Regulatory Approaches and Marketing Approvals: A Comparison of Three Systems

Kazuo Yano, Tokyo Women's Medical University, Tokyo, Japan; Waseda University, Tokyo, Japan; Joint Graduate School of Tokyo Women's Medical University and Waseda University, Tokyo, Japan
Masayuki Yamato, Tokyo Women's Medical University, Tokyo, Japan

Abbreviations

ATMP	Advanced therapy medicinal product
BLA	Biologics license application
CAT	Committee for Advanced Therapies
CBER	Center for Biologics Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Federal Code of Federal Regulations
CGTP	Current good tissue practice
CHMP	Committee for Medicine Products for Human Use
CMC	Chemistry, manufacturing, and controls
CPD	Citrate phosphate dextrose solution USP
GCP	Good clinical practice
GCTP	Good manufacturing practice for gene cellular, and tissue-based products
GLP	Good laboratory practice
GMP	Good manufacturing practice
GPSP	Good post market study practice
EC	European Commission
EEC	European Union
EMA	European Medicines Agency
ES cell	Embryonic stem cell
EU	European Union
FDA	Food and drug administration
FFDC Act	Federal Food, Drug, and Cosmetic Act

HCT/P	Human cells, tissues, and cellular and tissue-based product
HPC	Hematopoietic progenitor cell
MHLW	Ministry of Health, Labor and Welfare
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMDRF	International Medical Device Regulators Forum
iPS cell	Induced pluripotent stem cell
PAL	Pharmaceutical Affairs Law
PHS Act	Public Health Service Act
PMA	Premarket Approval
PMDA	Pharmaceuticals and Medical Devices Agency
PMD Act	Pharmaceuticals, Medical Devices and Other Therapeutic Product Act
PREA	Pediatric Research Equity Act
PTC	Points to consider
POC	Postexploratory clinical trial
RMP	Regenerative medicine product
Q & A	Question and answer
RMAT	Regenerative medicine advanced therapy
SCAD	Scientific advice database
SECG	Small entity compliance guide
SMEs	Micro-, small- and medium-sized enterprises
US	United States

Legislation, Rule, and Guidance of Human Cell-Based Products

Human cell-based products belong to a relatively new class of medical products. As of January 2018, these products have been classified as human cells, tissues, and cellular and tissue-based products (HCT/Ps) in the United States (US), advanced therapy medicinal products (ATMPs) in the European Union (EU), and regenerative medicine products in Japan.

United Sates

In the US, the Food and Drug Administration (FDA) is the regulatory body responsible for the oversight of medical products. Its comprehensive framework of activities comes from a history of legislation dating to the Pure Foods Act of 1906. Today, regulations under this framework encompass not only chemical drugs and devices, but also biologics, vaccines, and more recently, human cell-based products. However, for biologically-derived products, the relevant regulatory framework is supplemented by rules authorized under Sections 351 and 361 of the Public Health Service (PHS) Act of 1944, which define biological products and provide the FDA with the authority to control communicable diseases. Title 21 of the Federal Code of Federal Regulations, Part 1271 (referred to as 21 CFR Part 1271) outlines regulations for HCT/Ps (Fig.1) (Table 1). The FDA defines HCT/Ps as products "containing or consisting of human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient". It classifies HCT/Ps into following three groups according to risk:

(1) *Low risk products*: considered current medical practice, procedures such as organ transplant and blood transfusion are not subject to FDA preapproval (21 CFR Parts 1270, 1271.15)
(2) *Medium risk products*: referred to as "361 HCT/P products" under the section 361 of the PHS Act, which governs their use. These products must be (1) minimally manipulated, (2) intended for homologous use (as reflected by the advertising and labeling of the product), but (3) not manufactured or combined with "another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent", and do not incur new clinical safety concerns, and (4) do "not have a systemic effect" and are "not dependent upon the metabolic activity of living cells for their primary function" (unless they are for autologous use, for allogenic use in the first-degree or second-degree blood relative, or for reproductive use). Such 361 HCT/Ps are subject to establishment registration, product listing, and other requirements such as donor eligibility and current good tissue practice, but they are not subject to premarket approval or clearance (21 CFR Part 127.10).
(3) *High risk products*: referred to as "351 products" under the section 351 of the PHS Act that governs their regulation. These include any cell-based products that do not fulfill all of the four above-mentioned criteria for medium-risk "361" products and therefore require a full premarket biologics license application (BLA). They must follow the same premarket and postmarket regulation as medical devices, drugs, or biologics (21 CFR Part 1271.20).

On December 13, 2016, an "Act to accelerate the discovery, development, and delivery of 21st century cures, and for other purposes" cited as "21st Century Cures Act" was enacted by the Senate and House of Representatives of the United States Congress. In response,

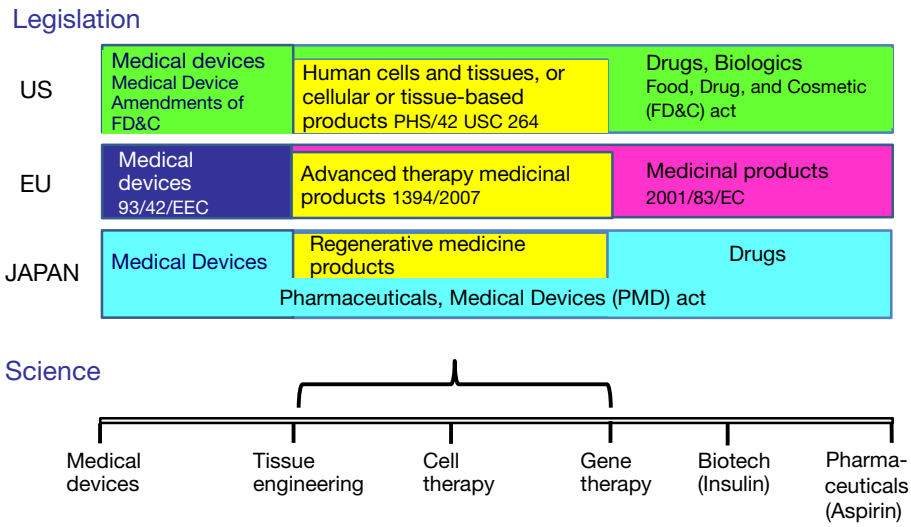

Fig. 1 Legislation on cell therapy, gene therapy, and tissue-engineering products in the United States, the European Union, and Japan. *EC*, European Commission Regulation; *EEC*, The European Union Regulation; *EU*, European Union; *FD&C act*, Food, Drug, and Cosmetic act; *PHS act*, Public Health Service act; *PMD act*, Pharmaceuticals, Medical Devices act; *US*, United States. In the United States, cell therapy, gene therapy, and tissue-engineering products are classified as human cells, tissue, and cellular and tissue-based products (HCT/Ps) under the Public Health Service (PHS) act of 1944 which define biological products and in Title 21 of the Federal Code of Federal Regulations of 2001, Part 1271 (21 CFR Part 1271), which outlines regulations for HCT/Ps. In the EU, these products are classified as advanced therapy medicinal products (ATMPs) under the regulation (EC) No 1394/2007 which consist of gene therapy medicine products and somatic cell therapy products, and tissue engineered products. In Japan, the products are categorized as Regenerative Medicine Products under the PMD Act.

Table 1 Classification, definition, and regulation of human cell and tissue products in the United States, the European Union, and Japan

Country or area	*Classification*	*Definition*	*Regulation*	*Classification of medical products*
US	Human cells, tissues and cellular and tissue-based products (HCT/Ps) 351HCT/P[a] 361HCT/P[b]	Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient	21CFR 1271	Biologics (HCT/Ps regulated as drug or biologics or medical device)
EU	Advanced therapy medicinal products (ATMPs) Gene therapy medicinal product[c] Somatic cell therapy medicinal product[c] Tissue engineered product[c]	Any of the following medicinal products for human use: a gene therapy medicinal product; a somatic cell therapy medicinal product; a tissue engineered product which contains or consists of engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue	Regulation (EC) No 1394/2007	ATMPs (drug)
Japan	Regenerative medicine products Cell based product[d] Gene therapy product[d]	Any products processed from the cells of a human or animal, with the purpose to reconstruct, repair, or reform the physical structure of a human or animal, or to treat or prevent the disease of a human or animal (cell-based products); Any products that are introduced into the cells of a human or animal to promote the development of a gene in the body to treat illness of a human or animal (gene therapy products)	Pharmaceuticals and Medical Devices Act	Regenerative medicine products

US, the United States; *EU*, the European Union; *21 CFR*, Code of Federal Regulation, Title 21; *EC*, European Council.

