

Source-Cell Storage Systems for Allogeneic Cell Therapy Products: Comparison of the Regulatory Systems in Target Countries

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ABSTRACT

Background: This study aimed to analyze autologous and allogeneic cell therapies. A gap analysis of source-cell storage regulations and guidelines of allogeneic cell therapies was performed for regulatory authorities in target countries, including the USA, EU, Japan, and Korea.

Methods: Cell-storage regulations and guidelines regarding allogeneic cell therapy products framed by regulatory authorities were comparatively analyzed.

Results: Of 41 cell therapies, 10 allogeneic cell therapies were selected, and their source cells were categorized based on 3 types of cell storage, namely cell bank (n=6) in the USA, Japan, and Korea; cell stock (n=2) in the EU; and drug substance (n=2) in Korea. In the gap analysis of cell storage regulations and guidelines by the selected regulatory authorities, cell storage systems have regulations and guidelines similar to those stipulated by regulatory authorities, except for the regulation of source-cell changes. Most allogeneic cell therapies used cell banks for cell storage. Thus, to ensure the safety of allogeneic cell therapy, more detailed criteria must be established for source-cell changes in cell storage systems.

Conclusion: Regulatory authorities can ensure a safer and more effective supply of therapy products to the public by harmonizing the regulations associated with allogeneic cell therapies.

Keywords: Cell therapy product; Allogeneic cell therapy product; Cell storage; Regulatory system; Regulatory science; Gap analysis

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Cell therapy products are classified as advanced therapy medicinal products (ATMPs) [1]. They are derived through the physical, chemical, and biological manipulation of cells using various processes, such as the *in vitro* culture of autologous, allogeneic, or xenogeneic cells [2,3]. Cell therapy products are closely related to gene therapy

products when the latter employ cells as the source of the therapeutic agent. These hold the promise of providing a cure or treatment for diseases that cannot be managed using conventional medicines and procedures [1,4-6].

Currently, the market for and investment in cell therapy products are focused on the development of allogeneic-

ic cell therapy products that have some advantageous over autologous cell therapy products [7,8]. The former is available for immediate delivery because manufacturing can be completed in advance and the product can be stored for later use; conversely, for the latter, manufacturing begins only after the patient has acquired a condition [9]. Additionally, for companies practicing large-scale manufacturing, the former is a more economically advantageous business model than the latter [8,10].

The source cells of allogeneic cell therapy are generally frozen and stored, and regulatory authority has regulated source cell storage as the starting point of the manufacturing process [8,11,12]. Source cells for manufacturing allogeneic cell therapy products possess an inherent risk of contamination by an infectious agent such as a virus; infectious agents could then be amplified during the production process, owing to either the origin of the cells or some flaws in the manufacturing process [13–15]. Therefore, appropriate quality control tests are performed throughout the process, i.e., from receipt of the source cells to release of the product. For cell therapy products, collection of the cells is managed during the “manufacturing process” step whereas the quality control of drug substances and the completed drug is managed during the “specification and tests” step [11]. Although a large number of safety-related test reports, donor screening, and laboratory tests can be exempt for autologous products, this is not the case for allogeneic cell therapy products [13,16].

Recently, a safety issue was raised in Korea regarding the source cells of a cell line [10]. After inspection, the Korea Ministry of Food and Drug Safety (MFDS) stated that no problem was found regarding the cell storage system [17]. However, another issue related to source cells was raised concerning the cell-based gene therapy Invossa-K [18]. Similarly, important issues related to source cells for allogeneic cell therapy products have emerged, even though more rigorous safety regulations are being continuously developed for allogeneic cell therapy products than for autologous cell therapy products [19]. Moreover, allogeneic cell therapy products are continuously being developed [20].

Previous studies have described and summarized specific regulations for cell therapy products [21–27]. However, despite concerns regarding the storage of source cells for allogeneic cell therapy products, the relevant regulations have not yet been comparatively analyzed. The

goals of this study were as follows: (1) to investigate the latest overall cell therapy products, including autologous and allogeneic cell therapy, to check the market authorization status; (2) to analyze the current status of source cell storage for allogeneic cell therapy products and perform gap analysis of the source cell storage regulations and guidelines for allogeneic cell therapy in countries with advanced regulatory systems, namely the US, EU, Japan, and Korea.

METHODS

Specification of Research Subjects

For the selection of research subjects, eligibility criteria were applied to i) cell, tissue, and gene products listed as of June 2021 by the International Society for Cell & Gene Therapy (ISCT), a global society that focuses on cell therapy products worldwide, and were certified as “category A,” according to the International Organization for Standardization (ISO); and ii) products listed on the website of each regulatory authority, after being double-checked and updated [28]. The inclusion criteria for selecting cell therapy products was based on Petriccinai et al. [1]. for clinical perspectives of cell-based therapy based on the level of manipulation. The exclusion criteria were obtained from the standards for minimal manipulation used by the regulatory authority to avoid any issues regarding safety (extent of maintaining biological properties) [11,29,30]. Accordingly, allogeneic cell transplantation, which is a surgical procedure, was excluded. This is because transplantation is minimally manipulated and is not included in the allogeneic cell therapy that is substantially manipulated. The following were also excluded: countries where a given product was not marketed, products whose market authorization (MA) had been revoked as of June 2021, and gene therapy. Allogeneic cell therapy products were selected with reference to the founding regulatory members of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Korea. The regulatory systems of cell storage in Korea were compared with those of the ICH-founding regulatory members, namely the US, EU, and Japan [31]. These members were considered to be advanced in terms of their regulatory framework and thus were expected to assist new ICH member countries such as Korea, which became a member in 2016 [32].

Data Collection

Data from the ISCT website were collected to investigate cell therapy products worldwide; further updates were made by visiting the websites of the regulatory agencies. Based on the data collected, autologous and allogeneic products were classified according to cell type, name, MA holder, approved country.

