Response to Comments Received to the 8h edition of Standards for Cellular Therapy Services

Please note that public comments that were submitted address the proposed 8th edition of CT Standards, and not the final version. The changes are best understood when the proposed Standards are compared to the final published version. The program unit has elected to make the substance of public comments that were submitted a part of this document. This document does not represent a full summary of significant changes to the 8th edition of CT Standards. Guidance that appears with the 8th edition of CT Standards in the Standards Portal provides a more in-depth look at the additions, deletions and changes and the rationales behind those decisions that what appears below.

Standard	Comment	Change made?	Outcome
1.0	I recommend adding key activities such as testing and distribution to the list of activities to align with standard 1.2.2, for example: "….including, but not limited to cellular therapy product procurement, processing, storage, *testing, distribution*, administration *and post-administration monitoring*; medical management of donors and patients; determination of donor eligibility; and key quality functions"	Yes	The committee agreed with the intent of this comment and added the terms, "testing" and "distribution" to the standard ensuring that the standard matches 1.2.2 as well as covering all elements that are covered in this edition of *Standards*.
1.1.3.2	The eligibility criteria may need to be changed in standard 1.1.3.2: Doctoral degree in 1-year relevant experience or Master degree in life science with 5 years' laboratory experience on cord blood /cellular therapy products. Finding relevant cellular therapy, laboratory instrument handling, regenerative medicine doctorates in Asian countries is very difficult. Since these kinds of regenerative medicine, cellular therapy and relevant equipment handling is new and are being for practiced there very recently and are limited. Most of the doctorate's in Asian countries did their doctorate in classical life sciences like botany, zoology, biochemistry etc. thus, they don't have any experience on regenerative medicine, cellular therapy and relevant equipment handling. Unlike US and other western countries, in Asia, here medical doctors like MD/MS don't have a PhD.	No	The committee did not feel that a change was needed at this time. The committee feels it is paramount that all laboratory directors have doctoral degrees in a relevant field. It should also be noted that individuals who do not meet these requirements are able to submit a request for variance if they feel they can meet the standard in an alternative fashion.
1.2	Under the CGMPs, the quality unit must be independent from the manufacturing, facility and medical oversight. Furthermore, the quality unit must have the final authority and oversight for the release of the final product. Quality unit is also responsible for approving validation plans and reports.	No	The committee did not feel that a change was needed at this time. The committee felt that this change would not be able to be met by the breadth of facilities that are accredited under these *Standards*.
1.2.5	The Standard as written sounds like the quality plan could be reviewed once and never again. Suggest adding 'periodically' or 'at defined intervals'.	Yes	The committee did not feel that these additions were needed at this time. The committee did add "Standard 6.1.5 applies" to the standard as this standard requires that all policies, processes and procedures are reviewed at least every two years.
1.3, 1.4	I suggest moving these standards to chapter 10.	No	The committee noted this comment but did not feel that the change was necessary. It was noted

			that by having these standards in chapter 1, it ensures that executive management has to be involved in the affected processes.
2.1.6.1 (New)	Would the 10-hours of CE required need to be in the topic of cellular therapy specifically?	No	The committee's response to this comment is that the 10 hours of continuing education would have to be related to the activity each facility is seeking accreditation for.
4.3.1 #3 (New)	Please include the term "medical" prior to "order" in standard statement 3) to be consistent with standard statements 1) and 2). Recommended Wording: 3) Responsibility for the clinical facility to provide the <u>medical</u> order for procurement or processing.	Yes	The committee agreed with this comment and the term "medical" was added to subnumber 3 per the request.
4.3.1	The standard has the processing and procuring facilities as responsible for the medical orders. However, the orders come from the clinical facility. The respective facility is responsible for ensuring agreements are in place, not responsible for obtaining the orders from the clinical group.	No	The committee noted this comment but as this standard appears under the "Agreements" section, facilities need an agreement related to the activity occurring. The standard does not require which facility provides the agreement.
4.3.6, #1	Our facility would also like the CT Standards Committee to detail what is meant by "Summary of records of CT Product Administration" per Std. 4.3.6, #1. There is no information in Guidance. Our facility has agreements to obtain Clinical outcome data (per 5.31) and agreements to receive a summary of adverse events suspected to be linked to the CT product. However, in the instance where a CT lab transfers to cells to another facility (not linked to the processing facility) - our facility is unclear what value is added by having agreements to obtain a summary of the administration - other than of course getting adverse event and engraftment outcome data.	No	The committee did not feel that a change was needed at this time. As the standard falls under chapter 4, the standard should focus on the agreement between facilities concerning which records of administration are included. The committee will be writing guidance that will assist in the implementation of this standard.
4.3.6, #1	For consistency, also include a cross reference to address standard statement 1). Add reference to 5.29.5 (Records of Administration).	No	The committee did not feel that a cross reference would be appropriate in this instance as the totality of what appears in 5.29.5 would not be applicable in all cases.
4.4.1	Please revise the standard to state: Therapeutic and scientific claims in educational and promotional materials shall comply with applicable regulations and be revised by the medical director and relevant Independent ethics committee, **<u>as appropriate</u>.** Independent ethics committee should only be required to review educational and promotional materials relating to research or clinical trials.	Yes	The committee edited the standard by removing the clause, "…and relevant Independent ethics committee." from the standard. The committee felt that the clause "as appropriate" would be difficult to assess and that the clause should be removed as noted in the comment, this would be under the purview of the medical director.