[a]351HCT/P is regulated under sections 351 of the Public Health Service Act (42 the United State Code) according to in 21CFR1271.20 which is described as not meet the criteria of 21CFR1271.10 and not qualify for any of the exception of 21CFR1271.15 which removed and implanted in same individual during same surgical procedure. The HCT/P is regulated as drug, medical device, and/or biological product.

[b]361HCT/P is regulated under sections 361 of the Public Health Service Act (42 the United State Code) which is described as minimally manipulated, intended for homologous use only, not involved the combination of cells or tissues with another article according to in 21CFR1271.10. No premarket approval is required.

[c]Gene therapy medicinal product, somatic cell therapy medical product, and tissue engineered product are regulated under the regulation (EC) No 1394/2007.

[d]Regenerative medicine products which include cell-based product and gene therapy product are regulated under the clause 2 of Pharmaceuticals, Medical Devices Act (PMD) Act.

the FDA established a new category of regenerative medicine products that would include a select population of qualifying "351 products" that target life-threatening diseases, designated "Regenerative Medicine Advance Therapy (RMAT)" products. For these products FDA would develop alternative approval pathways with surrogate endpoints and initiate the development of new standards for evaluating regenerative medicine therapeutics.

European Union

In the European Union, the Commission of the European Communities issued the Commission Directive 2003/63 EC of June 25, 2003 relating medicinal products for human use that included ATMP in the Annex which described as gene therapy medicine products and somatic cell therapy medicine products (Fig. 1) (Table 1). In the Annex, gene therapy medicine products are defined as "products obtained through a set of manufacturing processes aimed at the transfer, to be performed either in vivo or ex vivo, of a prophylactic, diagnostic or therapeutic gene (i.e., a piece of nucleic acid), to human/animal cells and its subsequent expression in vivo". These products can be developed from autologous, allogenic or xenogeneic cells or administered using vectors capable of inserting genetic material. Somatic cell therapy medicine products are defined as "the use in humans of autologous, allogeneic, or xenogeneic somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means". Manipulation can include, for example, the expansion or activation of autologous cell populations ex vivo (e.g., adoptive immuno-therapy) or the use of allogeneic and xenogeneic cells associated with medical devices used ex vivo or in vivo (e.g., microcapsules, intrinsic matrix scaffolds, biodegradable or not).

In the field of regenerative medicine, the classification of tissue-engineered products often differs among the European Union Member States. In some, the engineered product was considered to be a medicinal product but in others, a medical device. To resolve this difference, the European Parliament and the Council of the European Union issued Regulation (EC) No 1394/2007 of European Parliament and of the Council of November 13, 2007 on advanced therapy medicinal products (ATMPs). These regulations defined ATMPs and identified how they must comply with existing market authorization requirements and the postmarketing pharmacovigilance rules. They also established a new Committee for Advanced Therapies (CAT).

In the European Union, ATMPs are subclassified as gene therapy medicine products, somatic cell therapy products and tissue engineered products. A tissue engineered product was defined as a product that "contains or consists of engineered cells or tissues" and "is presented as having properties for, or is used in or administered to human being with a view to regenerating, repairing, or replacing a human tissue" (Fig. 1) (Table 1).

To provide a transitional period, gene therapy medicine products and somatic cell therapy products that were on the European Union market in compliance with national or Community legislation on December 30, 2008, were required to comply with the Regulation no later than December 30, 2011. Tissue engineered products that were on the European Union market in compliance with national or Community legislation on December 30, 2008, were required to comply with this Regulation no later than December 30, 2012.

Japan

In Japan, the Ministry of Health, Labour and Welfare (MHLW), and the Pharmaceuticals and Medical Devices Agency (PMDA) originally attempted to employ existing policies for drugs and medical devices to regulate human cell-based products. The relevant regulatory framework was included in Clause 2, Definition of the Pharmaceutical Affairs Law (PAL) of 1960. For practical purposes, processed autologous or allogenic human-derived cells and tissue have used the notification pathways for either drugs or medical devices because of no category existed for such products in the PAL. Cells/tissue-engineered (manipulated) products were defined as drugs or medical devices containing or consisting of manipulated autologous or allogeneic human cells and tissue that apply chemical treatment or altering biological properties through combination with genetic engineering to artificially proliferate or activate cells and tissue for purpose of curing disease or repairing or regenerating tissues.

On November 25, 2013, PAL was partially revised and reissued as the "Act on Ensuring Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, and Other Products", referred as PMD Act (Fig. 1) (Table 1). In the PMD Act, regenerative medicine products (RMPs) were identified as a new category in the existing regulatory framework. RMPs were divided into two groups: (1) products processed from the cells of a human or animal, with the purpose to reconstruct, repair, or reform the physical structure of a human or animal, or to treat or prevent the disease of a human or animal (cell proceeding products), and (2) products introduced into the cells of a human or animal to promote the development of a gene in the body to treat illness of a human or animal (gene therapy products). In the Government Ordinance of the PMD Act, RMPs were categorized in more detail to specify "human cell processing products" to include (1) human somatic cell processing products, (2) human somatic stem cell processing products, (3) human embryonic stem cell processing products, and (4) human artificial pluripotent cell processing products, and "gene therapy products" to include (1) products derived from plasmid vectors, (2) products derived from virus vectors, and (3) gene expression treatment products.

Guidance Documents

Guidance documents are references developed by regulatory agencies to communicate their views on specific issues. According to FDA's definition, a guidance document is defined as the FDA's current thinking and recommendations on a topic, unless specific regulatory or statutory requirements are cited. Similarly, the European Medicines Agency (EMA) issues guidelines and reflection papers that provide recommendations. In Japan, notifications are generally defined as documents to inform specific or nonspecific persons on particular issues. In this section, all documents which refer to a guidance document, guideline, reflection paper, or notification and Japan are described as guidance documents.

Guidance documents in the United States

In the US, an initial guidance, "Points to Consider (PTC) in Human Somatic Cell Therapy and Gene Therapy" was finalized as "Guidance for Industry: Human Somatic Cell Therapy and Gene Therapy" serves as the high-level reference on HCT/Ps and gene therapy products. Many additional guidance documents, such "Chemistry, Manufacturing, and Controls (CMC)", "Establishment Registration and Listing", "Eligibility Determination for Donor and Testing/Screening", "Current Good Tissue Practice (CGTP), "Clinical Trials", and "Small Entity Compliance Guide (SECG)" have also been issued (Table 2). To differentiate autologous versus allogeneic products, the FDA published an autologous cell-related guidance titled "Guidance on Application for Products Comprised of Living Autologous Cells Manipulated Ex Vivo and Intended for Structure Repair or Reconstruction; Availability". Further, cell-specific guidance documents for products such as those related to knee cartilage, pancreatic islet cells, placental/umbilical cord blood were issued (Table 2).

Notably, specific guidance documents for different types of allogeneic human cell-based products, including allogeneic pancreatic islet cell products, unrelated allogeneic placental/umbilical cord blood products, and cellular therapy for cardiac disease were issued. According to aforementioned guidance documents, seven (7) unrelated allogeneic placental/umbilical cord blood products have already been approved (see section "Hematopoietic progenitor cells (HPCs)").

Guidance documents that are not specific to allogeneic human cell-based products can also be important to consult. For example, guidance documents on expedited programs for regenerative medicine and device evaluation provide information on the use of the accelerated approval pathway for RMATs. This system is similar to the conditional and time-limited approval in Japan and conditional market authorization in EU.

