

Standards for Cellular Therapy Product Services, 3rd edition

Summary of Significant Changes

The following table summarizes many of the significant changes made to the 3rd edition of *Standards for Cellular Therapy Product Services*; it is not, however, exhaustive. Not all changes contained in the *Standards* have been incorporated in detail. Many of the changes that result in the reorganization of a section cannot be fully appreciated without consulting the 3rd edition of *Standards* in conjunction with this table; therefore, the numbering follows that of the 3rd edition and, where appropriate, the corresponding standard number in the 2nd edition is included in parentheses. In cases where a standard has been re-numbered, but the substance of the standard has not changed, there is often no entry listed in the table. Like the crosswalk published with the *Standards*, this table is offered to assist individuals in updating their facility’s policies, processes, and procedures to conform to the 3rd edition. Use of this table should not take the place of a thorough, line-by-line analysis of each standard. Please note that this summary includes examples of comments submitted by users of the document, along with the program unit’s rationale in making or not making a revision to the document.

3rd edition standard number (2nd edition number in parentheses if changed)	Source of Change (Changes are made either in response to public comments or as the result of a program unit decision made prior to the public comment period.)	Outcome Following Program Unit Discussion <u>(Please note that public comments address the proposed <i>Standards</i>. The changes are best understood when the proposed <i>Standards</i> is compared to the final published version. The program unit has elected to make the substance of public comments a part of this document.)</u>
1.1.2.1	Committee decision	The program unit elected to add the following sentence to standard 1.1.2.1, “When the laboratory director delegates these responsibilities to a designee, the laboratory director shall retain ultimate responsibility.” The program unit felt that it was necessary to ensure that the designee concept be addressed for laboratory directors as it had been for the medical director in standard 1.1.2.2. As with the medical director, the ultimate responsibility for any decisions made by the laboratory director designee will fall with the laboratory director. As a result of this change, the term “designee” was defined in the Glossary.
1.1.2.1, 1.1.2.2	Public comment submitted, no change made	Comment: Is a standard needed to require identification of which responsibilities are delegated and to whom? Outcome: No change made. The SPU noted that in both standards that the role of the designees is defined both by who grants the responsibility as well as what said responsibility is.

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1.2.1	Committee decision	This standard previously required executive management to define and document a policy for achieving and maintaining quality in a number of activities, described in a list following the workflow of chapter 5, Process Control (donor selection, procurement, processing, and so on.) The CT SPU replaced this list with language requiring that executive management document the policy for achieving and maintaining quality in “ <u>all activities covered by these CT Standards.</u> ” This change was made for brevity.
1.2.2	Committee decision	The CT SPU elected to remove the term “documented” from standard 1.2.2 and instead placed a pen symbol (✍) to ensure that quality system records are maintained.
1.2.4	Committee decision	The CT SPU elected to change the title of this standard from “Management Representative” in the 2nd edition to “Quality Representative” in the 3rd edition. The CT SPU felt that this title better reflected the activities and duties described in the standard below for the individual performing this duty.
1.2.4.1	Public comment submitted, change made	Comment: The proposed revision will require that executive management only review the quality system on an annual basis and that management do so on a quarterly basis. Management is not defined in the glossary and could be interpreted to mean only supervisory employees. As we interpret it, this represents a lowering of the existing standard. Was this the intent of the CT SPU? Outcome: The CT SPU made a revision to the proposed wording as a result of this comment. The standard now reads, “This individual shall report to <u>executive</u> management at least quarterly on quality system activities and to other staff as appropriate.” The revision requires that the quality representative report to “executive management,” rather than “management.”
2.2.2	Committee decision	The CT SPU elected to add the following clause to standard 2.2.2 for clarity, “The facility shall establish and maintain policies, processes and procedures for identifying job-specific or quality-systems-related training needs...” The CT SPU felt that this addition strengthened the standard.
2.2.3	Committee decision	The CT SPU elected to re-write standard 2.2.3 as such, “Evaluations of competence shall be performed first before independent performance of assigned activities, again within 6 months of initial employment, and annually thereafter.* Standards 4.2.1 and 4.2.2.2 apply. ”*42 CFR 493.1451(b)(8). The program unit made this change for clarity. The more stringent requirements for CLIA regulated activities are still addressed in the footnote.
2.2.3	Public comment submitted, no change made	Comment: CLIA applicability for Cellular therapy seems to be an area of current discussion, confusion and concern. Would it be possible for AABB to issue some guidance, perhaps in the form of an Association Bulletin, or at least a summary of the issues and "ongoing discussions" on this topic? Outcome: The program unit agreed with the comment and that guidance on this topic is needed. Guidance will be published in <i>Standards Source</i> .
2.2.3.1 in the 2 nd edition	Committee decision	Standard 2.2.3.1 was deleted from the 3rd edition as a result of the changes to standard 2.2.3. Standard 2.2.3.1 was deemed redundant and unnecessary.
3.1	Committee decision	The CT SPU elected to edit this standard to read: “The facility shall establish and maintain policies, processes, and procedures to control, maintain, and monitor critical equipment. Measuring and test equipment shall be used in a manner that ensures that the measurement limitation is known and is consistent with the measurement capability that is required. ” The program unit elected to delete this section as they were deemed redundant per standards 3.1.1 and 3.1.1.1 (see below).

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3.1.1.1 #3	Committee decision	The CT SPU elected to add the term, “limitations” to the list of items that must be included in the process for equipment calibration.
3.1.1.4 (3.1.1.3 #5)	Committee decision	The CT SPU elected to separate former subnumber 5 out of 3.1.1.3 into its own stand alone standard. The program unit felt that standard 3.1.1.4 needed to be moved out from the list due to its importance. The term “tracking” was replaced with “tracing” as well. This change was made throughout the document wherever it is used in the context of traceability.
Chapter 4	Public comment submitted, change made	Comment: Please be consistent in the use of the terms ‘facilities,’ and ‘parties.’ Outcome: The CT SPU considered this comment and agreed that a change was necessary. However, it should be noted that the term “parties” is not intended as a synonym for “facilities.” As such, a definition of “parties” was created and reads as follows: “Entities or individuals who have entered into an agreement.”
4.1.3.1	Public comment submitted, change made	Comment: The amount and type of cellular therapy product to be collected should be added to this standard, i.e. collection endpoints should be defined in the medical order for procurement. Outcome: The CT SPU agreed with the intent of this comment and has added a sentence to the standard. The new sentence requires that the physician order include procurement goals.
4.1.3.2	Committee decision	The CT SPU elected to add a new sentence to this standard. The new requirement states, “Specific instruction for cell processing and preservation shall be provided in the order as appropriate.” This addition was made to address standards interpretations requests that had been put forward during the “life” of the 2 nd edition.
4.1.3.2 (proposed edition)	Public comment submitted	Comment: This standard refers to standard 5.17.2, which addresses the determination of acceptable values or ranges for product characteristics. How does that apply to this standard? Cell dose makes sense, but not ranges. Are processing facilities really supposed to let physicians request products with a specific viability, recovery, etc? Suggest deleting this reference or clarifying intent. Outcome: The CT SPU agreed. As a result of this comment, the reference to standard 5.17.2 was deleted.
4.1.3.2	Public comment submitted, no change made	Comment: Other than in the cases of directed donation, this requirement for obtaining a medical order for processing, preservation of storage should not apply to cord blood. The standard also requires that the order include specific instructions for cell processing and preservation. Please clarify what types of products this requirement would encompass. Outcome: The CT SPU noted that the standard applies whenever an intended recipient has been identified. The CT SPU did not make a change in response to this comment.
4.1.3.3	Public comment submitted, no change made	Comment: Should the medical order for administration also identify a specific product and amount (cell number) rather than just the “type” of CT product? This is particularly important as frequently more than one product is stored for a patient and there is often more than one bag per product. Outcome: The CT SPU reviewed this comment and felt that a change at this time was not necessary. These issues should be defined by the facility. The CT SPU will use <i>Standards Source</i> as a means of providing examples and guidance for this standard.