4.5.3, #1	We suggest moving 'applicable."	Yes	The committee agreed with this comment and removed the clause "if applicable" as it is deemed difficult to assess.
4.8.1, #2	Please note that establishments must ensure that the contract manufacturing or testing facilities that they use are in compliance with applicable regulatory requirements (21 CFR 1271.150(c)(iii). Compliance with accreditation standards would not be sufficient.	Yes	The committee agreed with this comment and added a cross reference to standard 5.12.10 which requires that facilities follow the regulations as stipulated by their Competent Authority.
4.5A. I. F	The language utilized during the informed consent process will be reviewed and approved by a qualified healthcare professional. If questions arise during the informed consent process, the donor will be directed to a qualified healthcare professional. Informed Consent is standardly conducted during the enrollment process for private banking. All educational and promotional materials are already required to be reviewed and approved by the facility's medical director, per AABB standard 4.5.1	No	The committee notes that the standard does not require a qualified healthcare professional be a part of each component of the informed consent process, just in cases where the consenter may have questions that require answers that require the individual responding be qualified to do so.
4.5A, I. F	We are in agreement that the person presenting information or answering questions during Informed Consent to a prospective donor should be a qualified health care professional who is familiar with the cellular therapy procedure(s). This is particularly important with respect to public bank collection sites actively recruiting donations of cord blood for unrelated cord blood transplants, which require the relinquishment of certainty that the unit will either be banked or if banked, ever available for the donor's future use. Since each birthing parent or couple must make an autonomous decisions regarding the final disposition of their baby's cord blood, and that decision may preclude some future potential benefit, it would be highly unethical to withhold full and balanced informed consent at the time of donation. However, we would raise the concern that just because a health care professional is familiar with the cellular therapy procedure(s), that the individual may not have the donor's best interests in mind if the informed consent is not complete or well balanced. The decision tree for parents interested in preserving their child's cord blood should begin with whether or not they want to save the unit for their own or their family's potential benefit, which is certainly their right, even if highly speculative. Therefore, the burden of the qualified health care professional is to first make certain the family understands the potential value of the cord blood unit to their baby or other family member before making an irreversible decision to either donate or discard the unit. We strongly disagree that any person is or should be required to present information or answer questions to a parent banking their baby's cord blood privately. This is neither necessary nor appropriate for parents who are making	No	The committee did not think a change was needed at this time. The donor informed consent process, the materials provided, and the qualifications/training necessary for the individuals responsible for obtaining consent should be designed to be consistent with accepted prniciples of informed consent and decision-making. In addition, as it is a medical procedure, a qualified health care professional should be available to answer parent questions.

	an autonomous decision to preserve their baby's cord blood in a private bank. Such a requirement is orver reaching and could easily be construed as coercion. This is particularly problematic if the person presenting information and answering questions at the time of informed consent weighs public good over private intentions or benefits. The "qualified health care professional" may for instance be committed to enrolling public donations for unrelated transplant procedures, where they are keenly aware of the unmet need for donated units, while the same individual may not be "qualified" to help parents gain awareness of clinical studies currently underway, particularly those using autologous cord blood to treat brain injuries. Under this scenario a regrettable disserve to parents and children might result, if for example, the newborn suffers from a brain injury and data is later available demonstrating that some efficacious benefit of an autologous infusion might have been achieved if the unit had remained under the control of the family and been available following the diagnosis. Private banks currently fulfill the requirement to provide informed consent within the enrollment service agreement. This informed consent does inform parents that they have the option to donate their baby's cord blood unit to a public bank if available at their birthing institution. The vast majority of parents considering private banking do so well in advance of their delivery date. As such they have ample opportunity to speak with family, friends and their attending obstetrician. Should the unit ever be required for their child, sibling, or qualified relative, the parents will be required to consent to release the unit to the treating physician, who is very informed with respect to the specific cell therapy treatment at hand. Furthermore, those parents at the time that clearly have intimate knowledge of the actual intended use for which they have themselves requested the unit under their responsibility as legal guardians. With these considerations we respectfully offer the following recommendations: 1) Do not make 4.5A, F a blanket requirement for private banking. This may have unintended consequences, as in the case of any future autologous or related need where the absence of a banked unit may be regrettable and actually result in harm, where other treatment options may not be available or effective. 2. Add a clause to qualify that the requirement is specifically limited to the process of recruiting cord blood units donations for unrelated use. Example – The person presenting information or answering questions during informed consent, associated with the recruitment of donors for public banking, shall be a qualified health care professional who is familiar with the cellular therapy procedure. 3. And further stipulate that a. Such familiarity with the cellular therapy procedures should include experimental procedures, even if not yet fully vetted clinically, which might in		

