tracking system, you contact the veterinary hospital and inform them of the potential risk of infection. You also provide them with the distinct identification code related to the ACTP derived from the infected donor. Using the sticker placed in the veterinary medical records, the veterinary hospital can identify and treat affected recipients and report any adverse drug experiences back to you.

XX. COMPLAINT FILE

A. General

Recording and evaluating complaints is important for monitoring the safety, identity, strength, quality, and purity of the ACTP.

B. Procedures

You should establish and maintain procedures for the review, evaluation, and documentation of complaints, and the investigation of complaints as appropriate.

C. Complaint file

You should maintain a record of complaints that you receive in a file designated for complaints. The complaint file should contain sufficient information about each complaint for proper review and evaluation of the complaint (including the distinct identification code of the ACTP that is the subject of the complaint), and for determining whether the complaint is an isolated event or represents a trend. You should make the complaint file available for review and copying upon request from FDA.

D. Review and Evaluation of Complaints

You should review and evaluate each complaint and determine whether an investigation is necessary. An investigation may include referring a copy of the complaint to another establishment that performed manufacturing steps pertinent to the complaint. When no investigation is made, you should 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. Complaints related to adverse events or product defects/manufacturing defects should be reported to FDA.

XXI. CGMP DEVIATIONS

CGMP deviations are deviations from the applicable sections in this guidance or from applicable standards or established specifications that relate to preserving quality or preventing contamination of the ACTP. You should report CGMP deviations that may result in adverse events or product defects/manufacturing defects to the product sponsor and to other establishments that may be impacted by the deviation. These other establishments may include establishments performing downstream processing steps on the same ACTP, establishments using tissue from the same donor (e.g., if you discover that the donor did not meet acceptance criteria), and establishments and sponsors of other ACTPs that you process that may have been impacted by the deviation (e.g., if you discover that an ACTP was contaminated and there is a risk of cross contamination to other ACTPs processed in your facility). If the ACTP is in distribution and the CGMP deviation may result in an adverse event, it should be reported to FDA within 3 working days.