Combination products are therapeutic and diagnostic products that combine drugs, devices, and/or biological products. Several guidance documents provide assistance in understanding jurisdictional approaches, requests for designation and classification, interpretation of the term "chemical action", early development issues, new contrast imaging indications, postapproval changes, technical information, and the application of current good manufacturing practice (Table 3). The guidance documents, "Minimal Manipulation of Structural Tissue" and "Device Used to Process Human Cells, Tissues, and Cellular and Tissue-Based Products" are helpful to review the classification of the product.

Guidance documents in the European Union

In the European Union, the Committee for Advanced Therapies (CAT) and the Committee for Medicine Products for Human Use (CHMP) with other committees and working groups have been developing scientific guidelines and reflection papers (Table 4) based on the product life cycle of ATMPs (Fig. 2). To support developers and research and development activities in companies, a series of the template letters to obtain protocol/procedure assistance and scientific advice from the EMA or parallel scientific advice from the FDA were issued after circulating the new framework and procedures for Scientific Advice and Protocol Assistance in 2006 (Table 4).

Several standard operating procedures and work instructions have also been made available: the science advice procedure, the scientific advice and protocol assistance procedure, the procedure of final advice letter, the peer review system by the Committee for Medicinal Products for Human Use (CHMP), the procedure of Scientific Advice Database (SCAD), the procedure for the submission of a request for scientific advice or protocol assistance to a final answer to applicant, and the organization of the working groups supporting the meeting (Table 4).

To give special support for micro-, small- and medium-sized enterprises (SMEs), EMA issued a guideline and user guide for relevant certification procedures (Table 4).

Since the ATMPs are classified into three main types, including gene therapy medicines, somatic-cell therapy medicines, and tissue-engineered medicines, the classification of ATMPs is an important first step for product developers. EMA issued scientific recommendation and reflection papers as well as an overview of comments received on the reflection paper to address such classification issues (Table 4). The EMA encouraged developers to address questions on borderline classification with other regulatory bodies, such as those responsible for medical devices, as early as possible. After delivering the scientific recommendations on ATMP classification by the Committee for Advanced Therapies (CAT), the EMA publishes the outcome of the assessment of the classification of ATMPs as summary reports (Fig. 3 and Appendix 1). According to the summary reports from CAT between 2009 and September 2017, 81 allogeneic cell-based products, 99 autologous cell-based products, 58 gene therapy products (including both gene-modified allogeneic and autologous cell-based products), and 18 therapy products not considered as advanced have already been classified. The number of classified ATMPs are escalation year by year: approximately 10–20 products for 2009–13, 29 in 2014, 37 in 2015, 50 in 2016, 50 from January to September in 2017.

Table 2 Guidance documents of HCT/Ps and gene therapy products in the US

Year	*Name of guidance document*	*Note*
Human somatic cells therapy and gene therapy		
1998	- Guidance for Industry Guidance for Human Somatic Cell Therapy and Gene Therapy (March 1998)	- Regulatory frame work for somatic cell and gene therapy products
Chemistry, manufacturing, and controls information and establishment description		
1997	- Guidance for the Submission of Chemistry, Manufacturing, and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products (Docket No. 95N-0200, January 1997)	- Information of chemistry, manufacturing and control (CMC) and establishment description section for a biologics license application (BLA)
2008	- Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Application (INDs) (April 2008)	- Human somatic cell therapy IND, recommendation of CMC information
Human cells, tissues, and cellular and tissue-based products: establishment registration and listing		
2001	- Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing (Federal Register Vol. 66, No.13 P5447-5469, Final Rules January 19, 2001)	- Final rules of establishment registration and listing regarding human cells, tissues and cellular and tissue-based products (HCTPs)
2004	- Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing (Federal Register Vol. 69, No. 17, P3823-3826, Interim Final Rules January 27, 2004	- Excepted human dura matter and human heart valve allograft from the definition of HCT/Ps
Validation of procedures for processing		
2002	- Guidance for Industry: Validation of Procedures for Processing of Human Tissues Intended for Transplantation (March 2002)	- Written procedures to prevent infectious diseases contamination or cross-contamination during tissue processing for 21 CFR 1270 as well as 21 CFR 1271
Eligibility determination for donors and testing and screening		
2004	- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (Federal Register Vol. 69, No.101, P29786-29834, Final Rule May 25, 2004)	- Final rules of donor's eligibility for HCTPs
2004	- Guidance for Industry: Recommendations for Obtaining a Labeling Claim for Communicable Disease Donor Screening Tests Using Cadaveric Blood Specimens from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (November 2004)	- Performing studies to support modifying the indication for use to include testing cadaveric blood specimens to screen donor of HCT/Ps
2005	- Human Cells, Tissues, and Cellular and Tissue-Based Products; Donor Screening and Testing, and Related Labeling (Federal Register Vol. 70, No.100, P29949-29952, Interim Final rule May 25, 2005)	- Screening and testing of HCT/Ps donor and related labeling
2007	- Guidance for Industry: Certain Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Recovered From Donor Who Were Tested For Communicable Disease Using Pooled Specimens or Diagnostic Tests (Federal Register Vol. 72, No. 15, P3149-3150, Final rule January 24, 2007)	- Communicable diseases using pooled specimens or diagnostic tests
2007	- Human Cells, Tissues, and Cellular and Tissue-Based Products; Donor Screening and Testing, and Related Labeling (Federal Register Vol. 72, No.117, P33667-33669, Final rule June 19, 2007)	- Final rules of donor screening and testing, and labeling for HCTPs
2007	- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (August 8, 2007)	- Establishment making donor eligibility determinations
2008	- Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus Form Donors of Whole Blood and Blood Components Intended for Transfusion and Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (April 2008)	- Recommendation for testing of donation of whole blood and blood components and HCT/P donor specimens for West Nile Virus using FDA licensed donor screening assay
2008	- Guidance for Industry: Certain Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Recovered From Donor Who Were Tested For Communicable Disease Using Pooled Specimens or Diagnostic Tests (April 2008)	- Communicable diseases using pooled specimens or diagnostic tests
Current good tissue practice for manufacturers of human cellular and tissue-based products		
2004	- Current Good Tissue Practice for Human Cells, Tissues, and Cellular and Tissue-Based Product Establishment; Inspection and Enforcement (Federal Register Vol. 69, No.226, P68612-68688, Final Rule November 24, 2004)	- Final rules of inspection and enforcement for current good tissue practice (CGTP) of HCTPs
2011	- Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufactures of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (December 2011, Final Guidance)	- Recommendation for complying with CGCTP requirement

Table 2 (Continued)