	the future benefit the child themselves, their sibling or another member of the immediate family. Only in this way will families considering the donation of their baby's cord blood ben properly informed as to all of their options and potential consequences should they make a decision not to bank the unit privately.		
4.5A, II. D	Is the nature of disease from the neonatal donor relevant in the reporting to the cord blood bank?	No	The committee noted this comment and feels that the nature of the disease is important as it can cause potential risk to the recipient.
4.5A, II. D	How does reporting of conditions or diseases not immediately present at the time of cord blood procurement align with the 10 year post creation/final disposition record keeping requirements (see standard 6.2.9)? Should there also be a requirement for notification to the facility when the cord blood bank is notified? The standard as proposed is confusing. Restating the standard to apply to the informed consent itself, as opposed to the consenter's agreement, helps clarify the requirement, and makes the standard itself both enforceable and auditable. Recommended Wording: D. **The consent shall contain an agreement** ~~The consenter shall agree~~ to provide information to the cord blood bank if the neonatal donor later develops a disease that may pose a risk to a recipient.	No	The committee noted this comment but did not think this change would be appropriate.
5.0	Suggest adding a record retention requirement to this standard.	No	The committee did not feel this was needed as this requirement to maintain records of all policies, processes and procedures is included in standards 1.2.3 – 1.2.3.5.
5.1	The terminology in this standard is not consistent with standard 5.2.1 (e.g. does not include purity).	Yes	The committee added the term "product" to the standard to remain consistent with the language in standard 5.2.1 as described in the comment.
5.1.2.2 (New)	In the absence of an external proficiency program couldn't the standard use requirements like BB/TS, i.e., "there shall be a system for determining the accuracy and reliability of test results (again, guidance could be available to describe alternatives). The current requirements to "include comparison of test results from an outside laboratory" are very restrictive and an option that might not be available to laboratories that are isolated or restricted (e.g., Andorra, some Chinese locations) or that their business is too competitive to encourage relationships with outside labs. It could cause requests for variances, as a result.	No	The committee did not feel that a change was needed given the importance of, if access is not available to an external proficiency program, comparing test results to an outside laboratory.
5.1.2.3	Suggest removing the record retention requirement from this standard as it is already covered in standard 5.1.2.	No	The committee did not feel that a change was needed. The record retention requirement does not cascade through all substandards unless indicated in the record retention chart.

5.3 (5.31)	According to CGMPs, analytical methods or assays must be validated. Section 5.2 addresses process validation only. According to FDA regulation, 21 CFR 211.165(e) "The accuracy, sensitivity, specificity and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance to 211.194(a)(2). Please also refer to the following guidance for additional information: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm386366.pdf	No	The committee did not think that a change was appropriate at this time. The committee notes that for an agreement, test validation at the contracted laboratory would have to occur to ensure that laboratory meets the requirements in the standards. The committee feels that standards 5.2.3 and 5.2.4 cover this as well.
5.5.2.1, #10 (5.4.2.1, #10)	Please change the verbiage in subnumber 10 to be parallel with the language in 5.1.5.6 – "Certification of Analysis, manufacture's insert, or equivalent, if applicable."	Yes	The committee agreed with this comment and the change was made.
5.5.2.1, #10 (5.4.2.1, #10)	Revise to state: Certificate of Analysis or manufacturer's insert, **or equivalent**, if applicable. Consistent terminology with other references to Certificate of Analysis, such as Clause 5.10.1 12), which currently states: At the time of receipt, incoming cells, tissues, and organs shall be inspected, sampled, and/or tested, as appropriate, to determine their acceptability. Standards 5.8.2 and 5.9.6 apply. Records of the following shall be maintained: 12) Certificate of Analysis or manufacturer's insert **or equivalent**, if applicable.	Yes	As noted above, the committee made the change as requested.
5.5.3.1 (5.4.3.1)	Under Qualification of Material (5.5.3) if materials are not considered to be drugs or devices, and are not of appropriate grade, is there an option to perform additional testing prior to use? We don't really define grade but the materials must be of the appropriate quality. If they are not of appropriate grade, am I correct that we would put such items under 5.5.3.1 or perhaps 5.5.4 as they would not be approved by a competent authority.	No	The committee noted this comment but did not feel that a change was needed at this time. The committee notes that facilities have the options of performing one of the three options and do not have to perform all three. Facilities are required however to perform testing
5.5.3.1, #3 (5.4.3.1, #3)	**"**Investigational New Drug (IND) exemption, investigational device exemption, or other permitted by the FDA or relevant competent authority." This sentence is not clear and needs to be clarified. IND is not an exemption. Materials that are evaluated under INDs and IDEs do not necessarily provide assurance for safety and efficacy for all intended uses, but for a specific investigational product manufactured per IND or IDE. If this standard is only related to qualification of components (e.g. critical reagents), please note that qualification is required under CGMPs (21 CFR 211.84(d)(2)).	Yes	The committee agreed with this comment and added the clause, "…device approval for the specific material and indication…" for clarity and accuracy.
5.6.4 (5.5.4)	Irradiation and Leukocyte Reduction - Suggest removing 'if application' and putting in guidance how to address when they feel it does not apply to them (usually it does apply.)	Yes	The committee removed the term "if applicable" per the request. Given the significant effect leukoreduction may have on cellular therapy

