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REVIEW

Quality compliance in the shift from cell transplantation to cell therapy in non-pharma environments

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Abstract
Along with academic and charitable organizations, transfusion centers have ventured into the stem cell field, with the aim of testing of novel cell-based therapeutics in a clinical setting for future marketing approval. The fact that quality management structures, which are required for compliance with good scientific practice regulations, were originally designed for product development in corporate environments represents a major challenge for many developers. In this *Commentary*, challenges that non-pharmaceutical institutions must overcome to translate cell-based products into clinical therapies will be discussed from a quality standpoint. Furthermore, our development experience for a mesenchymal stromal cell–based therapy will be shared as a case study.

Key Words: *cell-based therapeutics, Good Laboratory Practices, Good Manufacturing Practices, product development, quality compliance*

Take-home messages

- Academic institutions and transfusion centers currently lead early-stage clinical development of cell-based therapeutics.
- New regulatory categorization of traditional blood and tissue products as cell-based therapeutics entails more rigorous quality standards.
- We share our experience in the development of cell-based medicinal products in a non-profit institution from a standpoint of quality compliance, which may be of practical use to other cell therapy developers.

Introduction

Exploiting the potential of stem cells through the development of novel manufacturing procedures provides an unlimited source of cell-based therapeutics and an alternative to blood and tissue donation [1]. Consequently, cell-based therapeutics are envisaged as the next pillar in medicine [2–5] because they build on traditional cell transplantation approaches to deliver patient-tailored interventions [6]. The main difference between traditional and modern approaches is that procedures used for cell therapy often include extensive manipulation and/or use of cells for a new or different function; thus, the resulting products are categorized as drugs. To ensure patient safety, specific regulatory and quality requirements are applied to cell-based medicinal product (CBMP) development programs, which must comply with current Good Laboratory [7–9]/Tissue [10,11]/Manufacturing [12–14]/Clinical [15–19]/Distribution [20] Practice (GxP) standards according to US Food and Drug Administration (FDA) and European Medicines Agency (EMA) legislative frameworks [21]. Furthermore, the complex nature of living CBMPs requires a significant endeavor to properly address aspects such as product identity, purity, potency and safety within the appropriate quality assurance environment.

The expertise of blood, transfusion and tissue centers in cell and tissue collection, donor testing

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Table I. Approved human cell–based therapeutics.

Product	Cell type	Cell source	Manufacturer
In the United States[a]			
Provenge	Immunotherapy	Autologous	Dendreon Corporation
Laviv	Fibroblasts	Autologous	Fibrocell Technologies Inc
Carticel	Chondrocytes	Autologous	Genzyme Biosurgery
Gintuit	Keratinocytes and fibroblasts in bovine collagen	Allogeneic	Organogenesis, Inc
Allocord	Hematopoietic progenitor cells	Allogeneic (cord blood)	SSM Cardinal Glennon Children's Medical Center
Hemacord	Hematopoietic progenitor cells	Allogeneic (cord blood)	New York Blood Center
Ducord	Hematopoietic progenitor cells	Allogeneic (cord blood)	Duke University School of Medicine
Unbranded	Hematopoietic progenitor cells	Allogeneic (cord blood)	Clinimmune Labs, University of Colorado Cord Blood Bank
Unbranded	Hematopoietic progenitor cells	Allogeneic (cord blood)	LifeSouth Community Blood Centers, Inc
In Europe[b]			
Chondroselect	Chondrocytes	Autologous	TIGenix
MACI	Chondrocytes	Autologous	Genzyme
Provenge	Immunotherapy	Autologous	Dendreon Corporation
In Canada and New Zealand [26]			
Prochymal	Mesenchymal stromal cells	Autologous	Osiris Therapeutics, Inc
In Japan [26]			
JACE	Epidermis	Autologous	Japan Tissue Engineering Company (J-TEC)
JACC	Cartilage	Autologous	Japan Tissue Engineering Company (J-TEC)
In Korea [26]			
Hearticellgram-AMI	Mesenchymal stromal cells	Autologous	Pharmicell
Cartistem	Mesenchymal stromal cells	Autologous	Medipost

With the exception of blood products, the products include a substantial manipulation in their manufacture. Only approved human cell–based medicines were included.
[a]http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/.
[b]http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124.

and banking positions them advantageously to bring cell therapies to the bedside because these centers are usually located in or adjacent to hospitals, which ensures availability of source tissue. Furthermore, their direct contact with researchers, clinicians and patients has already driven initiatives for the development of a range of new cellular therapies. Indeed, some traditional blood-related products have been marketed as therapeutics in an attempt to continuously improve product quality (Table I). Even though FDA regulatory oversight is not currently required for "minimally manipulated" blood products, The New York Blood Center raised the level of quality by registering Hemacord, a product consisting of allogeneic hematopoietic progenitor cells obtained from cord blood.

Quality standards

Current quality standards in cell transfusion (such as voluntary accreditation schemes administered by AABB, JACIE, FACT, NetCord and others) serve to promote patient care and excellence in laboratory practice by standardizing procedures for the collection, analysis, banking and release of cells for transplantation. As the use of blood-related products grows, substantial efforts have been made to harmonize accreditation of cellular therapies at a global level. The scope of such initiatives (AHCTA, www.ahcta.org) are limited to traditional cell transplantation products, whereas requirements for marketing authorization of CBMPs are essentially the same as for biologics and small molecules manufactured in traditional pharmaceutical settings. Regulatory compliance and approval entails performing nonclinical studies, defining product quality specifications and confirming safety and efficacy profiles in clinical trials. Rather than voluntary, GxP compliance is mandatory in the development of cell-based therapeutics.

Current Good Manufacturing Practice (GMP) standards describe methods to ensure proper design, monitoring and control of manufacturing processes and facilities. Adherence to GMP regulations ensures the identity, potency and purity of drug products by adequately controlling manufacturing operations to prevent contamination, mix-ups, deviations, failures and errors. Compliance involves establishing strong quality management systems and standard operating procedures, obtaining and documenting appropriate quality raw materials, detecting and investigating deviations and maintaining reliable testing laboratories in which trained personnel perform validated processes with the use of qualified equipment. GMP must be addressed within