To investigate the source cell storage system for allogeneic cell therapy products, market authorized allogeneic cell therapy products were listed according to name of product, approved country, indication, and year of MA. The approval reports and regulations displayed on the website of the regulatory authorities in each country were used to analyze their cell storage regulatory system. In addition to the regulations, guidelines were identified and included in the study. Although the guidelines lack legal effect, they are indicative of the general regulatory goals of the regulatory authority and thus influence standards, especially in Korea [33,34]. However, data from an article containing an interview with the representative of a regulatory authority in Korea were used when the year of approval of the disclosed report on the cell storage system was found to be out of date [17]. In addition, as hospital exemption is applied before MA and does not require MA, the regulations and guidelines for hospital exemption are excluded. On the website of each regulatory author-

ity, the following key terms were used for data collection depending on the research object: "advanced therapy medicinal products," "biological products," "biologics," "advanced biopharmaceuticals," "market authorization," "cellular product," "cell therapy product," "cell-based medicinal product," "cell line," "cell bank," "donor," "regenerative medicine," "regenerative medicinal product," and "variation regulation" (Table 1).

Domains Used for Comparison

Identification of allogeneic cell therapy products and comparison of cell storage status

Selected cell therapy products were classified to prioritize the autologous and allogeneic products within the classification, and the products were listed according to cell type, name, MA holder, approved country, and year of MA. To compare allogeneic cell therapy products, the selected products were specified. The list was refined according to name of product, approved country, indication, and year of MA; moreover, the data on the source cell storage status for each corresponding product were clearly stated.

Comparison of cell storage systems among targeted authorities

A list of the regulations and guidelines of regulatory agencies under the targeted authorities was created and

Table 1. List of regulatory authorities and other organizations used for data collection

Research engine	Data type	Purpose of data collection	Key term
ISCT (www.isctglobal.org)	Listed data	Identifying cell therapy products	Name of listed products
FDA (www.fda.gov) EMA (www.ema.europa.eu) PMDA (www.pmda.go.jp) NIFDS (www.nifds.go.kr)	Report	Identifying cell storage status for allogeneic cell therapy products	Name of allogeneic cell therapy products
e-CFR (www.ecfr.gov) FDA EMA EUR-Lex (eur-lex.europa.eu) PMDA MHLW (mhlw.go.jp) Elaws (https://www.e-gov.go.jp/) MFDS (www.mfds.go.kr)	Regulation guideline	Regulations and guidelines related to cell storage system	Advanced therapy medicinal products Biological products Biologics Advanced biopharmaceuticals Marketing authorization Cellular product Cell therapy product Cell-based medicinal product Cell line, Cell bank Donor Regenerative medicine Regenerative medicinal product Variation regulation

ISCT=International Society for Cell & Gene therapy, listed the regulatory authorities, FDA=Food and Drug Administration, EMA=European Medicines Agency, PMDA=Pharmaceuticals and Medical Devices Agency, NIFDS=National Institute of Food and Drug Safety Evaluation, CFR=Code of Federal Regulations, MHLW=Ministry of Health, Labour and Welfare, MFDS=Ministry of Food and Drug Safety.

analyzed. A gap analysis was then conducted based on four categories previously mentioned as safety issues in Korea: (i) regulatory system for donors, (ii) cell storage system, (iii) regulatory system of cell storage test items/ methods, and (iv) regulatory system of cell storage system changes for new donors. Ten subcategories were generated: (i) regulations concerning donor selection, (ii) data related to donor selection, (iii) regulatory system of cell banks, (iv) other methods of cell storage, (v) criteria used to determine methods of cell storage, (vi) regulatory

system of cell storage test items, (vii) regulatory system of cell storage test methods, (viii) data related to cell storage, (ix) changes in MA concerning cell storage system for new donors, and (x) other methods of cell storage system changes for new donors (Fig. 1). Each category was classified based on whether it was regulated or suggested by the guidelines, and a gap analysis was then conducted in two steps: first, we analyzed the regulatory system of the donors and the method of cell storage; second, we analyzed the regulatory system

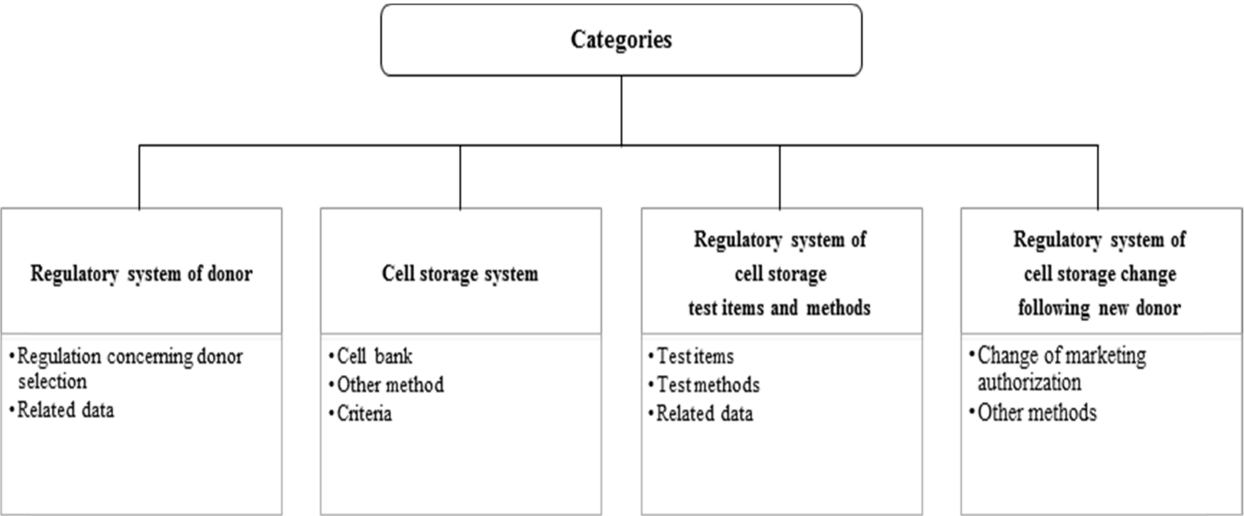


Fig. 1. Categorization of cell storage systems for gap analysis and comparison.