Year	*Name of guidance document*	*Note*
Mandatory reporting of adverse reactions		
2005	- Guidance for industry: MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (November 2005)	- MedWatch mandatory reporting form, Form FDA 3500A for HCT/Ps, especially "361" HCT/Ps (21CFR1271.10)
Transparency of FDA's jurisdictional determination		
2006	- Guidance for Industry and FDA Staff: Minimal Manipulation of Structural Tissue Jurisdictional Update (September 2006)	- Intended to improve the transparency of FDA's jurisdictional determination, especially Tissue Reference Group for 361 HCT/P
Clinical trials for gene therapy products		
2006	- Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patient in Clinical Trials Using Retroviral Vectors (November 2006)	- Manufacture of gene therapy retroviral vector products intended for in vivo or ex vivo use and to follow-up monitoring of patients who have received retroviral vector products
2006	- Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for delayed Adverse Events (November 2006)	- Recommendations regarding the design of studies to include the collection of data on delayed adverse events in subjects who have been exposed to investigational gene therapy products
2006	- Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for delayed Adverse Events (November 2006)	- Recommendation on delayed adverse events
Small entity compliance guide for human cells, tissues, and cellular and tissue-based products		
2007	- Guidance for Industry: Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Small Entity Compliance Guide (Federal Register August 2007)	- Intended to help small entity establishment
Serological tests of Trypanosoma cruzi infection		
2009	- Guidance for Industry: Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Whole Blood and Blood Components for Transfusion and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (Register Vol.74, No.57, P13211-13213, March 26, 2009)	- FDA approval of BLA for ELISA test system for detection of antibodies to *Trypanosoma cruzi*
Allogeneic pancreatic islet cell products		
2009	- Guidance for Industry: Consideration for Allogeneic Pancreatic Islet Cell Products (Federal Register Vol.74, No.179, 47805, September 17 2009)	- Recommendation of allogeneic pancreatic islet cell products for the treatment of Type 1 diabetes mellitus
Unrelated allogeneic placental/umbilical cord blood products		
2009	- Final guidance for industry: Minimally manipulated. unrelated, allogeneic placental/umbilical cord blood intended for hematopoietic reconstitution for specified indication, Federal Register (74FR53753) October 20, 2009	- Recommendations to manufacturers applying for licensure of minimally manipulated, unrelated allogeneic placental/umbilical cord blood, for specified indications
2011	- Guidance for industry and FDA staff: investigational new drug application (INDs) for minimally manipulated. unrelated, allogeneic placental/ umbilical cord blood intended for hematopoietic reconstitution for specified indication, Federal Register (76FR46303) August 2, 2011	- Advice to potential sponsors to assist in the submission of an IND for certain minimally manipulated hematopoietic stem/progenitor cells from placental/ umbilical cord blood
2014	- Guidance for industry: biologics licenses applications for minimally manipulated, unrelated allogeneic placental/umbilical cord blood intended for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system, Federal Register (79FR12508) March 5, 2014	- Recommendations for manufacturers, generally cord blood banks, to apply for licensure of minimally manipulated, unrelated allogeneic placental/umbilical cord blood
2014	- Guidance for industry and FDA staff: investigational new drug applications for minimally manipulated, unrelated allogeneic placental/umbilical cord blood intended for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system, Federal Register (79FR12509) March 5, 2014	- Advice to potential sponsors, such as cord blood banks, registries, transplant centers, or individual physicians serving as sponsor-investigators, to assist in the submission of an investigational new drug application (IND) for certain hematopoietic progenitor cells from placental/umbilical cord blood (HPC, Cord Blood)
Cellular therapy for cardiac disease		
2010	- Guidance for Industry: Cellular Therapy for Cardiac Disease (October 2010)	- Recommendation on the design of preclinical and clinical studies and on CMC information to IND
Potency tests for cellular and gene therapy products		
2011	- Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products (January 2011)	- Recommendation for developing tests to measure potency in certain products
Plasmid DNA vaccine and therapeutic cancer vaccines		
2011	- Guidance for Industry: Clinical Consideration for Therapeutic Cancer Vaccines (October 2011)	- IND for therapeutic cancer vaccine with recommendation on critical clinical consideration
Products intended to repair or replace knee cartilage		
2011	- Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage (December 2011)	- Recommendation about certain information of IDEs or INDs intended to repair or replace knee cartilage

(*Continued*)

Table 2 (Continued)

Year	*Name of guidance document*	*Note*
Preclinical assessment of investigational cellular and gene therapy products		
2013	- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013)	- Recommendations on the substance and scope of preclinical information needed to support clinical trials for investigational cellular therapies, gene therapies, therapeutic vaccines, xenotransplantation, and certain biologic-device combination products
Environmental assessments for gene therapies, vectored vaccines, and related recombinant viral or microbial products		
2015	- Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products: Guidance for Industry (March 2015)	- Recommendations on considerations when assessing whether to submit an Environmental Assessment for gene therapies, vectored vaccines, and related recombinant viral or microbial products
Design of early-phase clinical trials of cellular and gene therapy products		
2015	- Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products: Guidance for Industry (June 2015)	- Recommendations regarding clinical trials in which the primary objectives are the initial assessments of safety, tolerability, or feasibility of administration of investigational product
Design and analysis of shedding studies for virus or bacteria-based gene therapy and oncolytic product		
2015	- Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products: Guidance for Industry (August 2015)	- Recommendations on how to conduct shedding studies during preclinical and clinical development
Assay development for immunogenicity of therapeutic proteins		
2016	- Guidance for Industry: Assay Development for immunogenicity of Therapeutic proteins (April 16, 2016)	- Recommendations to facilitate industry's development and validation of 18 immune assays for assessment of the immunogenicity of therapeutic protein products during clinical trials
Microbial vectors used for gene therapy		
2016	- Recommendations for Microbial Vectors Used for Gene Therapy: Guidance for Industry (September 2016)	- Recommendations concerning IND submissions for microbial vectors used for gene therapy in early-phase clinical trials
Deviation reporting for human cells, tissues, and cellular and tissue-based products		
2017	- Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-Based Products Regulated Solely Under Section 361 of the Public Health Service Act and 21 CFR Part 1271: Guidance for Industry (September 2017)	- Recommendation of deviation reporting for HCT/Ps
Expedited programs for regenerative medicine therapies and device evaluation		
2017	- Expedited Programs for Regenerative Medicine Therapies for Serious Conditions: Draft Guidance for Industry (November 2017)	- Recommendations on the expedited development and review of these therapies
2017	- Evaluation of Devices Used with Regenerative Medicine Advanced Therapy: Draft Guidance for Industry (November 2017)	- Consideration of evaluating the device used with Regenerative Medicine Advanced Therapies
Same surgical procedure exception for human cells, tissues, and cellular and tissue-based products		
2017	- Same Surgical Procedure Exception: Questions and Answers Regarding the Scope of the Exception; Guidance for Industry; Availability (Same Surgical Procedure Exception and Adipose Tissue Final Guidance) Federal Register, November 17, 2017 (82 FR 54289)	- Provides tissue establishments and health care professionals with FDA's current thinking; this guidance supersedes the Adipose Tissue Draft Guidance
Minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products		
2017	- Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use; Guidance for Industry and Food and Drug Administration Staff; Availability (Minimal Manipulation, Homologous Use, and Adipose Tissue Final Guidance) Federal Register, November 17, 2017 (82 FR 290)	- Provides HCT/Ps manufactures, healthcare providers, and FDA staff, with FDA's current thinking on the regulatory criteria of minimal manipulation and homologous use

CMC, Chemistry, Manufacturing and Control; *BLA*, Biologics License Application; *IND*, Investigational New Drug Application, *HCT/Ps*. Human Cells, Tissues and Cellular and Tissue-based Products (HCTPs); *21 CFR 1270*, The Code of Federal Regulation Title 21, Section 1270; *21 CFR 1271*, The Code of Federal Regulation Title 21, Section 1271; *CGTP*, Current Good Tissue Practice; *FDA*, The Food and Drug Administration; *IDEs*, Investigational Device Exemptions.

A multitude of scientific guidelines for cell-therapies, tissue engineering, and gene therapy, have been published. But guidelines are typically not specific for allogeneic cell therapies (Table 4). The requirements of "Good Laboratory Practice (GLP)", "Good Clinical Practice (GCP)", and "Good Manufacturing Practice (GMP)" also must be considered for ATMPs like other medical products. For later stages of development and commercialization, guidance has also been issued relating to marketing authorization procedures for ATMPs and pharmacovigilance for advanced therapies. In the European Union, ATMPs like other medicinal products, are eligible for reexamination of CHMP opinions. Although relatively few ASTMPs have yet to reach the market, the European Union is aggressive about assisting novel ATMPs. For example, Glybera applied for a marketing authorization as the first gene therapy product in the world.