	We have always told them that if they do not perform something outside the scope of their business to simply state that in their procedures. Ex. Our facility does not deal with cadaveric organs or tissues. Explaining the above is a common dialogue we have with initial cell therapy facilities since they commonly think only of the four walls of their facility and not of the hand off points. Adding 'if applicable' would exacerbate the situation.		products, this standard applies to all facilities, however if a facility had a product that this would not apply to, they would merely have to explain that in their standard operation procedures.
5.6.4 (5.5.4)	The addition of the wording "if applicable" is in conflict with the explanation. The explanation states that if activities are not performed, policies, processes, and procedures shall indicate this, indicating the standard *is applicable*, regardless.	Yes	As noted above the committee made the suggested change and removed the clause "if applicable."
5.7.1.3	Sample Traceability - When samples are collected from the donor, 2 independent identifiers should be required. Standard 5.13.3 requires this for product collection. The processing facility should then have a means of connecting the test results on the donor to the product.	No	The committee did not feel a change was needed at this time. They point to standard 5.14.4 which requires that a donor's identity be confirmed by two independent identifiers.
5.8	5.8 Split out labels, labeling and labeling controls into separate standards. See rewrite of this section just below: ********** 5.8 Labels, Labeling, and Labeling Controls, and Labeling The facility shall have policies, processes, and procedures for labels and labeling of products and samples. 5.8.1 Labels (PREVIOUSLY APPEARED AS PART OF 5.8) At a minimum, they shall address: 1) The acquisition and creation of cellular therapy product label templates. ✎C 2) Verification that the label stock meets facility-defined specifications. ✎C 3) The qualification, review, and approval of labels before use. Standard 6.1.2 applies. 5.8.1.1 ~~**5.8.3**~~Product Nomenclature Product names and descriptions on product labels shall use the terms and definitions found in the Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.* *http://www.iccbba.org ✎C 5.8.1.1.2 ~~**5.8, #6**~~ The implementation of ISBT 128 labeling by July 1, 2018.	No	The committee did not feel that such a change in format was appropriate for this edition of Standards. The committee will consider this request when work begins on the proposed 9th edition.

	5.8.2 ~~5.8, #4, #5~~Label Controls 1) The controls in place to ensure proper cellular therapy product identification. 2) The control of label inventory and templates, including discard. Chapter 6, Documents and Records, applies. 5.8.3 ~~5.8.1~~Labeling of Containers of Source Materials All containers of source materials, in-process cellular therapy products, and final products shall be labeled in accordance with Reference Standards 5.8.1A, Requirements for Labeling of Cellular Therapy Products, and 5.8.1B, Requirements for Labeling Shipping Containers. 5.8.3.1 ~~5.8.1.1~~Regulated investigational products shall be labeled according to local and/or national regulations. 5.8.3.2 ~~5.8.1.2~~Products approved or licensed by applicable local and/or national governments shall be labeled according to the terms of licensure or approval. 5.8.4 ~~5.8.2~~Packaging and Labeling Labeling information shall be verified for accuracy and completeness. 5.8.4.1 ~~5.8.2.1~~The procurement facility shall verify labeling immediately after procurement. 5.8.4.2 ~~5.8.2.2~~The processing and/or storage facility shall verify labeling at the following times, at a minimum: 1) Upon receipt at the processing and/or storage facility. 2) At facility-defined in-process steps, including transfer to a different storage location and removal/retrieval of attached segments and/or samples, if applicable. 3) At completion of processing and/or before storage. 4) Before distribution or issue. 5.8.4.3 ~~5.8.2.3~~The administering facility shall verify labeling before administration of the cellular therapy product.		
5.8, #6 (5.7, #6)	In support of the comments above to link the standards for Product Nomenclature to the implementation of ISBT 128 labeling by July 1, 2018, emphasis needs to be placed on seeking the proper source of information for both requirements (Standard Terminology for Blood, Cellular Therapy, and	No	The committee points to the fact that standard 5.8.3 which requires that facilities use ISBT nomenclature for labeling. For a facility creating