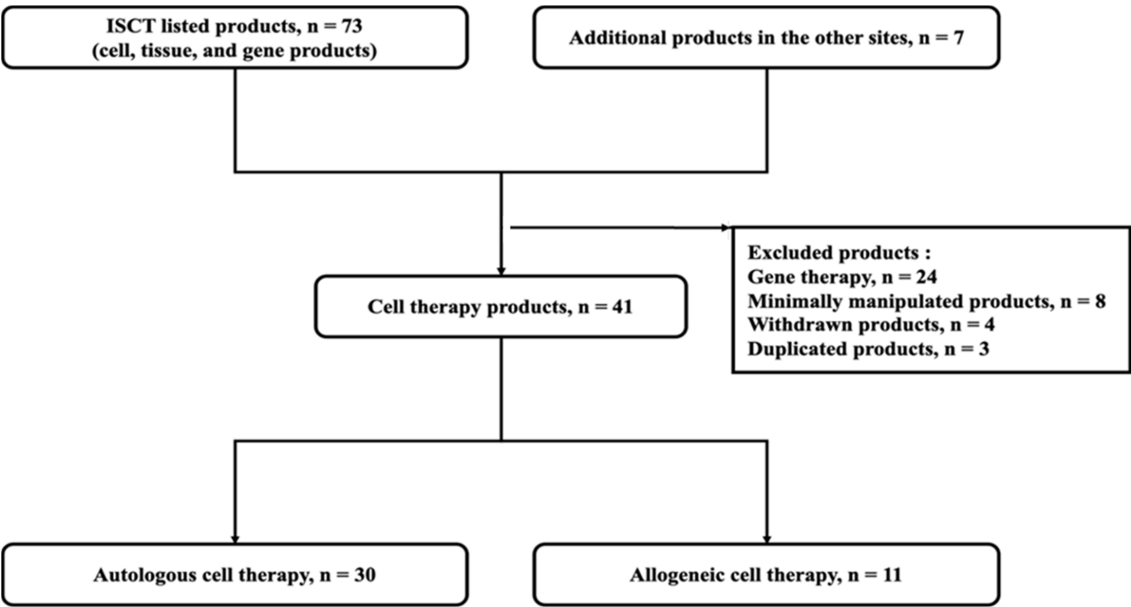


Fig. 2. Diagram for selecting and classifying cell therapies that met the inclusion/exclusion criteria.

of cell storage test items/methods and the regulatory system of cell storage system changes for new donors, according to the cell storage system of each country. The details for each country are subsequently described. As a selected cell therapy product may be approved in several countries, the number and percentage of each product are presented for each country, based on whether the product is autologous or allogeneic.

RESULTS

Identification of Allogeneic Cell Therapy Products and Comparison of Cell Storage Status

Forty-one cell therapy products approved out of a total of 80 products were selected from the ISCT website and the other sites that include regulatory authority websites and papers [35–44]. Thirty-nine products were excluded for the following reasons: gene therapy, minimally manipulated products, withdrawn products, and duplicated products. As hematopoietic progenitor cells (HPC) cord products are manufactured as minimally manipulated, they were excluded. Additionally, these products have different classification criteria in different countries. HPC cord products are not classified as good manufacturing practice (GMP) products in the US [45]. As this study is regarding the source cell management system for allogeneic cell therapy under GMP of pharmaceutical companies, HPC cord products were finally excluded. The proportion of autologous cell therapy products (30/41, 73.2%) was heavily weighted against allogeneic cell therapy products (11/41, 26.8%) (Fig. 2). Various types of source cells are used in manufacturing cell therapy. Chondrocytes were the most commonly used type for autologous cell therapy; keratinocytes, fibroblasts, and stem cells were mostly used for allogeneic cell therapy (Table 2).

Cell Storage Status of Allogeneic Cell Therapy Products

From June 2021, ten allogeneic cell therapy products satisfied the inclusion/exclusion criteria of this study—four in the US, two in the EU, one in Japan, and three in Korea. Their source cells were organized into three types of cell storage systems: cell banks, drug substances, and cell stocks (Table 3). The source cells of the market authorized allogeneic cell therapy products can be cryopreserved as cell banks in the US, Japan, and Korea; cell stocks in Korea and the EU [17,46–53]; and drug substances in Korea [17].

Comparison of Cell Storage Systems Based on Regulations and Guidelines

The regulations and guidelines of governing bodies in the US, the EU, Japan, and Korea are presented in Table 4 [54–80]. A gap analysis was conducted to compare the regulations and guidelines related to the cell storage system in the regulatory authorities (Table 5).

For all four regulatory authorities, donor selection was mandatory under the regulations [11,29,55,65,66,70–72]. The relevant data for donor selection were collated based on the guidelines of all regulatory agencies except those of the EU [13,30,61,63].

For donor selection, data on the medical history and infectious diseases of the donor were used to evaluate donor eligibility. These items were defined by regulations and the detailed information and methods suggested by guidelines in the US, Japan, and Korea [11,13,30,54,55,61,72]. In contrast, these items were defined by regulations alone in the EU [29,65,66].

All four regulatory frameworks allowed source cell storage as cell banks. However, in the EU and Korea, this was carried out according to the rules defined by both the regulations and guidelines [11,16,29]; in the US and Japan, only guidelines were provided [30,61–63,75]. Source cells could also be cryopreserved as drug substances in Korea, as defined by the regulations, and donor cells could also be cryopreserved as cell stocks according to the guidelines in the EU and Korea. In Korea, the cell stock-related guidelines was published in February 2020. Additionally, the EU has outlined criteria to determine cell stocks; these are similar to the Korean guidelines [11,68,78].