Table 3 Guidance Documents of Combination Products in the US

Year	*Name of guidance document*	*Note*
Jurisdictional information and marketing application user fees		
2004	- Guidance for Industry and FDA Staff: Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product	- Information on submission and resolution of formal disputes regarding timeliness of premarket review of a combination product
2005	- Guidance for Industry and FDA Staff: Application User Fees for Combination Products (April 2005)	- Marketing application user fees for combination products
2006	- Minimal Manipulation of Structural Tissue (Jurisdictional Update) (September 2006)	- Improvement of transparency of FDA's jurisdiction determination
2007	- Devices Used to Process Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (July 2007)	- Improvement of transparency of FDA's jurisdiction determination
	- Draft Guidance for Industry: Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells; Availability (Federal Register Vol.72, No.143, 41080-41081, July 26, 2007)	- Certain cell selection devices that minimally manipulate autologous Peripheral Blood Stem Cells (PBSCs) at the point of care for specific clinical indications, and the applicability of the requirements to such PBSCs
Early development consideration		
2006	- Guidance for Industry and FDA Staff: Early Development Considerations for Innovative Combination Products (September 2006)	- Context for initial discussion on the type of scientific and technical information for innovative combination products
New contract imaging indication		
2009	- Guidance for Industry: New Contract Imaging Indication Considerations for Device and Approved Drug and Biological Products (December 2009)	- New indication for Imaging contract enhancement of medical imaging devices and imaging drug/biological products
Request for designation and classification		
2011	- Guidance for Industry: How to Write a Request for Designation (RFD)	- Clarification of the type of information in the RFD
2017	- How to Prepare a Pre-Request for Designation (Pre-RFD), Draft Guidance for Industry (January 2017)	- Information of Pre-Request for Designation process for obtaining a preliminary assessment
	- Classification of Products as Drug and Devices & Additional Products Classification Issues: Guidance for Industry and FDA Staff, Final Guidance (September 2017)	- Information on issues of Requests for Designation and other classification activities
Interpretation of the term "Chemical Action"		
2011	- Guidance for Industry and FDA Staff: Interpretation of the Term "Chemical Action" in the Definition of Device under Section 201(h) of the Federal Food, Drug, and Cosmetic Act, Draft Guidance	- Information about meaning of "Chemical Action" in the of device definition
Postapproval change of combination product		
2013	- Guidance for Industry and FDA Staff: Submission for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA	- Principle to determine the type of marketing submission for postapproval change of a combination product that is approved such a biological license application (BLA), a new drug application (NDA), or a device premarket approval application (PMA)
Technical information for glass syringes		
2013	- Guidance for Industry and FDA Staff: Glass Syringes for Delivering Drug and Biological Products: Technical Recommendations to Supplement International Organization for Standardization (ISO) Standard 114040-4, Draft Guidance (April 2013)	- Additional technical recommendations on glass syringes for delivering drug and biological products
Technical information for pen, jet, and related injector		
2013	- Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (June 2013)	- Technical and scientific information in a market application for a pen, jet, or related injector device
Human factors study		
2016	- Human Factors Studies and Related Clinical Study Considerations in Combination Product design and Development, Draft Guidance for Industry and FDA Staff (February 2016)	- Recommendations on Human Factors information in a combination product investigational or marketing application
Current good manufacturing practice requirements		
2017	- Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products, Final Guidance (January 2017)	- Final rule on current good manufacturing practice requirements for combination products

FDA, The Food, Drug Administration; *RFD*, Request for Designation; *BLA*, Biological License Application; *NDA*, New Drug Application; *PMA*, Premarket Approval Application; *ISO*, International Organization for Standardization.

Table 4 Guidance Documents of Advanced Therapy Medicinal Products in the EU

Year	*Name of recommendations*	*Note*
Support for advanced therapy for developers on research and development guidance for companies		
2006	- Overview of responses received from Interested Parties and EMEA Recommendations on the New Framework for Scientific Advice & Protocol Assistance (EMEA/31649/2006, 25 April 2006)	- New Framework for Scientific Advice & Protocol Assistance sets out initiatives
	- New framework for scientific advice & protocol assistance (EMEA/267187/2005/Rev.1 26 April 2006)	- The CPMP/CHMP scientific advice procedure
2015	- Template letter of intent for request of qualification of novel methodologies to the Scientific Advice Working Party (26 June 2015)	- Letter of intended for request of Qualification of Novel methodologies
2016	- CHMP protocol assistance scientific advice briefing document template (12 February 2016 Rev.1)	- Template for protocol assistance and scientific advice
2017	- General principles EMA-FDA parallel scientific advice (Human Medicinal Products) (EMA/309801/2017, April 2017)	- Program to provide parallel scientific advice (PSA) to sponsors
	- European Medicines Agency guidance for applicants seeking scientific advice and protocol assistance (30 June 2017 EMA/4260/2001 Rev. 9)	- A number of questions that users of the scientific advice or protocol assistance procedures
	- Dates of 2018 SAWP meetings and submission deadlines 20 July 2017, EMA/4267234/2014 Rev.1)	- Scientific advice, protocol assistance, qualification of biomarkers and parallel consultation (EMA/EUnetHTA) requests
	- Template letter of intent for parallel consultation EMA/EUnetHTA (4 July 2017	- Letter of intent for parallel consultation EMA and EUnetHTA
Standard operating procedures and work instructions		
2008	- Work instructions for validation of scientific advice and protocol assistance requests (WI/H/3039 03 October 2008)	- Scientific advice procedure
2009	- Work instructions for general dealings between SAWP secretariat and working parties, SAGs, committees and patients' organizations (WI/H/3036 26 November 2009)	- Organization of Scientific Advice Working Party and relevant working parties and groups
2012	- Work instructions for nomination of co-ordinators for scientific advice and protocol assistance (WIN/H/3137 07 May 2012)	- Scientific advice and protocol assistance procedure
	- Work instructions for organization of discussion meetings for scientific advice and protocol assistance (WIN/H/3042 16 May 2012)	- Organization of discussion meeting
2013	- Work instructions for finalization of scientific-advice and protocol-assistance letters (WIN/H/3196 10 January 2013)	- Procedure of final advice letter (FAL)
	- Work instructions for scientific-advice / protocol-assistance peer review (WIN/H/3139 06 May 2013)	- Peer Review system by Committee for Medicinal Products for Human Use(CHMP)
	- Work instructions for organization of Scientific Advice Working Party meetings (medicines for human use) (WIN/H/3195 11 June 2013)	- Organization of Scientific Advice Working Party
	- Work instructions for use of scientific-advice and protocol-assistance database (WIN/H/3040 24 June 2013)	- Procedure of Scientific Advice Database (SCAD)
	- Work instructions for organization of scientific-advice and protocol-assistance pre-submission meetings (WIN/H/3035 24 June 2013)	- Organization of pre-submission meeting
2015	- Standard operating procedure for scientific advice and protocol assistance procedure (SOP/H/3037, 1 December 2015)	- Procedure from submission of a request for scientific advice or protocol assistance to a final answer to the applicant
Certification procedures for Micro-, Small- and Medium-sized Enterprise (SMEs)		
2010	- Guideline on the minimum quality and nonclinical data for certification of advanced therapy medicinal products (EMA/CAT/486831/2008/corr, 15 October 2010)	- Minimum quality and nonclinical set of data that Small and Medium-sized Enterprises (SMEs)1 developing Advanced Therapy Medicinal Products (ATMPs)
2016	- Procedural advice on the certification of quality and nonclinical data for small and medium sized enterprises developing advanced therapy medicinal products (EMA/CAT/418458/2008/rev. 27 September 2016)	- Procedures, timelines and practical steps to be followed by the applicants and the EMA for the submission, evaluation of a certification application
	- User guide for micro, small and medium-sized enterprises on the administrative and procedural aspects of the provisions laid down in Regulation (EC) No 726/2004, that are of particular relevance to SMEs (July 2016)	- User guide for SMEs
Advanced Therapy Medicinal Products (ATMP) classification		
2013	- Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products in accordance with article 17 of regulation (EC) no 1394/2007 (EMA/CAT/99623/2009 Rev.1)	- Procedure and guidance for the steps to be followed by the applicant and the EMA for the ATMP classification
2015	- Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1, 21 May 2015)	- Guidance on the ATMP classification procedure
	- Overview of comments received on 'Reflection Paper on classification of advanced therapy medicinal products' (EMA/CAT/600280/2010 rev. 1; EMA/CAT/224106/2015 28May 2015)	- Overview of comments

Table 4 (Continued)