	Tissue Product Descriptions). Easy to do if they are linked together. Recently there are facilities who only seem to have adopted bits of the requirement, not realizing how codes are assigned, a license is required, etc. We are seeing "made up" codes, numbering schemes and misuse of fields because people just don't understand! (Toward that end, we are hoping AABB will plan to have an audioconference about what ISBT 128 labeling for CT really means and how it is intended/licensed to be used).		their own codes, they would be in violation of the standard.
5.8.3 (5.7.3)	Please note that for licensed HCT/Ps, non-proprietary names (proper names) must be reviewed and approved by the FDA. FDA has accepted product terminology by ICCBBA and ISBT 128 labeling only for certain 351 HCT/Ps (e.g. licensed cord blood products).	No	The committee reviewed this comment, however the naming conventions are not controlled by the Standards or the AABB. The decisions on naming are at the discretion of the facilities and ICCBBA.
5.11.3.1 (5.10.3.1)	Revise to read: The temperature **and/or liquid nitrogen level** of freezers where cellular therapy products are immersed in liquid nitrogen shall be recorded every 24 hours at a minimum. This ensures consistent terminology between standards 5.11.3 and 5.11.3.1, as current wording between standards 5.11.3 (continuous monitoring) and 5.11.3.1 (minimum every 24 hours) contradict one another. Additionally, the temperature of liquid nitrogen will not change. If products are immersed, and the level of liquid nitrogen is monitored, this should be sufficient to verify proper storage conditions Not all equipment for liquid nitrogen immersion has the capability to monitor temperatures (ie. BioArchives), only the level of liquid nitrogen.	No	The committee noted this comment but did not feel that a change could be made at this time. The committee will continue to review this standard and discuss what this change would mean with subject matter experts. Such a change at this time would require subsequent member feedback.
5.12.1.3 (5.24.1, #3)	There are several standards & reference standards that discuss the need for evaluating donor's risk for hemoglobinopathy. I cannot find any reference in the Neupogen package insert that points to an increase in adverse events for patients with hemoginopathy. However, there is a reference about patients with sickle cell disorders having rare but fatal sickle cell crisis. I think we need to first distinguish "hemoglobinopathy" vs. "sickle cell disease" because the former is a set of diseases involving hemoglobin synthesis problems such as sickle cell disease, thalassemia, hemoglobin S-C disease, while the latter is only one specific type of hemoglobinopathy. That said, there is a recent publication on this matter and the authors showed no increase in adverse events in African American donors with sickle cell trait as compared to Caucasian donors. Given the above, I would like to see the committee reevaluate the current recommendation for hemoglobinopathy evaluation, especially for the autologous donor population. Granted I can see a value in allogeneic donor population because the recipient should be forewarned if the donor has a heritable hemoglobinopathy disorder. Lastly, if the committee decides to retain	No	The committee noted this comment but did not think a change was needed at this time.Not narrowing the focus of the current standard will help ensure donor and recipient safety.

	this recommendation then I would urge that you further define what you expect as part of the evaluation process, i.e. asking for the donor for their personal medical history of hemoglobinopathy vs. performing hemoglobin electrophoresis vs. performing sickle cell screening test		
5.12.1.5.2 (5.24.1, #1)	Use ISBT 128 nomenclature for Marrow, i.e. HPC-Marrow.	Yes	The committee agreed with this comment and the change was made throughout the Standards.
5.12.2.2 (5.11.3.1)	Clarification needed for standard statement 3). Does this standard apply to all types of donors (allogeneic, allogeneic related, and autologous)? Not required for autologous products not cryopreserved. Recommend including an exception statement to 3) for investigational products. Recommended Additional Wording: ID testing for investigational products is performed as specified in the IND application.	No	The committee noted this comment but did not believe a change was needed at this time. The committee did not feel than an IND would be required in this case and confirmed this with the FDA.
5.12.2.8 (5.11.3.6)	Please note that in August 2016, FDA published a guidance document entitled Use of Nucleic Acid Tests to Reduce the Risk of Transmission of Hepatitis B Virus from Donors of Human Cells, tissues, and Cellular and Tissue-Based Products. The guidance recommends that HCT/P donors be tested for HBV using FDA-licensed NAT donor screening test. This is in addition to the donor screening tests for HBsAg and total anti-HBc. FDA recommends that the recommendation be implemented within 6 months after the guidance issuance date.	No	The committee noted this comment however could not make a change at this time as the referenced document is guidance. To make this change would be imprudent following the comment period and the committee will consider expanding this standard in the next edition.
5.12.2.8 (5.11.3.6)	Suggest converting this standard to a table or list for clarity.	Yes	The committee agreed with this comment and the standard was reformatted.
5.12.2.11 (New)	The new 5.12.2.11 is non-descript – how does this new standard ensure facilities react to emerging infectious disease outbreaks, such as Zika? It basically says - …shall define donor eligibility and suitability criteria….. It does not require a facility to respond to something new or emerging….	Yes	The committee noted this comment and in response edited the standard to require that action be taken when an emerging infectious disease is identified.
5.12.6.2 (5.11.7.2)	In 5.12.6.2, abnormal results are communicated to the donor **or** donor's physician while for cadaveric donors, these results are reported to appropriate authorities as required by law or regulation and made available to the donor's legal next of kin. For **live** donors, are there legal requirements to report positive test results for some diseases to appropriate authorities as well?	No	The committee did not feel that a change was needed at this time. The committee feels that the burden of showing what regulations may apply is the responsibility of the facility and not the AABB assessor to determine on site.
5.14.1 (5.13.1)	A medical order should be required for all product collections (live donor, invasive procedure, mobilizing agent administered, etc.) even if the recipient is unknown (except in the case of Cord Blood Collection for banking when the recipient is not known). There should be a medical order anytime an invasive	Yes	The committee agreed with this comment and elected to remove the clause "if the intended recipient of the cellular therapy product is