The regulatory systems and methods of cell storage test items differed between regulatory authorities. For related data for cell bank characterization, the rules were defined by the regulations and suggested by the guidelines [11,12,29]. Both the EU and Korea showed similar regulatory patterns by suggesting methods of characterization based on the guidelines [12,16]. Although the regulation provided a basis for drug substance management in Korea, the EU showed a tendency toward weak control of cell stock management based on the guidelines [11,68,78].

In the US, the guidelines provided suggestions on cell bank characterization [61–63], for which the specific test methods were defined by the regulations [56–59]. In Japan, the regulations did not define the rules and the guidelines acted as suggestions for characterization [74].

Table 2. List of selected cell therapies arranged based on the type of cells and cell therapy (autologous or allogeneic) [35–44]

Classification (n)	Type of cells	Product name	Company (approved in)	First MA (year)
Autologous (30)	Adipose cells	Queencell	Anterogen (Korea)	2010
		Novocart 3D ^a	B. Braun Medical (Switzerland)	2014
	Cartilage cells	CARTIGROW	RMS Regrow (India)	2017
		Chondron	Sewon Cellontech Co., Ltd. (Korea)	2001
	Chondrocytes	JACC	J-TEC (Japan)	2012
		MACI	Vericel Corporation (US)	2016
		Chondrocytes–T–Ortho–ACI	Orthocell Pty. Ltd. (Australia)	2017
		Spherox ^b	CO.DON AG (EU)	2017
			CO.DON schweiz GmbH (Switzerland)	
		CartiLife ^c	Biosolution Co., Ltd. (Korea)	2019
	Dendritic cells	Carticel	Genzyme Biosurgery (US)	1997
		CreaVax–RCC	JW CreaGene Corporation (Korea)	2007
		APCEDEN ^d	APAC Biotech (India)	2017
	Fibroblasts	Rosmir	Tego Science, Inc (Korea)	2017
		CureSkin	S-Biomedics Co., Ltd. (Korea)	2010
	Keratinocytes	laViv	Fibrocell Science, Inc. (US)	2011
		Holoderm	Tego Science, Inc. (Korea)	2002
		KeraHeal	Biosolution Co., Ltd. (Korea)	2006
	Mesenchymal stem cell	JACE	J-TEC (Japan)	2007
		Cellgram–AMI ^e	Pharmicell Co., Ltd. (Korea)	2011
		Cupistem ^f	Anterogen (Korea)	2012
		NEURONATA–R ^f	Corestem, Inc. (Korea)	2014
		Stemirac ^f	Nipro Corporation (Japan)	2018
	Osteoblasts	RMS Ossron	Sewon Cellontech Co., Ltd. (Korea)	2009
		OSSGROW	RMS Regrow (India)	2017
	Stem cells	Holoclar ^g	Chiesi Farmaceutici S.p.A. (EU)	2015
		HeartSheet ^h	Terumo Corporation, Ltd. (Japan)	2015
	T cells	Immuncell–LC	GC Cell Corp. (Korea)	2007
		PROVENGE	Dendreon Corporation (US)	2010
	Epidermal cell	Epicel	Genzyme Biosurgery (US)	1998
	Corneal epithelial cell	Nepic	J-TEC (Japan)	2020
Allogeneic (11)	Keratinocytes	Kaloderm	Tego Science, Inc (Korea)	2005
		KeraHeal–Allo	Biosolution Co., Ltd. (Korea)	2015
	Keratinocytes and fibroblasts	Gintuit	Organogenesis, Inc. (US)	2012
		OrcelTM	Ortec International (US)	2001
	Mesenchymal adult stem cells	DERMAGRAFT	Advanced Tissue Sciences, Inc. (US)	2001
		Transcyte	Shire Regenerative Medicine, Inc. (US)	1997
		Stempeucel	Stempeutics Research (India)	2016
	Mesenchymal stem cell	Alofisel ⁱ	Takeda Pharma (EU, Switzerland)	2018
		Cartistem ^j	MEDIPOST Co., Ltd. (Korea)	2012
		Temcell ^k	JCR Pharmaceuticals Co. Ltd. (Japan)	2015
		Prochymal ^l	Osiris (Canada, New Zealand)	2012

^aCarrier-coupled, ^bmatrix-associated, ^cbead-type, ^dmonocyte-derived mature, ^ebone marrow-derived, ^fadipose tissue-derived, ^ghuman corneal epithelial cells containing, ^hskeletal myoblast, ⁱadipose tissue-derived, ^jumbilical cord blood-derived, ^kbone marrow-derived, ^lhematopoietic progenitor cells.

MACI=matrix-induced autologous chondrocyte implantation, ACC=autologous cultured cartilage, ACI=autologous chondrocyte implantation, RCC=metastatic renal cell carcinoma, ACE=autologous cultured epidermis, Allogeneic=allogeneic cell therapy products, AMI=acute myocardial infarction, RMS=regenerative medical services, autologous, autologous cell therapy products, Co., Ltd.=company, limited, EU=European Union, GC=great commitment, GSK=GlaxoSmithKline, Inc.=incorporated, J-TEC=Japan Tissue Engineering Company, JW=Joong Wea, LC=liver cancer, MA=marketing authorization, Pty Ltd.=proprietary limited, S.p.A.=società per azioni, US=United States.