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4.1.4.1	Committee decision	In an effort to clarify the standard the CT SPU elected to replace the term “administering facility” with “appropriate parties.” The change was made to allow the standard to be more encompassing and to cover more than just an administering “facility.” The agreement might be made with a registry or with a group of clinical practitioners, for example.
4.1.4.2 # 1, 2	Committee decision	The CT SPU elected to replace the term, “procedures” in items (1) and (2) with “instructions.”
4.1.4.2 #3, 4	Committee decision	The CT SPU elected to change the requirement for “records” of product administration and adverse events to a “summary of” those records. The program unit’s intent is to clarify that copies of original detailed patient charting records are not required.
4.1.4.2, 4.1.4.3	Public comment submitted, no change made	Comment: Change ‘facility or registry’ to ‘parties’ to match 4.1.4.1 & 4.1.4.4 Outcome: The CT SPU elected to maintain the clause, “facility or registry” in standards 4.1.4.2 and 4.1.4.3. Standard 4.1.4.1 address broad agreements regarding outcomes data; standards 4.1.4.2 and 4.1.4.3 are more specific and are agreements that would have to exist between facilities or with the registry.
4.1.4.3	Committee decision	The program unit elected to add the clause, “or registry” to the standard. The standard now reads, “The facility shall have agreements with the administering facility <u>or registry</u> for the creation and retention of records listed in Standards 5.20 through 5.20.8.”
4.1.4.4	Public comment submitted, no change made	Comment: Add ‘as appropriate’ or ‘if applicable.’ As the standard is worded it sounds like each party has to have an agreement with each of the other parties rather than with the appropriate party. This is a complex issue that merits guidance. Outcome: The CT SPU elected not to make this change. The CT SPU was reluctant to change this standard because, as the comment notes, this is a complex issue.
4.1.4.4	Public comment submitted, no change made	Comment: Suggested changing this from requiring that agreements address conditions for discard to simply require a policy for disposition of cellular therapy products. The facility should have a disposition policy, but it is not always feasible to broker the contents of agreements. Outcome: The CT SPU decided not to make this change. From a legal and ethical standpoint, the CT SPU felt it was important to require that agreements with the donor or individuals providing consent for the procurement and storage should also agree to conditions for product discard.
4.1.4.4	Public comment submitted, change made	Comment: Agreements regarding the terms and length of storage between the storage facility and the recipient’s physician are not applicable in private cord blood banking arrangements, where the agreements are made between the storage company and the donor’s legally authorized representative. The “if applicable” language in the 2 nd edition seems to have been omitted in the 3 rd edition. Please add the “if applicable” back in the 3 rd edition. Outcome: The CT SPU agreed with the comment and added “if applicable” to item (1) on the list.
4.1.4.4.2 (4.1.4.4.3), 4.1.4.4.3 (4.1.4.4.2)	Public comment submitted, change made	Comment: The standard about documentation of death or “no need” prior to discard should precede the standard addressing disposition of products for which there is no recipient, especially since 4.1.4.4.1 also addresses situations where there is an identified recipient for the product. Outcome: The CT SPU agreed with the comment and changed the order of these two standards.
4.2.1 #1	Committee decision	The CT SPU elected to re-write item (1) for clarity. The revised wording is intended to streamline the content and to remove the concept that facilities define the “extent” of control they are required to exercise over a supplier.

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4.2.1 #2	Committee decision	The CT SPU elected to re-write item (2) for clarity. The intent of the change was to remove the concept that facilities define the “extent” of control they are required to exercise over a supplier. The program unit re-wrote the standard to require that facilities “[m]onitor the performance of critical suppliers as needed based on the nature of the material or service and the impact on the quality of the cellular therapy product.”
4.2.1	Public comment submitted, no change made	<p>Comment: If you completely remove the concept that facilities "define the extent of control" over a supplier, who then is supposed to determine the extent? If there was confusion about this language, I suggest that the standard clarify that the facility does determine the extent of control, and to explain how this should be documented. Perhaps the requirement can be retained, but reword the standard to require that "the facility determine the extent of qualification and monitoring required based on the nature ... etc (as in 4.2.1 #2).</p> <p>Outcome: The CT SPU felt that keeping the language requiring that the facility “define the extent of control” for suppliers would not improve clarity. The program unit chose to keep the wording from the proposed edition.</p>
4.2.1.1	Committee decision	The CT SPU elected to add a new element to standard 4.2.1.1, which address procurement activities that are performed by a supplier. The new language reads: “The process shall address the training and qualifications of personnel who perform activities covered by these <i>CT Standards</i> .” The rationale behind the new language was to ensure that suppliers performing procurement also address qualifications and training of personnel. The program unit felt that this requirement was an important logical extension of the original standard.

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4.2.1.1	Public comments submitted, no change made	<p>Comment: During the comment period (November 5 – January 7) the program unit received many comments requesting that the addition made to standard 4.2.1.1 regarding the requirement that the process address training and qualification of personnel. Due to the volume of comments received in response to this standard, a summary of the most common types of feedback received is presented below.</p> <p><u>Comments:</u></p> <ul style="list-style-type: none"> ▪ There are over 2000 hospitals in my country and over 450 licensed midwives. It is physically impossible for one facility to train, assess and document the competency of every potential health care personnel that might become involved in procuring a cord blood unit, anywhere in the country. It is also an unnecessary duplication as all registered health care personnel are required by their college to maintain their training and competency. ▪ It seems that the definitions of “supplier” and “procurement” are in question. Is this meant to apply only to the personnel of other <u>collection</u> facilities? Supplier could also be interpreted as companies or their distributors who “supply” materials used in processing but not the human product. “Procurement” in the government setting refers to the purchasing function. Does this standard mean that we are responsible for verifying the training and competence of any clerk who might handle our orders for routine reagents and supplies? ▪ Application of this standard in a family cord blood bank setting is challenging. We communicate collection procedures to the collection staff in multiple ways - letters sent directly to the medical care providers when they assume responsibility for collecting a product for us, instruction sheets in each collection kit directed to the collector, and on-going interaction between the collection staff and our customer service staff who provide support from the time of enrollment through the shipping of the cord blood unit to our processing laboratory. In a family banking model, the business relationship is between the family and the bank, not directly between the collection site and our facility. Therefore the opportunity for documentation of training and competency at the collection site is limited. We believe that with the appropriate training and outreach activities as described above, at the OB level, physicians can perform high quality collections. <p>Outcome: The program unit took these comments into consideration. The program unit felt that the standard as written reflects current best practice, and does not place undue burden on the membership if implemented effectively. Note that the new language requires that the process address training and qualifications of personnel perform collection activities. It does not mean that the accredited facility has to individually qualify each person performing such a task. However, the facility is required to address this issue in their policies, processes, and procedures. Approaches to meeting this requirement will be discussed in future guidance.</p>
4.2.2	Public comment submitted, change made	<p>Comment: This standard cites 21 CFR 610.40(f). This regulation is not applicable to HCT/Ps, including 361 and 351 cell therapy products. Instead, you may want to cite 21 CFR 1271.80(c), which explains the requirement for CLIA certification or equivalent requirements as determined by CMMS, for donor testing laboratories. You may also want to refer to the FDA requirement that the laboratories performing donor testing for relevant communicable disease agents must register with FDA as an HCT/P establishment in accordance with 21 CFR 1271.10(b), and that those performing microbiologic testing on the products must do so as well, because such testing is considered processing (21 CFR 1271.3(ff)).</p> <p>Outcome: The program unit agreed with the comment and made the appropriate change.</p>