Year	Name of recommendations	Note
Cell-therapy and tissue engineering		
2008	- Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006 21 May 2008)	- Development, manufacturing and quality control as well as nonclinical and clinical development of cell-based medicinal products (CBMP) including somatic cell therapy medicinal products
	- Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products (EMEA/149995/2008, 20 November 2008)	- Optimal assessment of risk management plans of ATMPs
2009	- Guideline on xenogeneic cell-based medicinal products (CHMP/CPWP/83508/2009, 22 October 2009)	- Specific requirements for xenogeneic cell-based products
2010	- Reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee (CAT/CPWP/568181/2009, 08 April 2010)	- Specific points related to medicinal products containing in vitro cultured autologous chondrocytes intended for the repair of cartilage lesions of the knee
2011	- Reflection paper on stem cell-based medicinal products (EMA/CAT/571134/2009, 14 January 2011)	- Specific aspects related to stem cell-based medicinal products for Marketing Authorization Application
	- CHMP/CAT position statement Creutzfeldt-Jakob disease and advanced therapy medicinal products (EMA/CHMP/CAT/BWP/353632/2010, 23 June 2011)	- Recommendations of the CHMP Position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products
2013	- Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products (EMA/CAT/CPWP, 11 February 2013)	- Determination of the extent of quality, nonclinical and clinical data to be included in the Marketing Authorization Application (MAA)
2014	- Reflection paper on clinical aspects related to tissue engineered products (EMA/CAT/573420/2009, 19 September 2014)	- specific guidance on clinical testing for tissue engineered products
2016	- Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer (EMA/CHMP/BWP/271475/2006 rev.1, 21 July 2016)	- Guidance on specific requirements related to the development and validation of potency assays for cell based immunotherapy products
Gene therapy		
2001	- Note for guidance on the quality, preclinical and clinical aspects of gene therapy medicinal products (CHMP/GTWP/BWP/99, 24 April 2001)	- Recommendation with respect to quality, preclinical and clinical aspect of gene transfer medicinal products
2005	- Guideline on development and manufacture of lentiviral vectors (CPMP/BWP/2458/03, 26 May 2005)	- Quality aspects and nonclinical testing that are in general relevant for Lentiviral Vectors that are intended for ex vivo or in vivo application
2006	- Guideline on nonclinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005, 16 November 2006)	- Guidance on nonclinical inadvertent germline transmission testing needed to support clinical development of gene transfer medicinal products
2008	- Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products (EMEA/149995/2008, 20 November 2008)	- Optimal assessment of risk management plans of ATMPs
	- Guideline on nonclinical studies required before first clinical use of gene therapy medicinal products (CHMP/GTWP/125459/2006, 30 May 2008)	- Scientific principles on nonclinical studies required before the first use of a GTMP in human subjects
	- Guideline on scientific requirements for the environmental risk assessment of gene-therapy medicinal products (CHMP/GTWP/125491/06, 30 May 2008)	- Scientific principles and methodology to be used for the environmental risk assessment (ERA) of gene therapy GMO-containing medicinal products for human use
2009	- ICH Considerations: general principles to address virus and vector shedding (EMEA/CHMP/ICH/449035/2009, July 2009)	- Recommendations for designing nonclinical and clinical shedding studies
	- ICH Considerations: oncolytic viruses (EMEA/CHMP/ICH/607698/2008, October 2009)	- General principles for the clinical development of oncolytic viruses
	- Guideline on follow-up of patients administered with gene therapy medicinal products (CHMP/GTWP/60436/2007, 22 October 2009)	- Recommendations for clinical monitoring and follow-up after treatment with Gene Therapy (GT) medicinal products
	- Questions and answers on gene therapy (CHMP/GTWP/212377/08, 17 December 2009)	- Clarification and/or additional information in conjunction with the gene therapy medicinal products
2010	- Reflection paper on quality, nonclinical and clinical issues relating specifically to recombinant adeno-associated viral vectors (CHMP/GTWP/587488/2007 Rev. 1, 24 June 2010)	- Discussion on quality, nonclinical and clinical issues that should be considered during the development of medicinal products derived from AAV
2011	- CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products (EMA/CHMP/CAT/BWP/353632/2010, 23 June 2011)	- Recommendations of the CHMP Position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products
	- Reflection paper on design modifications of gene therapy medicinal products during development (CAT/GTWP/44236/2009, 14 December 2011)	- Insight into the types of studies that are likely to be required in an application dossier to support the modification in the product design introduced during development
2012	- Guideline on quality, nonclinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008, 13 April 2012)	- Guidance for the development and evaluation of medicinal products containing genetically modified cells intended for use in human

(*Continued*)

Table 4 (Continued)

Year	*Name of recommendations*	*Note*
2013	- Guideline on risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products (CAT/CPWP/686637/2011, 11 February 2013)	- Intention of the risk-based approach and details its methodological application
	- Reflection paper on management of clinical risks deriving from insertional mutagenesis (CAT/190186/2012, 19 April 2013)	- Discussion on the factors contributing to genotoxicity of vector integration, the strategies to reduce the risk associated to insertional mutagenesis and the assays to evaluate vector oncogenesis at the pre-clinical and clinical level
Good Laboratory Practice (GLP) requirements		
2017	- Good Laboratory Practice (GLP) Principles in Relation to ATMPS (26 January 2017)	- Specific to GLP for nonclinical safety studies involving ATMPs
Good Clinical Practice (GCP) requirements		
2009	- Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (ENTR/F/SF/dn D82009) 35810 03/12/2009)	- Specific to GCP for clinical trials involving ATMPs
Good Manufacturing Practice (GMP) requirements		
2010	- Annex 13 Investigational Medicinal Products (ENTR/F/AM/an D (2010) 3374)	- Specific to Investigational Medicinal Products
2012	- Annex 2 Manufacture of Biological active substances and Medicinal Products for Human Use (SANCO/AM/sl/ddg1.d.6(2012)860362)	- Specific to manufacture of biological active substances
2015	- Annex 16: Certification by a Qualified Person and Batch Release (12 October 2015)	- Specific to certification by a qualified person and batch release
2017	- Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (22 November 2017; should comply with this guideline no later than 22 May 2018)	- Specific to GMP requirements of ATMPs: EudraLex The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice
Marketing-authorization procedures for Advanced Therapy Medicinal Products(ATMPs)		
2009	- Procedural advice on the re-examination of CHMP opinions (EMEA/CHMP/ 50745/2005 Rev.1, 12 February 2009)	- Re-examination procedure for better guarantee for applicants/ Manufacture Application Holder's right
2011	- Procedural advice on the evaluation of combined advanced therapy medicinal products and the consultation of Notified Bodies in accordance with Article 9 of Regulation (EC) No. 1394/2007 (EMA/354785/2010, 11 February 2011)	- Procedure for interactions between the Agency (EMA) and CAT and Notified Bodies for medical devices in relation to the evaluation of combined ATMPs
2013	- Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products (EMA/CAT/CPWP)	- Determination of the extent of quality, nonclinical and clinical data to be included in the Marketing Authorization Application (MAA)
2017	- Dossier requirements for centrally authorized products (CAPs) (EMA/497021/2012 Rev. 24, 20 February 2017)	- Dossier requirements
	- Development of nonsubstantially manipulated cell-based ATMPs: flexibility introduced via the application of the risk-based approach (EMA/CAT/216556/2017, 3 July 2017)	- Possibilities and limitations of the risk-based approach using the example of an ATMP
2018	- Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) No 1394/2007 (EMA/630043/2008, 25 January 2018)	- Procedure for the evaluation of marketing authorization applications for ATMPs
Pharmacovigilance for advanced therapies		
2008	- Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products (EMEA/149995/2008, 20 November 2008)	- Specific aspects of pharmacovigilance, risk management planning, safety and efficacy follow-up of authorized ATMPs, as well as some aspects of clinical follow-up of patients treated with such products
Post-authorization safety studies: Questions and answers		
2017	- European Medicines Agency post-authorization procedural advice for users of the centralized procedure (EMEA-h-19984/03 Rev. 75 11 December 2017)	- Question and answers for post-authorization of marketing authorization holders MAHs)

EMEA, the European Agency for the Evaluation of Medicinal Products; *CPMP*, the Committee for Proprietary Medicinal Products; *CHMP*, the Committee for Medicinal Products for Human Use; *EMA*, the European Medicines Agency; *FDA*, the Food and Drug Administration; *PSA*, Parallel Scientific Advice; *SAWP*, the Scientific Advice Working Party; *EUnetHTA*, the European Network for Health Technology Assessment; *GMP*, Good Manufacturing Practice; *GCP*, Good Clinical Practice; *GLP*, Good Laboratory Practice; *ATMP*, Advanced Therapy Medicinal Product; SMEs, Small- and Medium-sized Enterprises; CAT, the Committee of Advanced Therapies; EC, the European Communities; WI, Working Instruction; *FAL*, Final Advice Letter; *SCAD*, Scientific Advise Database; *MAHs*, Marketing Authorization Holders; *CBMP*, Cell-Based Medicinal Products; *MAA*, Marketing Authorization Application; *ERA*, Environment Risk Assessment; *ICH*, The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; *GT*, Gene Therapy; *AAV*, Adeno-Associated Viral Vector; *CAPs*, Centrally Authorized Products.