Table 3. Cell storage status of allogeneic cell therapy products

Cell storage status	Name of product (approved)	Indication	First MA (year)
Cell bank	Kaloderm (Korea) [17]	Deep 2nd-degree burn Diabetic foot ulcer	2005
	Gintuit (US) [46]	Surgically created vascular wound bed in the treatment of mucogingival conditions	2012
	OrcelTM (US) [47]	Treatment of fresh, clean split-thickness donor site wounds in burn patients	2001
	DERMAGRAFT (US) [48]	Treatment of full-thickness diabetic foot ulcers	2001
	Transcyte (US) [49]	Temporary wound covering for surgically excised full-thickness and deep partial-thickness thermal burn wounds in patients who require such a covering prior to autograft placement	1997
	Temcell (Japan) [50]	Acute graft versus host disease following hematopoietic stem cell transplantation	2015
Cell stock ^a	Zamoxis (EU) [51]	Adjunctive treatment in haploidentical hematopoietic stem cell transplantation of adult patients with high-risk hematological malignancies	2016
	Alofisel (EU) [52]	Complex perianal fistulas in patients with Crohn's disease	2018
Drug substance ^b	Cartistem (Korea) [17]	Osteoarthritis	2012
	Keraheal-Allo (Korea) [53]	Deep 2nd-degree burn	2015

^aThe Korea guideline for cell stock was applied in February 2020. ^bDrug substance means that the donor cell recovered was cryopreserved without cultivation and cell bank. Allogeneic cell therapy was applied to the cell bank following the Advanced Regenerative Bio Act in August 2020.

EU=European Union, MA=marketing authorization, US=United States.

In Korea and Japan, the regulations controlled the “change in MA” regarding the manufacturing process related to donor changes, although detailed criteria are yet to be established [11,70,71]. Korea has suggested detailed criteria based on the guidelines but Japan did not [79]. If the source cells were cryopreserved as a cell bank, both the US and EU require approval by the regulatory authority prior to making donor changes [60,64,67]. Nonetheless, in the EU, where the source cells could be cryopreserved as a cell stock or cell bank, details of changes need to be stated in the submitted documents along with the application for product approval [68]. These requirements for donor changes in cell stocks applied equally to Korea [78]. In the US, while the regulations stated that prior approval by the regulatory authority should be attained to establish a new cell bank, specific standards were suggested by the guideline. Further, the distribution of cell therapy products needs to be delayed by at least 30 days after submission of the report, following protocol approval at the time of biological license application (BLA) [64].

US (FDA)

In the US, the regulations controlled the “data related to donor selection,” “cell storage system test methods,” and “change of source cells.” The details suggested by the guidelines pertained to donor eligibility data and methods, cell bank characterization and specific test methods, and the methods used for donor change and variation [55,57–64].

The regulations mandated that donor screening and testing be performed, whereas the guidelines suggested tests regarding cell preparation, donor screening, donor testing, and product formulation [55,63]. For the cell culture procedure that follows the collection of cells, the guidelines necessitated tests such as those for quality control and adventitious agent control in cell culture [61].

The guidelines provide guidance on the details of donor eligibility. For the development and characterization of the cell population, the first requirement is data on cell collection, including the cell type and donor selection criteria. Additionally, the exclusion criteria include the presence of infectious agents [61]. Accordingly, serological, diagnostic, and clinical history data were collected (Table 6).

Table 4. List of regulations and guidelines for cell storage system in the regulatory authorities

	Regulation	Guideline
US (FDA)	• Definitions, 21 C.F.R.§600.3 [54] • What requirements does this subpart contain? 21 C.F.R.§1271.45 [55] • Potency, 21 C.F.R.§610.10 [56] • Sterility, 21 C.F.R.§610.12 [57] • Purity, 21 C.F.R.§610.13 [58] • Identity, 21 C.F.R.§610.14, 2019 [59] • Changes to an approved application, 21 C.F.R.§601.12 [60]	• Guidance for human somatic cell therapy and gene therapy [61] • Points to consider in the characterization of cell lines used to produce biologicals [62] • Guidance for FDA reviewers; content and review of chemistry, manufacturing, and control (CMC) information for human somatic cell therapy INDs [63] • Chemistry, manufacturing, and controls changes to an approved application: Certain biological products; draft guidance for Industry [64] • Guidelines on good manufacturing practice specific to advanced therapy medicinal products [68] • Guideline on human cell-based medicinal products [12] • Guideline on the categorization of extension applications (EA) versus variations applications (V) [69]
EU (EMA)	• Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended [29] • Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 [65] • Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells [66] • Commission regulation (EC) No 1234/2008 of 24 November 2008 on concerning the examination of variations to the terms of marketing authorizations for human use and veterinary medicinal products [67]	• Guideline on ensuring quality and safety of products derived from processing human (allogenic) cells/tissue [30] • Technical guidance on quality of regenerative medicine products (human cell-processed therapeutic products) and non-clinical and clinical trials [73] • Derivation and characterization of cell substrates used for production of biotechnological/biological products [74] • General principles for the handling and use of cells/tissue-based products [75]
Japan (MHLW/PMDA)	• Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices [70] • Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices [71] • Ministerial ordinance on standards for manufacturing management and quality control standards for regenerative medicine products [72]	• Guideline on eligibility determination for donors of cell therapy products [13] • Guideline on the characterization of cell substrates used to produce biologicals [16] • Guidelines for setting test items for quality control of cellular therapy [77] • Guidelines on good manufacturing practice specific to advanced biopharmaceuticals [78] • Guideline on the comparability of biopharmaceuticals in manufacturing process changes [79] • Guideline for cell bank evaluation of cell therapy products [80]
Korea (MFDS)	• Act on the Safety of and Support for Advanced Regenerative Medicine and Advanced Biopharmaceuticals [2] • Regulations on the Bio-Pharmaceutical Product Approvals and Reviews [11] • Regulations on the Safety and Approval of 'Human cells, etc.' and Advanced Biopharmaceuticals [76]	

CFR=the Code of Federal Regulations, EU=European Union, EMA=European Medicines Agency, FDA=Food and Drug Administration, MFDS=Ministry of Food and Drug Safety, MHLW=Ministry of Health, Labour and Welfare, PMDA=Pharmaceutical and Medical Devices Agency, US=United State.

