2 Administrative and Regulatory Considerations for Apheresis Collection Facilities

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2.1 Introduction

Autologous mononuclear cells, collected by leukocytapheresis and cryopreserved, have virtually replaced marrow as a source of $CD34^+$ cells for autologous hematopoietic cell rescue after myeloablative therapy for myeloma and lymphomas. Furthermore, the recent introduction of chimeric antigen receptor T-cell (also known CAR T-cell) therapy involves removal of T-cells from the patient via leukocytapheresis and subsequently their modification so that they express receptors specific to the patient's particular cancer. As such, apheresis facilities, which perform those collections, are an integral and critical part such therapeutic modalities including allogeneic peripheral blood hematopoietic progenitor cell collections.

The field of cellular therapy which includes apheresis facilities as the cellular product collection facility is a highly regulated discipline. Over the world, different regulatory bodies are providing oversight at various levels. While in most countries, national regulations are in place provided by governmental authorities, for example, the Food and Drug Administration (FDA); there might be additional regulations at a state level. Furthermore, national regulations may follow directives from a state union (e.g., EU directives being obligatory for EU member states) or might be supplemented by standards published from nongovernmental organizations (see below). Although the latter are not legally binding, they might be regarded to represent the standard of care in legal cases where no laws apply.

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The FDA and Centers for Medicare and Medicaid Services (CMS) are the primary regulatory agencies providing federal oversight in the United States. In addition, state health departments and other agencies may provide some degree of regulatory oversight. In the European Union, the European Council and Commission provides oversight for those facilities, releasing directives that translate into national laws and regulations while oversight is provided by health authorities of the EU member states. In addition, individual countries might have their own regulatory frame. Individuals and apheresis facilities involved with cellular therapies should be familiar with the different requirements of these agencies.

Apheresis facilities also should be familiar with all relevant state/country and local laws and regulations, including professional licensure requirements for medical and laboratory personnel, as many states/countries (in the United States and worldwide) have regulations which apply to apheresis professionals. Further laws and regulations may cover equipment (apheresis instruments, collection sets, additive solutions, etc.). Furthermore, in some situations, apheresis facilities providing cell therapy products in other states/countries must comply with local regulations in the final destination.

It is important to distinguish between regulation and accreditation. Regulations have the force of law while accreditation standards are not legally binding. Cellular therapy facilities must follow the rules set by regulatory agencies. In contrast, accreditation agencies such as FACT-JACIE, AABB, or the Joint Commission (the United States only) publish specific sets of standards that need to be met in order to provide accreditation. Some regulatory agencies will grant deeming authority to selected accreditation agencies. For example, the CMS regulates laboratory testing through the Clinical Laboratory Improvement Amendments (CLIA). CMS accepts certain accreditation agency inspections. Table 2.1 summarizes agencies and organizations involved in regulation and accreditation of cellular therapy facilities including apheresis facilities. The scope of their regulatory oversight and/or accreditation is detailed on these organizations' respective websites.

Table 2.1 Regulatory or accreditation agencies involved in cellular therapies

Regulatory agencies	Accreditation organizations
The Food and Drug Administration (FDA)	AABB
Centers for Medicaid and Medicare Services (CMS)	Foundation for the Accreditation of Cellular Therapy (FACT)
Department of Homeland Security	The Joint Accreditation Committee—ISCT and EBMT (JACIE)
Nuclear Regulatory Commission (NRC)	National Marrow Donor Program (NMDP)
Environmental Protection Agency (EPA)	World Marrow Donor Association (WMDA)
Occupational Safety and Health administration (OSHA)	College of American Pathologists (CAP)
Council of Europe/European Commission	