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Reference standard 4.1.5A, II B	Public comment submitted, change made	<p>Comment: Move ‘If not obtained before procurement’ to the end of the sentence.</p> <p>Outcome: The program unit edited item I(B) to read as follows, “If not obtained before procurement, Consent for banking shall be obtained before or within 48 hours after procurement.”</p>
Reference standard 4.1.5A, II F (proposed edition)	Public comment submitted, no change made	<p>Comment: I believe the requirement for a physical assessment of the birth mother before consent should be modified and retained, not deleted. The timing, method, or documentation shouldn't be prescribed here, but there are very specific FDA requirements on this topic. <i>Suggestion</i> - A physical assessment of the birth mother shall be performed as a component of donor eligibility determination. The requirement should be moved from Informed Consent to Donor Eligibility.</p> <p>Outcome: The CT SPU reviewed this comment and elected to leave the requirement for a physical examination of the birthmother out of the Standards. Reference Standard 5.10A, General Requirements for Eligibility of Cellular Therapy Product Donors, requires a physical assessment of donors and birth mothers, but the <i>Standards</i> is silent on when that assessment should be performed.</p>
5.1	Public comment submitted, no change made	<p>Comment: Please consider adding that policies, processes and procedures are to be “carried out under controlled conditions <i>which conform to the requirements of these CT Standards and applicable laws and regulations including FDA guidelines.</i>”</p> <p>Item (2): What does ‘external standards’ mean? Is this too vague?</p> <p>Outcome: No change made. The CT SPU did not feel that the proposed addition would add value to the <i>Standards</i>. Executive management is responsible for compliance with all specified requirements, which includes AABB and FDA requirements. The CT SPU also believes that the term “external standards” is deliberately broad, and was envisioned to encompass a number of external regulatory sources.</p>
5.4	Committee decision	<p>The CT SPU elected to add the term, “safety” to this standard. The standard now reads, “The facility shall identify the reasons for a change and obtain the appropriate approval(s) before implementation. Any changes that may affect the <u>safety</u>, purity, potency, or efficacy of the cellular therapy product shall be validated before the distribution and issue of products for administration.”</p>

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5.5	Public comment submitted, change made	<p>Comment: Consider <i>defining</i> “<i>Quality Control</i>.” Possibly including some of the CAP language for QC requirements and review. Especially for quantitative analytic procedures. For example in CAP standards: Gen 3.0000: “Is there a written quality control program that clearly defines procedures for monitoring analytic performance, including establishment of tolerance limits, number and frequency of controls, corrective actions based on quality control data, and related information.” Gen 3.30070 talks about “procedures...established to verify the reliability of patient test results... Reliability includes elements of accuracy, precision and clinical discriminating power.” <i>BBTS Standards</i> 5.1.3 goes on to state “Results shall be reviewed and corrective action taken where appropriate”. This could be added to the <i>CT Standards</i>. QC should be tracked and trended and appropriate action taken. Concern: New facilities may not understand the need for quality control and it is hard to find a standard to cite when the facility is not performing QC as required to conform to good laboratory practices. For example in flow cytometry testing 2 types of controls need to be run: QC for the instrument and in-run controls which are carried through the procedure and treated the same way as the patient sample. Outcome: The CT SPU reviewed this comment and decided to include the term “analytical procedures” in the standard. In addition, the definition of “quality control” was revised for consistency. The standard now reads, “The facility shall establish a program of quality control that is sufficiently comprehensive to ensure that materials (including reagents), equipment, and analytical procedures function as specified.”</p>
5.6 (5.5.1)	Committee decision	The CT SPU elected to reformat the requirements concerning the management of materials. Previously, standards related to materials appeared through the “Process Control” chapter in order of workflow. The CT SPU reasoned that it would be more user-friendly to combine all standards related to materials into a new section. Standard 5.6 and related substandards concern the use and management of materials.
5.6.1.1 #10 (New)	Committee decision	Records of the receipt of materials must now include the quantity of a given material received. Standard 5.6.1.1 previously appeared as standard 5.13.1.2. “Quantity” is new item #10.
5.6.1.2 (5.13.1.3)	Committee decision	This standard addresses the emergency use of materials and previously appeared as standard 5.13.1.3. The CT SPU elected to remove the final sentence of standard 5.13.1.3 (in the 2nd edition) which stated the following: “A replacement product shall be made available, if possible.” The CT SPU reasoned that this statement was self-evident (that is, the recall of a product does not mean that the need for that product no longer exists.)
5.6.2 (5.5.1)	Committee decision	Based on the decision to create the “Materials Management” section, the second half of standard 5.5.1 (in the 2nd edition) now appears as standard 5.6.2. The language has not been significantly altered.
5.6.2.1 #1 (5.5.1.6 #1)	Committee decision	The CT SPU elected to revise this standard for clarity. The requirement has been re-written to omit “toxicity limits.” As such, the standard now requires that the qualification of materials that are not FDA-licensed or –approved for human use be based partly on “[m]edical literature supporting the use of the material for the specified purpose.” The language about “toxicity limits established by the medical literature” was removed because not all materials have published toxicity limits.

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5.6.5.1 #1 (5.5.1.5 #1)	Committee decision	The CT SPU elected to remove the requirement concerning the use of material safety data sheets. The program unit feels that this is ultimately an issue that has to do with facilities and overall safety. Accordingly, the CT SPU did not believe that the standard should be a part of the process control chapter. In addition, requiring records of material safety data sheets but not providing additional information would not benefit the users. As an example, the <i>Standards</i> were silent on the location of material safety data sheets, and keeping material safety data sheets in an area where work is performed would mean that the data sheets could not be accessed if a hazardous leak occurred and the work area were to be quarantined. Accordingly, the CT SPU believes that this kind of issue is best understood to be a part of an overall facilities and safety plan.
5.7 – 5.20.8	Committee decision	A number of standards starting at 5.7 (previously 5.6.6) through 5.20.8 have been re-numbered.. This change was a result of the creation of section 5.6, Materials Management.
5.7 (5.5.2)	Public comment submitted, no change made	<p>Comment: Would it be reasonable for the section on methods and operational controls to include a statement encouraging facilities to bring their identification and labeling procedures into line with the with the international standards for nomenclature and labeling of cellular therapy products using ISBT 128 that have been published by the International Cellular Therapy Coding and Labeling Advisory Group (Transfusion 2007;47:1319-1327).</p> <p>Outcome: The CT SPU agreed with the spirit of this standard. A new requirement, standard 5.9.4, requires that product names and descriptions on product labels use the terms and definitions found in the “Standards Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.” See also standard 5.9.4 below.</p>
5.7, 5.7.1 (5.5.2, 5.5.2.1)	Public comment submitted, no change made	<p>Comment: Product traceability records should also include the <i>person responsible</i> for each step, particularly procurement. Standard 5.8.1.3 addresses person responsible for <i>sample</i> procurement only.</p> <p>Outcome: The CT SPU believes that the identification of individuals responsible for critical steps is an inherent aspect of traceability. Standard 1.1.1 requires that facilities identify which individuals and job functions have responsibility for certain tasks; standard 2.2.1.1 requires that records of personnel identification be maintained; and additional details appear in the workflow or process control (for example, standard 5.17.1 requires that processing records include the “names of persons responsible for each step.”</p>
5.7.1 #9 (New)	Committee decision	The CT SPU elected to add a new requirement to this standard. The new requirement appears as item (9) and requires that the “[d]isposition of cellular therapy by-products and waste” be addressed in the policies, processes, and procedures used for product manipulation. This addition is a result of requests for clarification and interpretation requests for the 2nd edition of <i>Standards</i> .
5.7.4 (5.5.2.4)	Committee decision	The CT SPU elected to add the term “Leukocyte Reduction” to both the title of the standard and the body. This change was made for clarity, since the content o the standard was not appropriately reflected in the title.