Table 5. Gap analysis and comparison of regulations and guidelines related to cell storage in the US, the EU, Japan, and Korea

Category	Sub-categories	US (FDA) [55-64]	EU (EMA) [12,29,65-68]	Japan (MHLW/PMDA) [30,70-72,74,75]	Korea (MFDS) [11,14,16,77-79]
Donor	Donor selection	◎	○	◎	◎
	Common related data	Donor selection criteria Serological, diagnostic, and clinical history data Donor screening and testing	Donors selection criteria Laboratory tests required for donors	Diagnosis by interview Examination Viral safety management Donor screening	Donor selection criteria Characteristics of donor Medical and social history Screening test
Cell storage system	Cell bank	△	◎	△	◎
	Other methods	X	△ Cell stock	X	Drug substance ◎ Cell stock △
	Criteria	N/A	△	N/A	Drug substance ○ Cell stock △
Cell storage test items/methods	Test items	Cell bank △	Cell bank ◎ Cell stock △	Cell bank △	Cell bank ◎ Drug substance ◎ Cell stock △
	Test methods	Cell bank ○	Cell bank △ Cell stock △	Cell bank △	Cell bank △ Drug substance △ Cell stock △
	Related data	Cell bank Tests for characterization	Cell bank Tests for characterization Cell stock In accordance with the cell bank	Cell bank Tests for characterization	Cell bank Tests for characterization Drug substance Specification and test Cell stock In accordance with the cell bank
Cell storage system changes for new donors	Change in marketing authorization	Cell bank ◎	Cell bank ○ Cell stock X	Cell bank ○ (not clear)	Cell bank ◎ Drug substance △ Cell stock X
	Other methods	Cell bank △ (submit report)	Cell bank X Cell stock △ (addressed in marketing authorization)	Cell bank X	Cell bank △ Drug substance △ Cell stock △ (addressed in marketing authorization)

◎=mentioned in both regulation and guideline, ○=mentioned in regulation, △=in guideline, X=no data, EU=European Union, EMA=European Medicines Agency, FDA=Food and Drug Administration, MFDS=Ministry of Food and Drug Safety, MHLW=Ministry of Health, Labour and Welfare, PMDA=Pharmaceutical and Medical Devices Agency, US=United States.

The guidelines suggested that information regarding the cell storage system, explaining the production of the cell therapy product, and details about the materials, such as the cells and the cell bank system, be included [63].

Once the cells are screened for the cell line, the guidelines suggest that the cell bank system is generated to ensure uniformity of cells throughout the production

cycle [61,62]. The establishment of a cell bank is appropriate in cases where cell therapy products are repeatedly produced from the source cells. The cell stock should be managed by a cell bank system commonly used as a “two-tiered system” [61]. To establish the cell bank, tests pertaining to the origin of the cells, the process of cell storage, characteristics, and the presence of adventitious

Table 6. Specification and test method data required for the donor eligibility and the cell storage system in the US, the EU, Japan, and Korea [11,12,14,16,30,56-59, 61-63,66,74,75,77,80]

A. Donor eligibility

Universal	Region specific differences		
	US (FDA)	EU (EMA)	Japan (MHLW/PMDA) Korea (MFDS)
• Medical and social history data • Donor test - HIV-1, 2 - HBV - HCV - Syphilis - HTLV-1, 2^a	• Donor test - CJD (screening only) - CMV^b	-	• Donor test - Parvovirus B19 infection - CMV - EBV - WNV • Donor test - CMV^b - <i>Chlamydia</i>^c - <i>Neisseria gonorrhea</i>^c

B. Cell storage system

Systems	Region specific differences				
	Universal	US (FDA)	EU (EMA)	Japan (MHLW/PMDA)	Korea (MFDS)
Cell bank characterization	• Identity of cell • Purity of cell • Stability • Genetic stability • Adventitious agent (only tumorigenicity in the EU and Japan)	• Test for activity of cell • Test for cell maturation • Process critical to product safety - Culture conditions - Cryopreservation, storage, and recovery of the MCB	-	-	• Potency of cell
Drug substance characteristics	-	Not applicable	Not applicable	Not applicable	• Name • Appearance • Sterility • Free from mycoplasma • Endotoxin • Free from adventitious virus • Total cell count • Cell survival rate • Identity • Purity • Potency

^aHTLV-1, 2 are tested for donors of viable leukocyte-rich cells or tissues in the US and Korea and for donors living in or originating from high-incidence areas or with sexual partners originating from those areas or where the donor's patients originate from those areas in the EU.

^bCMV is tested for donors of viable leukocyte-rich cells or tissues.

^c*Chlamydia* and *Neisseria gonorrhea* are tested for donors of germ cells or embryonic cells.

CJD=Creutzfeldt-Jakob disease, CMV=cytomegalovirus, EBV=Epstein-Barr virus, EU=European Union, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HTLV=human T-lymphotropic virus, MCB=master cell bank, MHLW=Ministry of Health, Labour and Welfare, MFDS=Ministry of Food and Drug Safety, PMDA=Pharmaceuticals and Medical Devices Agency, STR=short tandem repeat, US=United States, WNV=West Nile virus.

agents were performed (Table 6), as suggested by the guidelines [61–63]. Tests for sterility, purity, and identity are controlled by the regulations [56–59].

To change an approved license, the FDA submission requirements are defined by regulations relating to the specific item; however, substantial changes, including changes in the cell line or cell bank, are categorized as needing prior approval supplement (PAS) [60]. Furthermore, the guideline suggested that a report be submitted to the FDA at least 30 days prior to distribution, in the case of the establishment of a cell bank based on a new human donor. For this to be possible, however, a relevant protocol needs to be approved at the time of BLA [64].

EU (EMA)

In the EU, for donors, storage management, and source cell variation, regulations define allogeneic cells as the starting materials and have set out procedures for donation, procurement, and testing; cell bank establishment and tests during the manufacturing of the active substance; and master cell bank (MCB) changes [29,65–67]. However, guidelines cover cell bank characterization, cell stock establishment and changes, and MCB changes [12,68].

The regulations state that data should be provided for starting material donation, procurement, and testing. The strategy and monitoring used when allogeneic cells were pooled are described [29]. In addition, the origin and history of the cells should be described in a documented report, in compliance with the selection criteria for donors [65]. Once the cells have been collected from the donor, appropriate laboratory tests should be performed to obtain information on the medical and behavioral history and infectious diseases (Table 6) [66].