2.2 Human Cells, Tissues, and Cellular- and Tissue-Based Products (HCT/Ps)

In the United States, human cells, tissues, and cellular- and tissue-based products (HCT/Ps) are defined as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient (Code of Federal Regulations 2015). HCT/Ps can be derived from deceased or living donors (Table 2.2). The FDA established a comprehensive, tiered, risk-based regulatory framework applicable to HCT/Ps. These regulations, which were published in three parts (referred to as the "tissue rules") and contained in the code of federal regulation (CFR), more specifically in 21 CFR 1271, became fully effective on May 25, 2005, and are applicable to all HCT/Ps, including hematopoietic progenitor cells (HPCs), that are recovered on or after this date (Code of Federal Regulations 2014; FDA Tissue Guidances n.d.). This risk-based framework authorizes the FDA to establish and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases in HCT/Ps which are regulated solely under section 361 of the Public Health Service (PHS) Act [42 USC 264] (United States Code n.d.) (Table 2.3).

In the European Union, the EU directives 2004/23/EC, 2015/566, 2006/17/EC, 2006/86/EG, and 2015/565 currently apply (for updates, please consult www.eur-lex.europa.eu), while for advanced therapy medicinal products (ATMP) further regulations from the European Medicines Agency apply (www.ema.europa.eu).

The AABB, The Foundation for the Accreditation of Cellular Therapy (FACT), and the Joint Accreditation Committee ISCT and EBMT (JACIE) set voluntary cellular therapy standards (Table 2.4) including collection, processing, and administration (Allickson 2015; FACT 2015) with accreditation cycles of two, three, and four years, respectively. The principles of these standards and accreditation are based on a peer-based review process incorporating both medical and laboratory practice which is best suited to protect patient safety, improve cellular therapy practices, and protect the research environment. College of American Pathologists (CAP) transfusion medicine checklist (College of American Pathologists, Commission on Laboratory Accreditation 2015) includes cellular therapy and apheresis-specific requirements. The World

Table 2.2 Examples of HCT/Ps

From deceased donors[a]	From living donors[a]
Skin	Hematopoietic stem/progenitor cells from bone marrow, peripheral and cord blood
Dura mater	Other cell therapy products (e.g., pancreatic islets, mesenchymal stem/stromal cells, fibroblasts)
Cardiovascular tissues	Reproductive cells and tissues
Ocular tissues	
Musculoskeletal tissues	

[a]In general, but there are exceptions

Table 2.3 US regulations for manufacturers of hematopoietic progenitor cells

Type of HPC product	Regulatory category/ oversight	Key regulations (21 CFR except as noted)	FDA premarket licensure, approval, or clearance?
Minimally manipulated bone marrow, not combined with another article (with some exceptions) and for homologous use	Health Resources and Services Administration oversight	42 US Code 274(k)	Not applicable
Autologous or allogeneic related (1st or 2nd degree blood relative)-donor HPCs	PHS Act Section 361: HCT/Ps[a]	1271.10(a)[b] (must meet all criteria); 1271 Subparts A–F	No
Minimally manipulated Unrelated-donor peripheral blood HPCs, not combined with another article (with some exceptions) and for homologous use	PHS Act Sections 361 and 351: HCT/Ps regulated as drugs and/or biological products	1271 Subparts A–D Applicable biologics/drug regulations	Delayed implementation
Minimally manipulated unrelated-donor umbilical cord blood cells	PHS Sections 361 and 351: HCT/Ps regulated as drugs and/or biological products	1271 Subparts A–D	Yes (after October 20, 2011): BLA or IND application
HPCs that don't meet all the criteria in 21 CFR 1271.10(a)	PHS Sections 361 and 351 HCT/Ps regulated as drugs and/or biological products	1271 subparts A–D Applicable drugs/biologics regulations	Yes: IND and BLA

HPC hematopoietic progenitor cell, *CFR* code of federal regulations, *FDA* Food and Drug Administration, *PHS* public health service, *HCT/Ps* human cells, tissues, and cellular- and tissue-based products, *IND* investigational new drug, *BLA* biologics license application

[a]As defined by 2005 tissue regulations [21 CFR 1271.3(d)]