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(5.7.7.2, 2nd edition) – deleted in the 3 rd edition.	Public comments submitted, no change made	<p>Comment: During the comment period (November 5 – January 7) the program unit received many comments regarding the standard proposed as 5.8.7.2 (5.7.7.2 in the 2nd edition), which required that infectious disease testing be performed on fresh (non cryopreserved) samples of cord blood. Most of the comments submitted pointed out that criteria for samples used for infectious disease testing should be established by the test manufacturer. These comments argued that if it is acceptable per the manufacturer to use a non-fresh sample, AABB Standards should not prohibit this. Outcome: As a result of these comments, the CT SPU elected to delete this standard. Standard 5.10.3.2 (5.7.5.2 in the 2nd edition) requires that all donor infectious disease testing be performed in accordance with the manufacturer’s instructions. Additional specific requirements for the testing of cord blood donors, such as the timing of sample collection, are addressed in 5.10.5.</p>
5.8.1.3 (5.6.1.3)	Committee decision	The CT SPU elected to revise this standard for clarity. The term “tracking” was replaced with the term “tracing.” See standard 3.1.1.4 above. The standard now reads, “Samples and aliquots of cellular therapy products used for testing shall be labeled in a manner that ensures traceability permits tracking of the sample or aliquot to the cellular therapy product and/or person from whom it was taken...”
5.9.4	Committee decision	This new standard requires that product names and description on product labels use the terms and definitions found in the “Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.” The nomenclature can be reviewed at www.iccbba.org/standardterminology.pdf .
5.10 (5.7.1)	Public comment submitted, no change made	<p>Comment: Donor eligibility for cadaveric donors should include <i>travel history</i> and <i>cause of death</i> in light of the documented transmission of rabies from a cadaveric donor and the recent transmission of HIV and HCV, some extra requirements should be added regarding <i>high risk behavior, high risk travel and consent</i>.</p> <p>Outcome: The CT SPU agrees that these items are important in determining donor eligibility. Reference Standard 5.10B requires that cadaveric donor eligibility determination include a history of behavioral risk for exposure to infectious agents or diseases (this is performed through an interview with a family member or relevant source.)</p>
5.10 (5.7.1)	Committee decision	The CT SPU elected to revise this standard for readability and to ensure that the standard did not mirror the language from standard 5.12.1. The intent of the standard has not changed, merely the wording has been revised for clarity. The standard now reads, “Before the procurement of the each cellular therapy product, the procuring facility shall verify that for donor eligibility assessment and for obtaining determination shall be performed and informed consent obtained, in accordance with Reference Standards 4.1.5A, Informed Consent, 5.10A, General Requirements for Eligibility of Cellular Therapy Product Donors and 5.10B, Clinical Evaluation and Laboratory Testing of Donors.” This is part of a number of other changes that seek to clarify issues surrounding the responsibility for procurement activities.
5.10 (5.7.1)	Public comment submitted, no change made	<p>Comment: We propose that AABB change the terminology used in this standard from eligibility to suitability. Eligibility includes testing, which is not always completed at the time of procurement.</p> <p>Outcome: The CT SPU reviewed this comment but did not feel that a change at this time was needed. The CT SPU does not believe that the <i>Standards</i> limits donor eligibility to donor testing. In addition, the CT SPU is reluctant to make minor verbiage changes unless there is a clear reason to do so. The term “suitability” can also be understood to address only whether a donor is “suitable” for an intended recipient. This section is not intended to address donor/product selection but rather whether an individual is eligible to be a donor or not.</p>

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5.10, 5.12.1 (5.7.1, 5.9.1)	Public comment submitted, change made	Comment: How are these two standards different? Both use the clause, ‘before procurement’. Outcome: The CT SPU made minor changes to these standards. Standard 5.10 now requires that donor eligibility determination be performed at some point prior to procurement. On the other hand, standard 5.12.1 requires that the procuring facility verify, before procurement, that the determination has been completed. The facility that is physically procuring the product may not be responsible for the determination of donor eligibility. These two standards combine to ensure that the interface between these two facilities occurs smoothly to ensure that products are only procured from eligible donors.
5.10.3 (5.7.5)	Public comment submitted, no change made	Comment: This section should specify that infectious disease test results are to be obtained <i>before transplant</i> (product administration to a patient). Outcome: The CT SPU believes that this requirement is already addressed in a number of areas, notably in the requirements for final product release criteria that appear under standard 5.19.3.
5.10.3.2 (5.7.5.2)	Committee decision	The CT SPU elected to replace the phrase “test kits” with “donor screening assays.” The terms were replaced for clarity.
5.10.3.3 (New)	Committee decision	The CT SPU elected to specify the infectious disease tests that must be performed on cellular therapy products. Previously, the <i>Standards</i> listed infectious agents for which tests must be performed, but did not specify test methodologies. The standard now reads: “Tests for the following shall be performed: HBsAg, anti-HBc, anti-HCV, HCV RNA, anti-HIV1/2, HIV-1 RNA, and anti- HTLV-I/II, as well as a serologic test for syphilis.”
5.10.3.4 (New)	Committee decision	The CT SPU elected to add a standard explicitly requiring that infectious disease testing be performed in a manner that permits the timely determination of donor eligibility. The new language reads as follows, “Infectious disease testing shall be performed in a manner that permits the timely determination of donor eligibility. Standard 5.10.7.1 applies.”
5.10.4, 5.10.5, 5.10.6 (5.7.6, 5.7.7, 5.7.7.1, 5.7.8)	Public comment submitted, no change made	Comment: A medical and social history (to include travel) should be obtained at the same time the testing sample is collected. Outcome: The CT SPU believes this is covered in Reference Standard 5.10B. In addition, Reference Standard 5.10A requires that “[e]ligibility determination...be performed and approved in a manner and time frame that provides current relevant information and protects the safety of the intended recipient.”
5.10.6 (5.8.8)	Public comment submitted, no change made	Comment: Please stipulate when samples will be taken from cadaver – within 48hrs before death, within a certain period after death? Also, consider adding requirements for labeling and identifying the person responsible for collecting the sample. Outcome: The CT SPU did not feel that this addition was necessary. The standards under 5.10.6 already require that licensed test kits be used and that samples be taken before cessation of circulation, if possible.
5.10.6.4 (5.8.8.4)	Public comment submitted, no change made	Comment: Should dilutional effects be considered for non-cadaveric collections as well, such as private cord collection/family donated situation? Outcome: The CT SPU did not feel that this addition was necessary. With cadaveric donors, the sample for infectious disease testing may be difficult to replace. This is likely not the case with cord blood donations to family banks.