A cell bank can be established for the management of the source cells. This process is controlled by the regulations. For this, cell characteristics must remain constant, without changes in the number of passages, while performing tests for adventitious agents [29]. For allogeneic cell therapy products, a cell bank is recommended whenever possible. This is not mandatory but is suggested to prevent the introduction of infectious materials [67]. The tests performed for cell bank characterization complied with the rules stated by the ICH Q5D, as suggested by the guidelines [68], and appropriate characterization and testing for identity, purity, stability, karyology, and tumorigenicity were performed (Table 6) [12].

The EMA used the guideline suggestions for the cell stock with regard to the “limited number of passages” rather than those for the cell bank. In addition, the handling, storage, and release of cells for the cell stock complied with the principles described for the cell bank [68].

The regulations categorize changes in MCB as the variation in the active substances [67], which is placed under the regulation “Extensions of Marketing Authorizations,” to follow the same procedure as that for granting the initial MA to which it is related [69]. However, the details of the change in cell stock need to be stated in the submitted documents upon MA application for the product [68].

Japan (MHLW/PMDA)

In Japan, the regulations control the “related data for donor selection” and “cell storage test items/methods” regarding the manufacturing process and include “change in MA” [70–72], whereas the guidelines provide suggestions for donor eligibility testing, cell bank establishment, and test items and methods [30,73–75].

The regulations state the requirements for submission of data on the manufacturing process [71], whereas the guidelines suggest the data required for donor eligibility. These data include diagnosis by interview, viral safety management, donor screening, and examination [72]. The guidelines suggest the inclusion of “acceptance of cells as raw materials and clarified concrete treatment contents, necessary process management, and quality control content” [30].

For donor eligibility, the guidelines suggest donor testing for virus safety management, where the testing is performed in accordance with the latest scientific and technological standards (Table 6) [30,73,75].

The guidelines suggest that the manufacturing process should include cell bank establishment, for which the production, characterization, preservation, maintenance, and management methods should be described [30,75]. In addition, as Japan is an ICH founding member, ICH quality guidelines have been adopted and managed. Thus, the detailed process for cell bank establishment should be described, and appropriate characterization and testing should be performed (Table 6) [74].

As previously mentioned, the manufacturing process includes the establishment of a cell bank, and the regulations state that the notification procedure, following a change in the production method, should include obtaining approval by the regulatory authority, when an

approved item has to be partially modified, excluding minor parts, and when a significant change has to be made [70]. For minor changes, a reporting step should be included and the items should be specified. In contrast, a substantial change corresponds to a change in the production method that may influence the inherent features, characteristics, performance, and safety of the product in question or any change that may affect the quality, safety, or effectiveness of the product [71].

However, there is a lack of clearly defined regulations regarding whether changes in source cells for allogeneic cell therapy products would have an effect on product safety and efficacy.

Korea (MFDS)

In Korea, the regulations controls the “data related to donor selection” and “cell storage test items and methods” regarding the manufacturing process, including “changes in MA” [11]. The data required and the employed methods for screen donor eligibility, necessary considerations for the cell storage system, specific testing methods for cell bank establishment, and quality control test methods for drug substances are all suggested by the guidelines [13,16,77].

Currently, the regulations mandate the collection of data on cell type, donor selection, and tissue typing and those on the process of cell collection and proof of donor consent upon the collection of cells [11]. This requirement corresponds to that for the donor eligibility test. For the donor eligibility test, the guidelines suggest that the donor should be examined on their medical/social history using a questionnaire and that laboratory tests should be performed to confirm that the donor tested negative for infectious diseases; accordingly, the eligibility is determined (Table 6) [13].

For cell storage, the regulations are applied differently, depending on whether a cell bank has been established [11]. However, allogeneic cell therapy should be applied to the cell bank, depending on the regulations from August 2020. As suggested by the regulations, the cell bank is defined as “the storage of homogeneous cells obtained by culturing cells with identified characteristics under the same conditions in the same amount in multiple containers and under the prescribed conditions” [11].

Where a cell bank is established, characterization tests need to be performed. For this, the regulations mandated tests regarding identity of cell, purity of cell, potency of

cell, stability, genetic stability, adventitious agent (Table 6); specific methods for cell storage system are suggested in the guidelines [80].

The regulations state that specification and test methods should be established for a given drug substance. The relevant data included name, appearance, sterility, free of mycoplasma, endotoxin, free from adventitious virus, total cell count, cell survival rate, identity, purity, and potency (Table 6) [11]. The guidelines suggest specific test methods in which production intermediates are stored in several vials for use in the production of the drug, by which the corresponding products could be set as the drug substance during the manufacturing process [77].

The “manufacturing process” is defined by regulations as an item of product authorization; this item should be included in the license for the production and sales of medicinal products that are considered for changes in MA. Except for the manufacturing process or other minor factors that do not affect product quality, such as a change in the manufacturer’s address owing to a change in the administrative district, the regulations control all cases [11]. To change the source cells, the data should be included under “manufacturing process”. Further, the guidelines state that donor changes in the cell bank are an important factor and should be allowed a “change in MA” [78].

DISCUSSION

This study investigated and analyzed approved cell therapy and the status of cell storage for the selected products until 1 June 2021 in the US, the EU, Japan, and Korea. A list of cell therapies for analysis was compiled based on the products registered in the ISCT website and other sites. The regulations and guidelines of the regulatory authorities regarding cell storage were also reviewed through a gap analysis. Regulatory systems for donors, cell storage, cell storage test items/methods, and governing changes in the cell storage system for new donors were evaluated.