[b]21 CFR 1271.10(a) as applied to Section 361 (see full rule for details) requires that HPCs be (1) minimally manipulated, (2) for homologous use only, (3) not combined with another article (except water; crystalloids; or sterilizing, preserving, or storage agents with no new safety concerns), and (4) for autologous use or for allogeneic use in a first- or second-degree blood relative

Table 2.4 Cellular therapy accreditation

Organization	Standards review cycle
AABB	Two years
FACT	Four years
JACIE	Four years
NMDP	Two years
WMDA	Five years
CAP	Not set (yearly published updated check list)

Marrow Donor Association (WMDA) fosters international collaboration to facilitate the exchange of high-quality hematopoietic stem cells for clinical transplantation worldwide and to promote the interests of donors. WMDA is also accrediting and qualifying donor registries who follow its global standards that cover all aspects of unrelated hematopoietic stem/progenitor cell registry operations. The National Donor Marrow Program (NMDP) Standards set forth basic guidelines and requirements for programs working with the NMDP. The Standards encompass network participation criteria with requirements for transplant centers, recruitment centers, and product collection centers. The NMDP standards are designed to ensure that donors and patients receive high-quality care and that government standards are met (Table 2.4).

The Circular of Information for the Use of Cellular Therapy Products is jointly written by the AABB and multiple organizations involved in cellular therapy for users of certain minimally manipulated unlicensed cellular therapy products (AABB et al. 2016). It is getting revised periodically with representatives from all relevant organizations and many of the standard setting organizations require it will be included with the collected cellular therapy product when being shipped or transported.

In addition, the Alliance for Harmonization of Cellular Therapy Accreditation (AHCTA), which is under the umbrella of WBMT, encompasses all the above-mentioned accreditation organizations. AHCTA is working toward creating a global comprehensive single set of quality, safety, and professional standards which cover all aspects of the process from assessment of donor eligibility to transplantation and clinical outcomes of HCTs and related cellular therapies. AHCTA provides helpful documents to navigate the different sets of participating organizations' standards. Moreover, crosswalk documents comparing the different set of cellular therapy standards were created and are available on the AHCTA website (http://www.ahcta.org/documents.html). AHCTA also published a document on essential elements as a resource for new or developing programs, identifying the most important quality system elements for cells and tissues for administration.

Of note, the FDA regulations in 21 CFR Part 1271 require HCT/P manufacturers to have a tracking and labeling system that enables tracking each product from the donor to the recipient and from the recipient back to the donor. The HCT/P manufacturers are also required to inform the facilities that receive the products of the tracking system that they have established. ISBT 128 and equivalent systems in Europe, such as Eurocode, are considered an acceptable labeling system for those purposes.

2.3 Expert Opinion

Cellular therapy regulations and standards such as the FACT-JACIE cellular therapy standards ensure high-quality cellular therapy products as they standardize processes related to collection, processing and administration. Those standards are based on scientific literature, clinical practice, governmental regulations, and community inputs. Based on these standards, the accreditation agency offer accreditation to transplant programs in order to encourage health institutions and facilities performing bone marrow and peripheral blood transplantation to establish and maintain quality management systems impacting on all aspects of their activities

and to engage in continuous improvement. In order to be in compliance with the current edition of the standards, apheresis facilities need to review the new edition of the standards and use the accompanying guidance to understand the intent of the standards and how the change is different than their current process. In addition, each accreditation organization is providing tools to help make the transition smooth including a comprehensive summary of changes and a crosswalk comparing the previous edition to the new one.

2.4 Future Directions

Ideally, one set of standards which are comprehensive and acceptable by all organizations involved in regulating and accrediting apheresis facilities should be the goal. This will achieve a global comprehensive single set of quality, safety, and professional standards which cover all aspects of the process from assessment of donor eligibility to transplantation and clinical outcomes of HCTs and related cellular therapies and decrease the burden of apheresis facilities to be familiar with different sets of standards.

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