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5.10.7.2 (5.7.9.2)	Public comment submitted, change made	Comment: Please clarify the difference between standards 5.8.9.2 and 5.8.9.2.1 in the proposed edition. Outcome: In the proposed edition, current standard 5.10.7.2 appeared as standard 5.8.9.2 and did not specify to whom abnormal results should be communicated. This standard was followed by 5.8.9.2.1 which read, “When clinically significant abnormal results are identified, they shall be communicated to the recipient’s physician.” The CT SPU elected to delete standard 5.8.9.2.1 following the review of the standards and language clarifying that abnormal results should be communicated to “the recipient’s physician” was added to standard 5.10.7.2.
5.11.4 (5.8.4)	Public comment submitted, no change made	Comment: What is the rationale for the differences in timing for a complete blood count for mobilized donors (24 hours) and non-mobilized donors (72 hours)?. The proposed standard states that the sample should be obtained but does not require evaluation of the results. Outcome: The CT SPU reviewed this comment and noted that non-mobilized donors are typically stable. and as a result there would be no need to change the wording of the proposed standard. In addition, the CT SPU elected not to be prescriptive about the timing of the review of this record.
5.11.4 (5.8.4)	Committee decision	The CT SPU elected to edit this standard to differentiate between mobilized and non mobilized donorsto eliminate confusion. The standard has been re-written to read: <u>“For mobilized donors</u> (apheresis and marrow), a complete blood count, including platelet count, shall be obtained before mobilization and within 24 hours before each procurement procedure. <u>For non-mobilized donors and other donors who are hematologically stable, a complete blood count, including platelet count, shall be obtained within 72 hours before the first procurement procedure and within 24 hours before each subsequent procedure during a continuous series of collections.”</u>
5.12.3 (5.9.3)	Public comment submitted, change made	Comment: The word ‘disposables’ was used in this standard. Should this actually be ‘materials’? Outcome: The CT SPU changed the term “disposables” to “additives.” The standard now reads, “The facility shall identify lot numbers and expiration dates of all <u>additives</u> and critical materials used in procurement.”
5.12.4.1 #6 (5.9.4.1 #6)	Public comment submitted, change made	Comment: Suggest deleting the term ‘quantities’ or move it to clarify that it apples only to ‘reagents.’ It is hard to quantify some critical materials. This could imply keeping track of the number of syringes, needles, transfer packs etc used. Please limit recording of quantities to reagents or provide rationale for requiring it for all critical supplies. Outcome: The CT SPU agreed with the intent of this comment and made the suggested change. The item now reads, “Names, manufacturers, lot numbers, and reagents, and quantities of reagents used in procurement.” A similar change was also made to standard 5.17.1(#8), which appeared as 5.14.1 in the 2nd edition.
5.14.1 (5.11.1, 5.11.2)	Public comment submitted, no change made	Comment: Questions: 1) This standard requires that the label be verified. Are we verifying that there is a label or that the data contained on the label is correct? 2) Who should do the verifying? Does this mean a two-person clerical check? 3) What is the purpose of having the donor close by when this check is performed? Outcome: Responses: 1) To be in compliance with the standard, one must verify content of label. The language of this standard was revised to reflect this. 2) The <i>Standards</i> does not require a two-person clerical check. How this check is performed should be defined in the facility’s policies, processes and procedures. 3) The clear rationale for this is that verifying this information while the donor is close by represents the best opportunity to prevent a labeling error from occurring.

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5.15 (5.12, 5.12.1)	Committee decision	The CT SPU elected to merge these two standards into one, for clarity. The intent and requirements of the standards have not changed.
5.15.1 (5.12.1.1)	Public comment submitted, change made	Comment: Require conformance to <i>applicable laws and regulations for example IATA and US Customs</i> . Outcome: The CT SPU agreed with this comment and added a second sentence to the standard. It now reads: “The facility shall control packaging to the extent necessary to ensure compliance with specified requirements. <u>Federal and/or international transportation regulations apply.</u> ”
5.15.1 (5.12.1.1)	Public comment submitted, no change made	Comment: Is there a requirement for temperature stabilization and insulation during transport? Outcome: The CT SPU noted this comment but did not feel that it was necessary to include in the standard as it is an inherent aspect of the packaging process.
5.15.2 (5.12.1.2)	Committee decision	The CT SPU elected to re-write the standard by replacing the terms “validated and qualified” with “qualified.” The standard now reads, “Shipping containers shall be qualified at defined intervals to ensure they maintain temperatures within the acceptable range for the duration of transportation.” This is consistent with the quality management system approach of <i>validating</i> processes and procedures; equipment is <i>qualified</i> for use in a given process or procedure, and the functional role of the equipment is part of the validation of the process or procedure.
5.15.3 (5.12.1.3)	Committee decision	The CT SPU elected to re-write a number of standards addressing the temperature monitoring of products during transportation. There were several comments and standards interpretation requests during the life of the 2nd edition with regard to scope of this standard. One variance request, for example, involved a facility where cryopreserved products did not have continuous temperature monitoring when they were transported a short distance, from the processing/storage site to the administration site. However, in this case, the product was under the direct control of trained laboratory staff. As a result of this and other issues, the program unit adjusted the language to read: “When noncryopreserved products are transported between <u>or within</u> facilities, the extent of temperature monitoring shall be defined <u>and shall be appropriate to the duration of transportation.</u> ”
5.15.4 (5.12.1.4)	Committee decision	See standard 5.15.3 above. This standard now reads: “When cryopreserved products are transported <u>and are beyond the physical control of the facility,</u> the temperature of the shipping container shall be continuously monitored. <u>If the cellular therapy product remains under the physical control of the facility, the extent of monitoring shall be defined.</u> ”
5.16.1 (5.13.2)	Public comment submitted, no change made	Comment: What criteria should be considered when inspecting incoming cells, tissues, and organs? Do the inspection criteria need to be defined somewhere? What is the description of a product with or without contamination? Outcome: The CT SPU reviewed this comment and noted that further guidance would be provided in Standards Source concerning standard 5.16.1. In addition, 21 CFR 1271.265 requires that facilities “evaluate each incoming HCT/P for the presence and significance of microorganisms and inspect for damage and contamination.”

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5.16.1 (5.13.2)	Committee decision	The CT SPU made the following slight revisions to this standard, which address the receipt of incoming cells, tissues, and organs: -Changed timing of inspection from “upon arrival” to “at the time of receipt” in order to clarify that there may be a slight delay between physical delivery of an item and the time at which it is actually “received.” -#6: removed the term “visual” from the inspection requirement -#6(d): is a new requirement that requires inspection of “temperature acceptability” upon receipt. -#7: replaced the term “name” with “ identity ” of the person receiving and/or inspectin the product” -#8: the term, “quarantine” was added into this standard. The sentence now reads, “Indication of acceptance, quarantine , or rejection.”
5.17.1 #8 (5.14.1 #8)	Committee decision	The CT SPU elected to replace the term, “critical materials” with “reagents.” This change was made throughout the document as well. See the comment for standard 5.12.4.1 #6.

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5.18.1.2.4 (New)	Public comments submitted, change made	<p>Comment: During the comment period (November 5 – January 7) the program unit received many comments regarding standard 5.18.1.2.4 (5.16.1.2.4 in the proposed edition and new to the 3rd edition of <i>CT Standards</i>) concerning the requirement that cord blood products be stored at temperatures at or below -150 C. Due to the volume of comments received in response to this standard, a summary of the most common types of feedback received is presented below.</p> <p><u>Comments:</u></p> <ul style="list-style-type: none"> ▪ Many of us still have freezer between -120 and -150 for HPC-A. Those who rarely receive cords for transplantation may not be able to store them at below -150 C. They cannot always be put further down in the freezer because we do not always have racks that fit whatever cassette the cord may arrive in. These cord blood units could be stored in the qualified shippers but the appropriateness of this depends on how far ahead the cord is ordered and whether or not the transplant takes place as originally scheduled. ▪ Why are you choosing to only define a storage temperature for cord blood products and not other cryopreserved products? While it is important to align with other accrediting bodies, alignment should really be more focused on not contradicting other agencies rather than duplicating them. It does not make sense to set a storage temperature for one type of cryopreserved product only. ▪ We suggest this be changed to read: Cord blood products shall be stored at temperatures at or below -135 C. Studies demonstrated little difference in recovery from stem cells stored at -135 C, -150 C or – 197 C. In addition, New York State Department of Health Guidelines read: If the storage period exceeds one year, cells should be stored at a temperature of less than -130 degrees C." At least one published study plus our own experience in thawing cells for transplant has demonstrated that cells stored at -135 C or lower provide excellent viability & recovery. ▪ What is meant by “storage” in this instance? Is the standard meant to imply that long-term/permanent storage should be at or below -150C or does this also apply to initial storage? Due to the time-sensitive nature of HPC freezing, some facilities (ours included) have emergency freezing procedures in case of multiple controlled-rate freezer malfunction. The emergency back-up procedures involve the cord blood product initially being frozen at -80C for 48 hrs and then moved into long-term/permanent -150C liquid nitrogen storage in an effort to try and ease the freezing as much as possible in the absence of a control-rate freezer. ▪ Suggestion: Maximum should be in accordance with glass transition temp of -130C. <p><u>Outcomes:</u> Based on the feedback received, the program unit elected to revise the standard to read as follows, “Cord blood products stored for greater than one year shall be stored at a temperature at or below -150 C.” The rationale for including this standard in the proposed edition was in light of reports that cord blood products frozen and stored at temperatures above -150 C show different post-thaw viability from those frozen at temperatures below -150 C.</p>
5.18.1.3 (5.15.1.3)	Committee decision	<p>The CT SPU revised standard 5.18.1.3 due to the volume of clarification requests and standards interpretation requests to this standard during its inclusion as standard 5.15.1.3 in the 2nd edition. The standard now reads, “For each type of cellular therapy product, a set of product specifications shall be established. The stability of each type of cellular therapy product during storage shall be monitored through a stability program. Sampling and evaluation shall be performed, at a minimum, on an annual basis.* *21 CFR 211.166</p>