	procedure is performed (including sample collection and administering of growth factors etc.).		known at the time of procurement" and replaced it with "The procuring facility shall obtain a medical order before the procurement procedure other than for cord blood."
5.14.2 (5.13.2)	Suggest converting this standard to a table or list for clarity.	No	The committee noted this comment but did not feel that a change was needed.
5.14.2.1 (5.13.2)	Revise to allow the collection of a cord blood unit **before** completion of the determination of donor suitability; in particular, the health history. For cord blood collections, it is not always possible for all information to be obtained from the mother **before** procurement of the cord blood, including the complete assessment of infant donor health.	No	The committee did not feel a change was needed at this time. The committee notes that suitability has to be completed before procurement, however there are instances where eligibility has not.
5.14.3 (New)	Red Cross believes that the "topic header" to this standard appears to be missing. For example, the proposed Standard lists the topic header for 5.14.1 as **Medical Order for Procurement**; the proposed Standard lists the topic header for 5.14.2 as **Verification of Donor Suitability;** for 5.14.3, there is no topic header that defines the standard. If this is for Donor Eligibility, we are unclear on how to interpret this standard. It appears to be redundant with Standard 5.12.5 that pertains to the final determination of donor eligibility. In addition, the topic header for 5.12.5 appears to be missing. Please clarify the intent of Standard 5.14.3.	Yes	The committee agreed with this comment and in the process of reformatting and splitting "donor eligibility" from "donor suitability" the standard was given a header to ensure that it could be differentiated from standard 5.14.2.
5.14.3 (New)	Suggest adding, "…add ...determination of donor eligibility and/or suitability" to the standard.	No	The committee did not feel that a change was needed at this time and that the standard as written in its final form addressed this concern.
5.14.3 (New)	Clarification needed. Why does it matter if the intended recipient is known or unknown? Why wouldn't the donor eligibility be reviewed at procurement regardless (if available)?	Yes	The committee edited the standard from what appeared in the proposed edition removing the clause "If the intended recipient is known" for clarity and in light of this suggestion.
5.14.6.1 (5.13.5.1)	Is it necessary to define what other procurement details exist beyond this list?	No	The committee noted this comment and feels that the list is fully inclusive of what is needed for a procurement record.
5.17.1 (5.16.1)	See comment about 4.3.1 concerning agreements and obtaining orders. Here it has physician order. In 4.3.1, it is defined as medical order. Re: 4.3.1 - The Standard has the processing and procuring facilities as responsible for the medical orders. However, the orders come from the clinical	Yes	The committee agrees that ensuring the terminology throughout the standard remains consistent is paramount. To remain consistent, the committee also added

	facility. The respective facility is responsible for ensuring agreements are in place, not responsible for obtaining the orders from the clinical group.		the clause "except for HPC, cord blood manufacturing facilities…" to the standard.
5.17.5 (5.16.5)	Suggest adding a record retention requirement to this standard.	No	The committee did not think this change was needed at this time.
5.20 (5.19)	Revise to state: Expiration Dates **and/or** Stability of Products Expiry dates should be determined based on results of stability studies. Therefore, both should be viable options.	No	The committee did not feel that this change was appropriate at this time. The standard in question does address both issues, expiration dates and stability so the feeling is that the request is already covered.
5.23, #5 (5.22, #5)	Change donor to recipient or reword so it is clear that the product should be compatible with the recipient.	Yes	The committee agreed with the suggestion and replaced the term "donor" with "recipient."
5.24, #5 (5.23, #5)	Change donor to recipient or reword so it is clear that the product should be compatible with the recipient.	Yes	The committee agreed with the suggestion and replaced the term "donor" with "recipient."
5.25.1 (5.24.2)	Use of the terminology "define criteria" is confusing because standard 5.12.1 refers to defining criteria. Should this this standard be stating criteria must be met? Recommended Wording: ~~The facility shall defined~~ Criteria for the selection of donors or products **shall be met** before the initiation of any intervention that could potentially affect the health of a donor or recipient. This evaluation shall be conducted by a designated health care professional. For all products, donor suitability and eligibility. Standard 5.12 applies.	Yes	The committee reviewed this comment and based on the substance of it revised the standard. The standard has a new title, replacing "Donor Evaluation" with "Patient Evaluation." The committee also, edited the first sentence to read, "The facility shall have policies, processes, and procedures to define clinical indications and evaluation criteria for treatment." This allows the standard to run parallel to the language that appears in most standards that begin a section.
5.26	Provide clarification on how medications related to administration covered by graft-versus-host disease and infectious disease management?	No	The committee noted this comment and will address this issue in guidance.
5.29.3	Delete 'if applicable'. It sounds like it is up to the facility if they feel they need PPPs or if the physicians knows what to do that is good enough. Change to state: The clinical facility shall have PPP for the following if they are part of the clinic program.	Yes	The committee agreed with the submitted comment and removed the term "if applicable" from the stem of the standard.
5.8.1A, #22 (5.7.1A)	We are requesting an interpretation of Cellular Therapies Reference Standard 5.8.1A, specifically the standard that requires the statement "Properly Identify Intended Recipient and Product" appears on cellular therapy product labels. The requirement designates that statement is to be attached or (maybe) permanently affixed. The requirement is further footnoted by the statement, "If affixing or	No	The committee noted this comment but did not feel that a change was needed at this time.