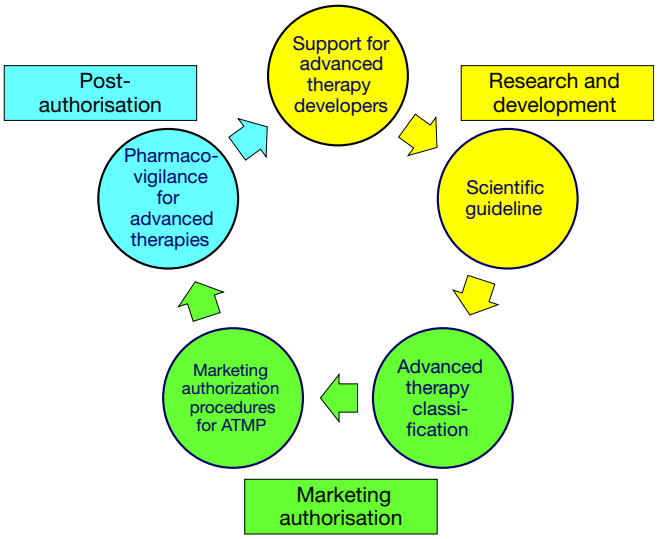

Fig. 2 Well-organized supporting system based on product life cycle of advanced therapy medicinal products. In the EU, the Committee for Advanced Therapies (CAT) and the Committee for Medicine Products for Human Use (CHMP) have supported, reviewed and oversighted the developers, applicants and manufacturers in the fields such research and development, market authorization, and postauthorization. For the support for advanced therapy for developers on research and development guidance for companies, a series of the template letters for protocol assistance and scientific advice and the procedures for the EMA. The scientific recommendations on ATMP classification are issued by the Committee for Advanced Therapies (CAT), which are useful for developer at the early stage of development because of choosing relevant scientific guideline for cell-therapy and tissue engineering, and gene therapy products. At the market authorization, conditional market authorization as expedited approval system in the European Union and market authorization under the exceptional circumstances as well as re-examination for premarket review are special market authorization system.

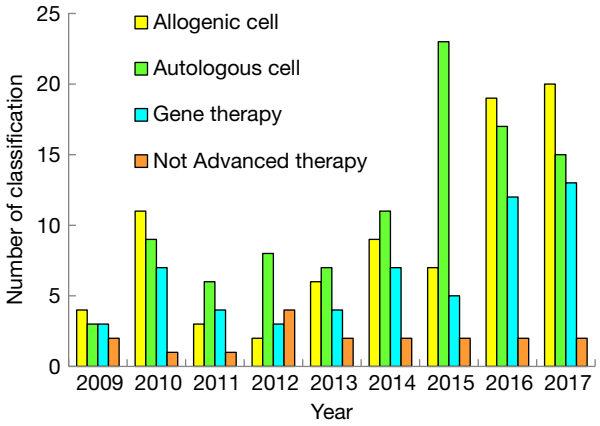

Fig. 3 Outcome of the assessment of the classification of advanced therapy medicinal products during 2009–17. In the European Union, advanced therapy medicinal products (ATMPs) under the regulation (EC) No 1394/2007 consist of gene therapy medicine products and somatic cell therapy products, and tissue engineered products. In this figure, cell-origin such as allogeneic or autologous is focused to categorize the products because of identifying the trend of development. According to the summary reports from 2009 to 2017 (until September), 81 allogeneic cell-based products, 99 autologous cell-based, 58 gene therapy products (gene-modified allogeneic and autologous cell-based products include), and 18 not advanced therapy products have already been classified by the Committee for Advanced Therapies (CAT). From 2014, the number of classification for ATMPs has been drastically increased: approximately 10–20 products for 2009–2013, 29 in 2014, 37 in 2015, 50 in 2016, 50 until September in 2017.

Guidance documents in Japan

In Japan, a series of notifications on Regenerative Medicine Products are available to support the application process (Table 5). Most of these notifications are written in Japanese but a series of standards for ensuring the quality and safety of medical products have been published as part of the approval application.

In Japan, the PMDA has established several mechanisms for consultation prior to clinical development, to assist the planning of clinical trials or to support the approval application. Applicants can apply for certain types of consultations: (i) procedure;

(ii) translational research; (iii) early development; (iv) nonclinical safety; (v) quality; (vi) raw materials; (vii) preexploratory clinical trial; (viii) postexploratory clinical trial (POC); (ix) preapproval application; (x) preclinical trial after granting conditional and time-limited approval; (xi) postclinical trial after granting conditional and time-limited approval; (xii) pre-GPSP; (xiii) post-GPSP; and (xiv) additional consultation.

Guidance documents and Q & A for ensuring of quality and safety of medical products have also been issued for allogeneic human cells and tissue, allogeneic human somatic stem cells, allogeneic human iPS-like cells, and allogeneic human ES cells. Furthermore, evaluation criteria for allogeneic iPS-like cell-based retinal pigment cells and articular cartilage regeneration treated by allogeneic human iPS-like cell-based products have also been issued. Other notifications are applicable to regenerative medicine products or autologous human cell products only.

Global Collaborations

Regulatory frameworks for HCT/Ps, ATMPs, and regenerative medicines have been established in the United States, the European Union, and Japan, respectively. However, international collaboration among regulatory authorities by partnerships such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) for pharmaceuticals and International Medical Device Regulators Forum (IMDRF) for medical devices have been formed. In 2017, the Summit of Heads of Medicines Regulatory Agencies Symposium, attended by the regulatory authorities of 23 countries and region was held in Kyoto, Japan. They declared that "regulatory convergence on regenerative medicines needs to evolve in order to better reflect the characteristics of the products".

Approved Products

All Approved Human Cell-Based Products

As of December 2017, 24 human cell-based products and gene therapy products, including 5 autologous human cell-based products, 15 allogeneic human cell-based products, and 4 gene therapy/cell-based gene therapies were approved in the United States (Tables 6–8; Fig. 4). In the EU, nine human cell-based products and gene therapy products, including five autologous human cell-based products, and four gene therapy products, were approved (Tables 6 and 8; Fig. 4). An additional allogeneic human cell-based product was granted a positive opinion from CHMP on December 14, 2017 (Table 6). In Japan, four human cell-based products—three autologous human cell-based products and an allogeneic human cell-based product—were approved (Tables 6 and 8; Fig. 4).

Approved Allogenic Human-Cell Based Products

Medical devices and biologics

In the United States, the final rule of establishment registration and listing concerning human cells and tissue products for human use was issued in 2001. The effective date for the final rule of current Good Tissue Practices (CGTP) for HCT/Ps was May 25, 2005, when the jurisdiction for many HCT/Ps was transferred from the Center for Devices and Radiological Health (CDRH) to the Center for Biologics Evaluation and Research (CBER).

Before changing the jurisdiction of the HCT/Ps, some HCT/Ps were approved as medical devices that might later be viewed as HCT/Ps. Dermagraft-TC (currently known as TransCyte), Apligraf, Composite Cultures Skin, Orcel, and Dermagraft were approved as wound covering for thermal burn, skin ulcers, diabetic foot ulcers (Table 6).