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5.18.2.1.1 (5.15.2.1.1)	Public comment submitted, no change made	<p>Comment: During the comment period (November 5 – January 7) the program unit received many comments regarding standard 5.18.2.1.1 (5.15.2.1.1 in the 2nd edition of <i>CT Standards</i>) concerning the requirement that cord blood products have integrally attached segments cryopreserved with the product. Due to the volume of comments received in response to this standard, a summary of the most common types of feedback received is presented below.</p> <p><u>Comments:</u></p> <ul style="list-style-type: none"> ▪ The standard should address removal of overwrap to access the attached segment and the fact that both overwrap and segments can be gone by the time the CBU is shipped to the transplant center. ▪ Suggested revision: Cord blood products shall have integrally attached segments cryopreserved with the product. Standard 5.8.1.3 and Reference 5.17B, Processing Tests for HPC, Cord Blood Products (#5), apply. Rationale: The wording of the standard implied that the cord blood bank must perform product testing (other than HLA typing) on the attached segment. <p><u>Outcomes:</u> The CT SPU reviewed these comments and concerning the references to other standards, the CT SPU felt that these cross references were important because Reference Standard 5.17B explicitly requires that confirmatory HLA testing be performed on a sample obtained from an integrally attached segment.</p>
5.18.2.1.1.1 (New)	Committee decision	Standard 5.18.2.1.1.1 is new and reads as follows: “The identity of the product and segment shall be confirmed by two individuals when integrally attached segments are removed.” This standard was added to ensure appropriate identification controls were in place.
5.19 (5.16)	Public comment submitted, no change made	<p>Comment: Should review by medical director (and/or laboratory director) be required prior to release?</p> <p>Outcome: The CT SPU reviewed this comment, but did not make the requested addition. Standards 1.1.2.1 and 1.1.2.2 define the medical and laboratory directors’ responsibility for all activities in the laboratory. A number of other levels of review and approval are specified in the requirements following 5.19, including by the medical and laboratory directors, as appropriate. The CT SPU believed that this addition would prove redundant.</p>
5.19.3.4.2 #2 (5.16.3.4.2 #2)	Public comment submitted, change made	<p>Comment: Please add the following to the standard: A statement that the communicable disease testing was performed by a laboratory that has been certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments or that has met equivalency requirements as determined by CMS <i>or is approved to perform such testing by the relevant regulatory body having jurisdiction</i>. CLIA and CMS typically only have authority within the United States. Non-US facilities operate under the regulatory authority of other bodies such as Health Canada. These other national and provincial/state regulatory bodies should be recognized as equivalent. This rationale is consistent with that proposed in the 3rd edition for accepting alternate proficiency testing programs when CMS-approved programs are not available.</p> <p>Outcome: The CT SPU reviewed this comment and agreed with the intent of what was put forward. To clarify that this standard is applicable for U.S. facilities, a reference to 21 CFR 610.40(f) was added to this standard.</p>

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5.19.3.4.2 (5.16.3.4.2)	Public comment submitted, no change made	Comment: Suggest revising the standard to read as follows: “For those products collected after May 25, 2005, at distribution/issue of allogeneic products, the following items shall accompany the product or be readily available wherever the product is located...” Products collected prior to May 25, 2005 are not required, per the FDA, to have this information provided at distribution. Outcome: No change made. The CT SPU believes that these items should accompany all products, not just those addressed in the Good Tissue Practices rule.
5.19.4 (5.16.4)	Public comment submitted, no change made	Comment: Suggested Revision: “Products that do not meet release criteria but are approved to be released by exception shall have documented approval by the medical director and transplant physician receiving hospital and documentation of reporting to appropriate regulatory agencies, if applicable.” Receiving hospital should have some latitude on how they want to handle these products. Notification of the receiving hospital should be sufficient. Outcome: The CT SPU reviewed this comment but did not feel that a change was appropriate at this time. The decision to use a product that does not meet release criteria is a clinical one, which is why the CT SPU believes that the transplant physician should be notified.
5.20.6 (5.17.6)	Public comment submitted, change made	Comment: Would Standards consider requiring that the product and the recipient be identified by two health care professionals immediately before administration? Outcome: The CT SPU changed the standard in response to this comment. Standard 5.20.6 now reads: “Immediately before administration of the final cellular therapy product, two individuals (or electronic equivalent) at the patient care service shall confirm the identity of the product and the intended recipient. Intended recipients shall be identified using at least two identifiers. Standards 2.2.2 and 4.1.4.3 apply.”
Reference standard 5.9.1A, footnote #7 (Reference standard 5.6.2.1A, footnote #6)	Public comment submitted, change made	Comment: This footnote provides an option for labeling to accompany the product when it is physically impossible to affix the applicable warnings and statements to the product container. This provision of the Reference Standard is fully consistent with the labeling requirement in 21 CFR 1271.370(b)(4). The FDA regulations do not address labeling attached with a tie-tag, but FDA appears not to have any objection to this practice for warning statements that cannot be permanently affixed to the container because of small container size or product storage in liquid nitrogen. However, note that the items to which this footnote applies can be “ <i>affixed or attached using a tie-tag.</i> ” In order to maintain consistency within this table, this footnote should read as follows: “If affixing <i>or attaching</i> the applicable warnings and statements to the container is physically impossible...” Outcome: The CT SPU agreed with the comment and made two changes in the footnote and legend that accompanies the reference standard. The footnote has been re-written to read: “If affixing or attaching the applicable warnings and statements to the container is physically impossible, then the labeling must accompany the human cells, tissues, and cellular- and tissue-based products.” With regard to the legend, the “A” has been edited as such, “A=affixed or attached using a tie tag ”
Reference standard 5.9.1 B (Appendix 2)	Committee decision	The CT SPU elected to move this table from the Appendices to the body of the <i>Standards</i> .

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Reference standard 5.9.1C (Reference standard 5.6.2.1B)	Committee decision	<p>The CT SPU made the following changes to reference standard 5.9.1C:</p> <ul style="list-style-type: none"> ▪ Rather than distinguishing between an “inner” and “outer” shipping container, the two columns now distinguish between information that must be part of the “shipping document” and those that are to be affixed to the “outer container.” Accordingly, the program unit added a new notation: “R=accompanying records.” As a result of this addition all of the items in the “shipping document” are required to be in accompanying records, whereas the items on the shipping container are required to be affixed or attached using a tie-tag. ▪ The CT SPU added a new footnote, “49 CFR parts 171-180 apply” which concerns U.S. Department of Transportation regulations for the packaging and shipping of biologic and biohazardous materials.
Reference standard 5.10A (Reference standard 5.7.1A)	Public comment submitted, no change made	<p>Comment: This standard uses the term “eligibility” but also makes reference to donor safety. This does not correspond to the term of eligibility used in the glossary. Outcome: While donor safety may not be part of the definition of “donor eligibility,” the CT SPU believes that the determination of donor eligibility should include an evaluation of whether the donor can tolerate the donation. The CT SPU reviewed the term “donor eligibility” and its use throughout the 3rd edition and determined that the standards as written reflect the intent of the program unit.</p>
Reference standard 5.10A, I, II (Reference standard 5.7.1A, I, II)	Public comment submitted, no change made	<p>Comment: These sections do not pertain to donor eligibility as defined within the glossary – they concern donor advocacy services and donor education. They should be deleted.. Outcome: The CT SPU disagreed with this comment.</p>
Reference standard 5.10A, II (Reference standard 5.7.1A, II)	Committee decision	<p>The CT SPU elected to replace the term, “consenter” with “legally authorized representative(s).” “Consenter(s)” is used in the context of informed consent.</p>
Reference Standard 5.10A, III, A. 4 (Reference standard 5.7.1A, III, D)	Committee decision	<p>The CTS SPU elected to revise the standard to read: 4) Donor eligibility records shall be reviewed before procurement associated interventions (eg, drug or growth factor administration or line placement) and/or administration of a conditioning regimen to the recipient. <u>The standard was revised for clarity.</u></p>