Forty-one approved cell therapy products were selected for this study. Autologous cell therapy is approved more than allogeneic cell therapy, which has 11 products worldwide. Although allogeneic cell therapy is more commercially efficient, allogeneic cell therapy, such as donor eligibility and marketing authorization, is also more difficult. The source cell of approved allogeneic cell therapy

is stored by the storage system, which includes the cell bank, cell stock, and drug substance. The cell stock is used in the EU, while guideline of the cell stock is applied in the EU and Korea. The reason why cell stock is only used for cell therapy in the EU is that the guideline for the cell stock was reviewed in February 2020, which has not yet been commercialized in Korea. The drug substance used or stored after cryopreservation without establishing a cell bank is only applied to two products in Korea. The drug substance is applied when the number of cells obtained from a single donor is limited [17].

Donor selection, donor eligibility, and donor consent were processed before the cell storage system was applied. While the US, Japan, and Korea apply both the regulations and guidelines for donors, the regulation for donating cells is only provided in the EU, which is Directive 2004/23/EC and Directive 2006/17/EC. However, the regulatory authorities do not have differences in related data, which is the requirement for donor selection and donor eligibility determination. In other words, the regulatory authorities regulate donor-related data at the same level.

The cell storage system can be controlled by the source cell to the cell bank in the four regulatory authorities. The other cell storage system is controlled by the cell stock in Korea and the EU and the drug substance in Korea [11,29,68]. The requirement of the cell stock is stated by guidelines that provide criteria for selecting the cell storage system as a limited number of passages [68]. The cell stock guidelines of the EU and Korea are similar. The test items, test methods, and related data of the cell stock require equivalent data from the cell bank. The regulations and guidelines for drug substances are only available in Korea. However, the source cells in allogeneic cell therapy should be controlled by the cell bank following the regulations on the Bio-Pharmaceutical Product Approvals and Reviews [11].

Change in the source cell is shown to be the most thorough regulation in the US. When changing the donor, the applicator should be approved before the change. If there is a protocol submitted in advance, the report should be submitted to the regulatory authority [60,64]. In the EU, the cell bank requires prior approval from the regulatory authority, such as the US. However, the cell stock guidelines suggest that the manufacturer does not need to submit data when the detail in variation is clearly stated in the submitted document with the Marketing Authorization Application [67,68]. In Japan, despite regulations on

the change in the cell collection and manufacturing process, the detailed criteria are yet to be determined [70,71]. The process for changing source cell donors in Korea is similar to that in the US, except that the report is not submitted to the regulatory authority [77]. For storage of the source cells as the cell bank in Korea, the change in the source cells should be regarded as an item of change in MA, depending on the guideline [79].

Invossa-K[®] approved for osteoarthritis in Korea was withdrawn from marketing authorization in 2019. Invossa-K[®] was reported to use allogeneic human chondrocytes, and allogeneic human chondrocytes introduced TGF- β 1 as a source cell. However, the source cell used for manufacturing invossa-K[®] was the renal cell named GP2-293 instead of human chondrocytes [36]. Kolon Life Science Company, who is the manufacturer of invossa-K[®] did not notify that it had already confirmed this fact through the short tandem repeat (STR) test. The MFDS withdrew the invossa-K[®] marketing authorization as an issue of safety, efficacy, and submission of false data. Korea had no source cell regulation for ATMPs, but the issue of invossa-K[®] raised the need for regulation. With the coming into force of the Advanced Regenerative Bio Act, human cells are now regulated [36,76]. Although invossa-K[®] was withdrawn in Korea, invossa-K[®] was determined to restart phase 3 of its clinical trials in the US [37]. The difference in these decisions is due to differences in regulation among the regulatory authorities. Harmonization among regulatory authorities is important for preventing the difference in these decisions.

Allogeneic cell therapy is more commercially efficient than autologous cell therapy and can be approved in two or more countries [7,8]. Examples for allogeneic cell therapy include Alofisel[®] and Prochymal[®], which are approved in the EU and Switzerland, and Canada and New Zealand, respectively. Pharmaceutical companies are focusing on the development of allogeneic cell therapy because of its effectiveness and impact. Harmonization can prevent the unnecessary loss of resources, including clinical trials, data analysis, authorization fees, in additional MA. It can lay the foundation for pharmaceutical companies to enter global markets. In addition, because allogeneic cell therapy is used in relatively small patient groups when compared to chemical products, it is necessary to detect safety issue and long-term safety and efficacy of allogeneic cell therapy in at least two countries. For this process to be efficient, harmonization that minimizes the differences

in systems of regulation, including cell storage, can help. Pharmaceutical inspection co-operation scheme (PIC/S) leads to international development, implementation, and maintenance of harmonized GMP standards. PIC/S suggests "Guide to GMP for medicinal products annex 2A Manufacturing of ATMPs for human use" in 2021. Source cell control is a part connected to GMP, such as the starting material and cell bank part mentioned in the PIC/S GMP guideline of ATMPs. PIC/S is establishing a high level of international harmonization with the PIC/S GMP guideline of ATMPs, including source cell control and network among the regulatory authorities [81].

Although allogeneic cell therapy is more commercially efficient, and promote a more frequent appearance of ATMPs for public health, the safety issues of source cells are inherent and fundamental. In particular, source cell changes should be managed and validated to ensure the safety of allogeneic cell therapy. Therefore, it is necessary to establish more detailed criteria for source cell changes in cell storage system. Applying advanced risk-based approach (RBA) in the source cell also can be a helpful tool to promote short-term and long-term safety [82]. In the future, researches which compare the regulations and guidelines of the regulatory authorities of RBA are needed to find out the harmonization and developing the regulatory science in the allogeneic cell therapy including source cells.

CONCLUSION

This study analyzed the approved allogeneic cell therapy and gap analysis of the cell storage system in the US, the EU, Japan, and Korea. Most allogeneic cell therapies use the cell bank for cell storage. The gap analysis results indicate that cell storage systems have similar regulations and guidelines to regulatory authorities, except for the regulation of changes in the source cell. It is necessary to establish more detailed criteria for source cell changes in cell storage system to ensure the safety of allogeneic cell therapy. The regulatory authority may ensure a safer and more effective supply of therapy to the public by harmonizing the regulations associated with allogeneic cell therapy.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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