	attaching the applicable warnings and statements to the container is physically impossible, then the labeling must accompany the human cells, tissue, and cellular- and tissue-based products." The standard makes no differentiation between labels for autologous products and labels for designated recipients.		
5.9.5A (5.8.5A)	Suggest adding "1271.65(b)(2)" to this footnote.	Yes	The committee agreed with this comment and the reference was added to the footnote.
5.12A, III, #6 (New)	Is the intention that we no longer require approval by the facility medical director before *procurement* of ineligible donors? (regulations require only documentation of the notification of the recipient's physician) Regardless, the standard was already duplicative of 7th edition, reference standard 5.11A, III, A, 6 for all donors. 7th edition: 5.11A, III, A, 6 = Procurement and use of products from allogeneic donors who do not meet eligibility (determined to be incomplete or ineligible) shall require written approval by the facility's medical director and recipient's physician. Assuming your recognition of that, Page 8 of 8th edition proposed standards, reference standard 5.12A, III, A, 6 indicates removal of procurement: Reference Standard 5.12A, #6 6) ~~Procurement and~~ Use of products from allogeneic donors who do not meet eligibility criteria (determined to be incomplete or ineligible) shall require written approval by the facility's medical director and the recipient's physician. Products shall be labeled appropriately. However, the language of the proposed standard 5.12A, III, A, 6 on page 68 does not match the proposed language for that standard on page 8, having also removed the facility medical director reference and adding in documentation of urgent medical need: 8th edition (proposed): 5.12A, III, A, 6 = Use of products from allogeneic donors who do not meet eligibility criteria (determined to be incomplete or ineligible) shall require written approval *and documentation of urgent medical need by the recipient's physician.* Product shall be labeled appropriately.	No	The committee reviewed the comment and did not feel that a change was needed at this time. The committee feels that the issue is addressed within the wording of the requirement as re-written.
5.12A, III, B, #4 (5.11A)	"DBD or DCD" not defined, please do so.	Yes	The committee agreed with this comment and the abbreviations were spelled out.
5.12B, II (5.11B)	Ref Std 5.12.B- Clinical Evaluation of Donor Eligibility section II includes asking "risk of any condition, such as malignancy or any inherited condition that could be transferred to the recipient by transplant". Our facility understands why you placed it in section 2 along with other questions you ask to protect the safety of the recipient, and agrees that they are excellent questions to	Yes	The committee reviewed this comment and edited the title of this section to read, "Clinical Evaluation to protect the safety of the recipient."

	ask to protect the safety of the recipient. However, our facility disagrees with the placement of this question here as it is under the header of section II that says "Donor Eligibility". Malignancy and inherited conditions are not defined by the FDA as RCDADs and do not have to be used when making the eligibility determination as defined by the FDA. Our facility understand that the FDA regulations are minimal and that AABB may choose to be more prescriptive. However, our facility disagrees that the results of the response (or lack thereof) to this question would lead to a determination of Ineligible, and including it in this section leads you to conclude that an affirmative response should render the donor ineligible. Our facility recommends that you move it to the table "History and Behavioral risk for exposure to..." and add footnote 6 to it like you do with Malaria - that clarifies that risks identified for these diseases - do not render the donor ineligible.		
5.12B (5.11B)	The use of "sepsis" in place of "bacteremia" is not medically accurate. Sepsis refers to the both clinical AND laboratory evidence of infection. If the intent is to have a term encompassing all types of infection, perhaps "clinically diagnosed infection or history of positive microbial culture" would be more appropriate.	No	The committee decided to use the term “sepsis” instead of “bacteremia.” The FDA defines an individual with sepsis as someone who has a relevant communicable disease agent or disease, and as such, maintaining this term was deemed the most accurate.
5.17A, B (5.16A)	HPC Products should not be included with all other CT Products they should be in a separate category as before in the 6th Edition. It is confusing for facilities and there are significant differences between HPC products and somatic cell products (or CT products containing cells other than HPCs). Consider: i) Returning to 3 categories: HPC, Cord Blood; HPC, other than cord blood (peripheral blood, marrow, etc.); Cellular Therapy Products (other than HPC) OR ii) Put all HPC together i.e. do not have a separate category for cord blood as it is not necessary & is actually confusing. Some requirements which apply to HPC, Apheresis and HPC, Marrow only appear under the HPC, Cord Blood category A point to consider in support of a separate "all cells other than HPCs" (Somatic Cell Therapy Products) category: The FDA Form for Establishment Registration includes the following categories for types of HCT/Ps (Human Cells, Tissues, and Cellular and Tissue-Based Products):	No	The committee reviewed this comment but did not think that a change was needed at this time. The extent of the change to move to three separate reference standards would be too large a change to put forth without member and public input.