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Reference Standard 5.10A, III, B, 1., b and c (New)	Committee decision	<p>The CT SPU added two new requirements to the eligibility criteria for living allogeneic donors:</p> <p>“b) Donor eligibility records shall be reviewed before procurement-associated interventions (eg, drug or growth factor administration or line placement).</p> <p>c) If the donor is deemed ineligible before procurement, the donor’s physician and/or procurement facility’s medical director shall provide written approval.”</p> <p>Item (b) adds more specificity to the general requirement that the procurement facility “verify that the determination of donor eligibility has been completed” (standard 5.12.1.) Item (c) complements a number of requirements concerning use of products from ineligible donors by addressing cases where the determination of ineligibility is made before procurement.</p>
Reference standard 5.10A, III, A. 5 (Reference standard 5.7.1A, III, B. 2)	Public comment submitted, change made	<p>Comment: Suggested changing this standard to read: “[u]se of products from ineligible, unrelated allogeneic donors in cases of urgent medical need shall require written approval by the facility’s medical director and the recipient’s physician <u>before procurement.</u></p> <p>There is potential for confusion here. For example, which facility’s medical director? If this is a donor safety issue, it is appropriate to have donor/apheresis center facility medical director written approval, but is not appropriate related to “eligibility” as defined in this glossary. The FDA requires the physician using the product to be notified of the ineligible status. (1271.65.b.3)</p> <p>Outcome: The CT SPU reviewed this comment and made a partial change based on what was submitted. The program unit did not agree with the removal of the clause, “the facility’s medical director” but did however change the standard to read as follows: “<u>Procurement and</u> use of products from allogeneic donors who do not meet eligibility criteria shall require written approval by the facility’s medical director and the recipient’s physician.”</p>
Reference standard 5.10A, III, A. 6, b (Reference standard 5.7.1A, III, B. 1, b)	Public comment submitted, no change made	<p>Comment: Regarding notification of ineligible donors - recommend adding “if applicable.” Sometimes an ineligible donor will not require notification. For example, if a cord blood donor (mother) travels to a CJD area and must therefore be classified as ineligible, the cord blood donor (mother) need not be notified.</p> <p>Outcome: The CT SPU reviewed this comment but did not feel that a change was necessary. The program unit reasoned that adding the phrase “if applicable” would actually create more confusion. Furthermore, individuals presenting to donate cellular therapy products should be educated as to whether their health history presents risk factors.</p>
Reference standard 5.10A, III, A. 6, c (Reference standard 5.7.1A, III, B. 1, c)	Public comment submitted, change made	<p>Comment: This standard is under the general heading of Ineligible Donors, but the language in the proposed edition includes a statement about nonconforming products. Can this be clarified? Do the two mean the same thing?</p> <p>Outcome: The CT SPU agreed with the intent of the comment. As a result, the program unit removed the term “nonconforming” and re-wrote the requirement to focus on whether the donor is eligible or not: “c) Identification and final disposition of previously collected products, if it is discovered that the donor does not meet donor eligibility criteria subsequent to procurement.”</p>

3rd edition number (2nd number if changed)	Source of Change	Outcome Following Program Unit Discussion <u>(Please note that public comments address the proposed <i>Standards</i>. The changes are best understood when the proposed <i>Standards</i> is compared to the final published version. The program unit has elected to make the substance of public comments a part of this document.)</u>
Reference standard 5.10A, III, B, 1, c (Reference standard 5.7.1A, II, B, 3)	Public comment submitted, change made	<p>Comment: This requirement that the donor’s physician and/or procurement facility’s medical director provide written approval for donors deemed ineligible before procurement would not seem to be applicable to cord blood donors. There are circumstances for both public and private cord blood banks where a donor would be drawn although they are ineligible. See the CJD comment above. Also, usually a facility’s medical director does not oversee procurement and would therefore not give approval. This seems to apply to apheresis donors and concerns their safety.</p> <p>Outcome: The CT SPU agreed with this comment, and in an effort to clarify this issue this requirement has been moved to appear directly under the heading for “living allogeneic donors.” Note that the requirement is not repeated under the “mothers of cord blood donors” heading.</p>
Reference standard 5.10A, III, B, 1, a (Reference standard 5.7.1A, III, E)	Public comment submitted, no change made	<p>Comment: Suggested Revision: “E. Evaluation and approval of donor eligibility shall be performed before the recipient receives marrow conditioning therapy. Interim health assessments shall be performed by a qualified person or persons during the mobilization process (if applicable) and through procurement.” The statement about the timing of the assessment in relation to mobilization of the recipient is not applicable to donor eligibility.</p> <p>Outcome: The CT SPU disagreed with this comment. Reference standard 5.10A has been re-written and ordered to clarify a number of issues, including that a review of donor eligibility records be performed before administration of a conditioning regimen to the recipient.</p>
Reference standard 5.10A, III, B, 2 (Reference standard 5.7.1A, III, F)	Public comment submitted, no change made	<p>Comment: We suggest the deleting all references to autologous donors here. Donor eligibility does not pertain to the autologous donor.</p> <p>Outcome: The CT SPU reviewed this comment and did not agree with the suggested revision and feels that a determination of donor eligibility for all donors (including autologous donors) is important and necessary. Some products intended for autologous use may be used for allogeneic administration; and there should be verification that the donor can proceed with the procurement.</p>
Reference standard 5.10B (Reference standard 5.7.1B)	Public comment submitted, no change made	<p>Comment: The <i>CT Standards</i> has listed the diseases for which testing must be performed – but the methodology has not been specified. Consider explicitly stating whether NAT testing is required.</p> <p>Outcome: Standard 5.10.3.3 (see comment above) specifies that testing for HCV RNA and HIV-1 RNA are required. The CT SPU always intended for AABB-accredited facilities to use the most sensitive methodologies available to them.</p>

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Reference standard 5.10B, Section I (Reference standard 5.7.1B, Section I)	Public comment submitted, no change made	Comment: This standard requires that you indicate an evaluation for anesthesia. Should this also include evaluation for administration of growth factors (e.g., pregnancy, auto immune disease)? Outcome: The CT SPU reviewed this comment, however no change was made. The CT SPU believes this would be part of a general physical examination and health history, which are already required.
Reference standard 5.10B, Section I, II (Reference standard 5.7.1B, Section I, II)	Public comment submitted, no change made	Comment: Should this section state that screening should be performed for the diseases considered relevant by FDA? Outcome: The CT SPU Noted that footnote (3) requires facilities to test for “other relevant infectious diseases or disease agents as required by the FDA.”
Reference standard 5.10B, Section II (Reference standard 5.7.1B, Section II)	Public comment submitted, change made	Comment: Should we require testing for Chagas? Outcome: The CT SPU added a requirement that a clinical evaluation of the donor’s s history of behavioral risk for exposure to for Chagas’ is required for allogeneic donors. Routine testing, however, is not required.
Reference standard 5.10B, Section II (Reference standard 5.7.1B, Section II)	Public comment submitted, no change made	Comment: Include West Nile Virus testing, and require that it be performed according to seasonal criteria as defined by the Center for Disease Control Outcome: The CT SPU agreed with the intent of this comment however no change was made. The program unit felt that requiring an evaluation for risk of WNV was sufficient. Testing can be performed as necessary.

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Reference standard 5.10B, Section II (Reference standard 5.7.1B, Section II)	Public comment submitted, no change made	<p>Comment: You include review of the autopsy report (if performed) in the list of items for clinical evaluation of a cadaveric donor. The definition of “relevant medical records” in 21 CFR 1271.3(s) includes other records besides the autopsy report that may reveal important information about risk factors for or clinical evidence of relevant communicable diseases in a living or cadaveric donor. Therefore, please consider adding “review of other relevant medical records” to this section. You could cite the regulation in 21 CFR 1271.3(s) and/or the Donor Eligibility Guidance Section IV.C, which provides more descriptions of and recommendations about the sources of information that are to be reviewed, if available.</p> <p>Outcome: The CT SPU decided not to make the suggested change at this time.</p>
Reference standard 5.10.7.1A, Cadaveric donors (Reference standard 5.7.9A, Cadaveric donors)	Committee decision	<p>The CT SPU elected to replace all entries for cadaveric donors under the column “Results Affect Donor’s Health?” to “Not Applicable.” While the impact of an abnormal result on the donor’s health is an important consideration for living donors (especially when a facility is trying to determine who should be notified of the abnormal test results), this is not the case for cadaveric donors.</p>
Reference standard 5.15.6A #1 (Reference standard 5.12.1.6A, #1)	Public comment submitted, change made	<p>Comment: Item number 1 in this Reference Standard includes a summary of processing records, infectious disease testing results, and testing records. According to 21 CFR 1271.55, records that must accompany an HCT/P after the DE determination is complete include several items that are not listed in this Reference Standard, such as a statement whether the donor has been determined to be eligible or ineligible (21 CFR 1271.55(a)(2)).</p> <p>Outcome: The CT SPU agreed with the comment received and made two changes. Item (1) now requires the following labeling items upon shipping of cellular therapy products: “Summary of processing records, statement of donor eligibility determination, infectious disease testing results, and testing records, including name, address, and emergency contact information for shipping/issuing facility.¹”</p> <p>In addition, a new footnote now cites, “21 CFR 1271.55(a)(2) and 21 CFR 1271.55(b) as indicated in the comment.</p>
Reference standard 5.17A, B, C (Reference standard 5.14A, B, C)	Public comment submitted, change made	<p>Comment: Why is the timing of the microbial testing only stipulated for cord blood? Should 5.15A and 5.15C also require microbial testing at the completion of processing?</p> <p>Outcome: The CT SPU noted the comment and placed decided to require that microbial contamination testing be performed at “completion of processing” for products other than cord blood.</p>

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Reference standard 5.17A (Reference standard 5.14A)	Committee decision	The CT SPU edited the last sentence of reference standard 5.17A to read as follows, “ The receiving or administering facility shall perform ABO group and Rh typing on a cellular therapy product or donor sample obtained at the time of procurement collection and compare to previous records.” This change was made for clarity.
Reference standard 5.17B #1(b) (Reference standard 5.14B, #1(b))	Public comment submitted, no change made	Comment: Suggested deleting the requirement to record results of ABO/Rh within 7 days of cryopreservation. Outcome: The CT SPU reviewed this comment, but felt that the recording of these results within 7 days was important ensures that ABO/Rh determination will be made on appropriate samples before cryopreservation.
Reference standard 5.17B #3 (Reference standard 5.14B #3)	Public comment submitted, no change made	Comment: Please change item #3 from “CD34 analysis or comparable analysis” to “suitable potency measurement performed before or after cryopreservation as appropriate.” Please include some suggested alternatives and how those might be made suitable (i.e., what validation work would be needed). Outcome: The CT SPU reviewed this comment, but did not make the requested change. The CT SPU believes that additional guidance may be necessary. The current language allows for “comparable analysis.” However, the CT SPU feels that removing CD34 from the standard is not appropriate at this time.
Reference standard 5.17B #4 (Reference standard 5.14B #4)	Public comment submitted, change made	Comment: 5.17A and 5.17C state: "Microbial contamination (culture for bacterial and fungal elements)." Should 5.17B also state (culture for bacterial and fungal elements)? Outcome: The CT SPU agreed with this comment and added “(culture for bacterial and fungal elements)” to #4.
Reference standard 5.17B #5 (Reference standard 5.14B #5)	Public comment submitted, no change made	Comment: Could 5.15B (5) require that these tests be performed before distribution <u>or issue for transplant?</u> <u>Products can then be shipped without the need to disturb the overwrap, if present.</u> Outcome: The CT SPU reviewed this comment and did not make this change. The CT SPU believes that this testing should be performed before the product is issued for administration.

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Reference standard 5.17B #5(c) (Reference standard 5.14B #5)	Public comment submitted, change made	Comment: Should screening tests be performed to detect critical genetic diseases, such as hemoglobinopathies and enzyme deficiencies? Outcome: The CT SPU added two new requirements to (5) as a result of this comment. They read as follows: <u>“b) hemoglobinopathy screening for allogeneic cord blood units on a sample obtained from the product or from the donor, c) functional assays for unrelated allogeneic cord blood units-for example, colony forming units or other appropriate assays.”</u>
Reference standard 5.17C #6 (Reference standard 5.14C)	Committee decision	The CT SPU elected to add the following requirement for completeness and clarity: <u>“If the final product contains red cells: 6) After receipt or before administration, ABO group and Rh typing shall be performed on a cellular therapy product or donor sample obtained at the time of procurement.”</u>
6.2.4	Committee decision	The CT SPU in an effort to make the standard complete added a clause to standard 6.2.4 requiring that records be stored in a manner “...that prevents mix-ups...” The CT SPU believes this requirement was implied, but decided to make it more explicit.
6.3	Public comment submitted, change made	Comment: The footnote to item #2 of this Standard includes citations to FDA Regulations and Guidance that are not applicable to computer records maintained in an HCT/P establishment. Only the FDA Guidance, January 11, 2002, “General Principles of Software Validation” seems relevant as a footnote to item #1 of this standard, which refers to records of validation of system software. Also, HCT/P establishments may validate or verify the performance of computer software, depending on whether the software is “custom” or “customized,” versus non-customized commercially available software (21 CFR 1271.160(d)). Therefore, you may want to consider revising item #1 of this Standard to “Validation <i>or verification</i> of system software...” Outcome: The program unit agreed with the comment submitted and edited the footnote. The footnote now includes the following: ¹ FDA Guidance, January 11, 2002, “General Principles of Software Validation”. 21 CFR 820.30 The FDA Guidances from May 11 and September 8 have been removed per the comment to ensure compliance with the FDA.
7.2.2.2.1 #3	Public comment submitted, no change made	Comment: This standard requires that the physician agree to discuss any risks associated with a nonconforming product with the recipient. We suggest that this requirement be deleted. The receiving hospital should have some latitude on how to handle units. Notification of the receiving hospital should be sufficient. Outcome: The CT SPU reviewed this comment and elected not to delete sub number 3. The program unit feels that it is the responsibility of the facility making the product available for clinical use to ensure that nonconforming aspects of the unit be discussed with the recipient or the recipient’s authorized representative.

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8.2, 8.2.1	Public comment submitted, no change made	<p>Comment: What about analytes that are measured but are not reported, such as those for informational value only?</p> <p>Outcome: The CT SPU reviewed this comment, but did not feel that a change was necessary at this time. The standard is geared toward CLIA-regulated testing and results that serve as the basis for diagnosis or treatment or a disease. Should further guidance be needed the CT SPU will include guidance in an upcoming issue of Standards Source.</p>
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