	k. PBSC (Auto/ Allo/ Family Related) o. Somatic Cell Therapy Products (Auto/ Allo/ Family Related) q. Umbilical Cord Blood (Auto/ Allo/ Family Related) Note: HPC products includes BM for AABB, however does not appear on FDA form because regulated by HRSA not FDA.AABB should still require same tests etc. as required for other HPCs		
5.17A, #1, c) (5.16A)	The term "donor lymphocyte infusion" is no longer an accepted term - consider using proper ISBT name or reference using the proper ISBT name as applicable to the product.	Yes	The committee agreed with this comment and edited the standard accordingly. Letter "c" now reads, "For T Cell, CD3+ cell count."
5.17A, #1, c) (5.16A)	Suggest deleting "Donor Lymphocyte" infusion as it is older terminology. Do you mean T-Cells or MNC? Also, 1) e covers relevant cell count.	Yes	The committee agreed with this comment and made the suggested change.
5.17A, #4, c (New)	Potency is defined as "the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result." (21 CFR 600.3(s)). The purpose of potency assay is to measure the biologic activities of the product that is relevant to the mode of action. The recommended assays, over all viability and CD34+ (and bone marrow is excluded for CD34) may be inadequate.	No	The committee noted this comment but did not feel that a change was needed at this time. The committee noted that the standard requires potency for the specific cellular therapy product and as such, these are the minimum the standards can require. Facilities are free to do further potency testing if they feel it is appropriate. The committee will provide guidance in the Portal to assist users in the implementation of the standard.
5.17B (5.16B)	We suggest that you include a statement regarding the FDA requirement for retention sample. According to 21 CFR 211.170, for product regulated as 351 products, an appropriately identified reserve sample that is representative of each lot in each shipment of each active ingredient shall be retained.	No	The committee noted this comment but did not feel at this point of the process it would be appropriate to make such a large change. The committee will consider this for the 9th edition however.
5.17B #1 (5.16B)	Testing for ABO/Rh type should appear for HPC apheresis and marrow products as it is on Cord Blood. Any HPC product should have ABO/Rh typing performed (on product and / or on sample collected at time of product collection). Not simply "If the product contains red cells" as is stated in current Standard (7th Ed 5.16A #6). That statement could appear for the "Other cells" category.	No	The committee reviewed this comment and did not feel a change was needed. This entry refers to product testing and not donor testing for ABO/Rh.

5.17B #5 b (5.16B)	Hemoglobinopathy TESTING (rather than SCREENING) although the standard goes on to say "on a sample from obtained from the product or from the donor," it would provide consistency with Standard 5.12.2 "Screening and Testing" and eliminate confusion between requirements for information obtained via health history screening and test results, both of which are required for cord if it is issued.	Yes	The committee agreed with this comment and replaced the term “screening” with “testing” to ensure that testing is performed.
5.17B, #7 PROPOSED (5.16B)	It is unclear if this standard is only for licensed cord blood banks or if all cord blood bank need to know what is in a US FDA license application and perform those tests as well.	No	Number 7 was new to the proposed standards and read, “ These tests shall be performed in addition to any testing required to conform to the criteria defined in a US FDA license application.” Based on this comment, the committee did not feel that the inclusion of this standard at this time was appropriate and removed it from the edition.
6.2.9.1 (New)	Please note that according to 1271.55(d)(4) and 1271.270(d), records for a specific HCT/P must be retained 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 HCT/P distribution, disposition, or expiration, whichever is latest. For 351 HCT/Ps, there are additional requirements for records in 21 CFR 211.180.	Yes	The committee agreed with this comment and created new standard 6.2.9.1 to address it and to ensure there was consistency between the FDA regulations and the Standards. The new standard reads as follows, “If the date of administration is unknown, records shall be retained for 10 years after the date of distribution, disposition, or expiration, whichever is latest. Applicable national, state, or local law may exceed this period.”
7.2.2.2.1, #2 (7.2.2.2.1, #3)	It is unclear why standard statement 3) was removed as good practice is to include the recipient in communication of out-of-specification or nonconforming values or results. Additionally this change does not align with FACT standard B 4.9.1. *B4.9 The Quality Management Plan shall include, or summarize and reference, policies and procedures on the management of cellular therapy products with positive microbial culture results that address at a minimum:* *B4.9.1 Notification of the recipient.* *B4.9.2 Recipient follow-up and outcome analysis.* *B4.9.3 Follow-up of the donor, if relevant.* *B4.9.4 Reporting to regulatory agencies if appropriate.*		The committee also added the term “recipient” to subnumber 2 to remain consistent with other standards setting organizations.

	B4.9.5 Criteria for the administration of cellular therapy products with positive microbial culture results.		
7.2.3	Change verbiage to say: … shall have policies, processes, and procedures that at a minimum ensure**.** It is not only the facility of <u>final</u> distribution that should comply - also collection & processing facilities should address	Yes	The committee noted this comment and added in a new opening sentence to the standard which reads as follows, "The facility shall have policies, processes, and procedures addressing…"
7.3.3 (New)	The processing facility should also be included. Also, non-engraftment (or graft failure) should be considered an Adverse Event	Yes	The committee agreed with the spirit of this comment (which was submitted as an element of 7.3 previously.) New standard 7.3.3 requires that the processing facility have a process to evaluate reported adverse events. Previously, standards 7.3.1 and 7.3.2 addressed this process in procurement facilities and in clinical programs. The new standard specifically covers processing facilities.
Chapter 9	Add new standards similar to 9.1 and 9.2 for "Root Cause Analysis process shall include:"	No	The committee noted this comment but did not think it was needed as this is covered in both 9.1 and 9.2 adequately.
10.1.3			The committee included the clause "including oxygen monitoring" in the standard for clarity.