After 2005, a product branded as Apligraf for another indication was marketed under the name, GINTUIT, but was approved as biologic to repair surgically created vascular wounds for mucogingival conditions (Table 6). GINTUIT received conditional Premarket approval (PMA) that depended on the conduct of a pediatric post marketing study. The product was later added to the discontinued list, indicating that it was not being marketed beyond 2014. Since a manufacturer failed to complete a post marketing study to clear the conditions on the PMA, the company has already received a "Notification of Noncompliance with Pediatric Research Equity Act, PREA". The company then replied to the FDA under the procedure titled "Response to PREA Noncompliance Deferral Extension Requested" that provides a reason for the delayed pediatric assessment and a date by which the company expects to submit the assessment. We need to understand why the product was on the Discontinued list or why the post marketing study was not completed by the due date because the reason was redacted for public disclosure in the response letter.

Hematopoietic progenitor cells (HPCs)

In the United States, umbilical cord blood has been used as source of hematopoietic stem cells for allogeneic hematopoietic stem cell transplant for over 20 years in the United States. According to the guidance on allogeneic placental/umbilical cord blood, hematopoietic progenitor cells from cord blood (HPC, Cord Blood) would be regulated as a type of human cell and tissue product after October 20, 2011. HEMACORD™ was approved on November 10, 2011 after clinical review, including published literature, indicated that sufficient evidence of efficacy and safety existed for treating patients with hematologic malignancy and nonmalignant indications. Six more HPCs, Cord Blood were approved: HPC, Cord Blood (No-Trade name) and Ducord in 2012; ALLOCORD and HPC, Cord Blood (No-Trade named) in 2013; HPC, Cord Blood (No-Trade name) and CLEAVECORD in 2016 (Table 7).

Table 5 Guidance documents of regenerative medicine in Japan

Year	Name of recommendations	Note
Consultation		
2012	- Operation guide of consultation by Pharmaceuticals and Medical Devices Agency (PMDA Notification No. 030270, 2 March 2012)	- Procedures and application forms for PMDA's consultations of Pharmaceuticals, Medical Devices, Regenerative Medicines, and Quasi-drugs
Clinical trial notification		
2014	- Clinical trial notification of cell-based products (Notification No. 0812-26, PFSB/MHLW, 12 August 2014)	- Notification of clinical trial plan of call-based products
2014	- Handling of clinical trial notification of cell-based products (Notification No.0812-1, MHLWSC/OMDE/ELD/PFSB/MHLW, 12 August 2014)	- Procedure and application forms for notification of clinical trial plan of cell-based products
Adverse effects/device deficiency report		
2014	- Adverse effects and device deficiency report of cell-based products during clinical trial (Notification No. 1002-23, PFSB/MHLW, 2 October 2014)	- Overview and report form of Adverse effects and device deficiency report of cell-based products
	- Consideration on adverse effects and device deficiency report of cell-based products during clinical trial (Notification No. 1002-1, MHLWSC/OMDE/ELD/PFSB/MHLW, 2 October 2014)	- Detailed description of Adverse effects and device deficiency report of cell-based products
	- Handling of adverse effects and device deficiency report of cell-based products during clinical trial (Notification No. 1107004, ORM/OS/PMDA, 7 November 2014)	- Handling procedure
	- Partial revision, handling of adverse effects and device deficiency report of cell-based products during clinical trial (Notification No. 0318001, ORM/OS/PMDA, 18 March 2015)	- Electronic submission system and its procedures
Product development		
2016	- Technical guidance on quality, nonclinical studies and clinical investigation of regenerative medicine product (human cell-based products) (27 June 2016, Administrative Notification)	- Consideration of quality, nonclinical studies and clinical investigation
	- Points to consider in conducting effectively for Strategic Regulatory consultations on quality and safety of cell- and tissue-based products during early development stage (check points)	- Check points for pre-consultation of quality, sterility test and negative tests for *Mycoplasama* of cell substrate, nonclinical safety studies
	- Document review for initial notification of clinical trial (30-day document review: check points)	- Check points of document review during 30 days after submitting clinical trial notification by PMDA
Standards: Biological raw materials standards		
2003	- Notification of the Ministry of health, Labour, and Welfare No. 210 (20 May 2003)	- Establishment of Biological Raw Materials Standard Biological Raw materials
2014	- Notification of the Ministry of health, Labour, and Welfare No. 375 (26 September 2014)	- Partial revision of Raw Materials Standard
	- Partial revision of Biological Raw Materials Standards (Notification No. 1002-27, PFSB/MHLW, 2 October 2014)	- Following Regenerative Medicine Products, partial revision
	- Operation of Biological Raw Materials Standards (Notification No. 1002-1, OMDE/ELD/PFSB/MHLW, Notification No. 1002-5, MHLWSC/OMDE/ELD/PFSB/MHLW, 2 October 2014)	- Operational manual of Biological Raw Materials Standards
2015	- Question and Answer on Biological Raw Materials Standards (Administrative notification, 30 June 2015)	- Q&A
Ensuring of quality and safety of medical products at the approval application		
2000	- Ensuring of quality and safety of medical products manufactured from human- or animal-based ingredients as raw materials (Notification No. 1314, PFSB/MHLW, 26 December 2000)	- Current thinking on treatment and use of cells and tissue-based medical products
2008	- Ensuring of quality and safety of medical products manufactured from autologous human cells or tissue (Notification No. 0208003, PFSB/MHLW, 8 February 2008)	- Current thinking on treatment and use of autologous human cells or tissue
	- Question and answer on ensuring of quality and safety of medical products manufactured from autologous human cells or tissue (Administrative notification, 12 March 2008)	- Q&A
	- Ensuring of quality and safety of medical products manufactured from allogeneic human cells or tissue (Notification No. 0912006, PFSB/MHLW, 12 September 2008)	- Current thinking on treatment and use of allogeneic human cells
	- Question and answer on ensuring of quality and safety of medical products manufactured from allogeneic human cells or tissue (Administrative notification, 3 October 2008)	- Q&A
2012	- Ensuring of quality and safety of medical products manufactured from autologous human somatic stem cells (Notification No. 0907-2, PFSB/MHLW, 7 September 2012)	- Current thinking on treatment and use of autologous human somatic stem cells
	- Ensuring of quality and safety of medical products manufactured from allogeneic human somatic stem cells (Notification No. 0907-3, PFSB/MHLW, 7 September 2012)	- Current thinking on treatment and use of allogeneic human somatic stem cells

(*Continued*)

Table 5 (Continued)

Year	Name of recommendations	Note
	- Ensuring of quality and safety of medical products manufactured from autologous human iPS-like cells (Notification No. 0907-4, PFSB/MHLW, 7 September 2012)	- Current thinking on treatment and use of autologous human iPS-like cells
	- Ensuring of quality and safety of medical products manufactured from allogeneic human iPS-like cells (Notification No. 0907-5, PFSB/MHLW, 7 September 2012)	- Current thinking on treatment and use of allogeneic human iPS-like cells
	- Ensuring of quality and safety of medical products manufactured from allogeneic human ES cells (Notification No. 0907-6, PFSB/MHLW, 7 September 2012)	- Current thinking on treatment and use of allogeneic human ES cells
Evaluation criteria of next generation medical devices		
2010	- Official announcement on evaluation criteria of next generation medical devices and regenerative medicine products (Notification No. 0118-1, OMDE/ELD/PFSB/MHLW, 18 January 2010)	- Annex-3: Evaluation criteria on cell sheets of severe heart failure therapy - Annex-4: Evaluation criteria on cell sheets of corneal epithelial cells
	- Official announcement on evaluation criteria of next generation medical devices and regenerative medicine products (Notification No. 0528-1, OMDE/ELD/PFSB/MHLW, 28 May 2010)	- Evaluation criteria on cell sheets of corneal endothelial cells
	- Official announcement on evaluation criteria of next generation medical devices and regenerative medicine products (Notification No. 1215-1, OMDE/ELD/PFSB/MHLW, 15 December 2010)	- Evaluation criteria on articular cartilage regeneration
2011	- Official announcement on evaluation criteria of next generation medical devices and regenerative medicine products (Notification No. 1207-1, OMDE/ELD/PFSB/MHLW, 7 December 2011)	- Evaluation criteria on cell sheets for periodontal therapy
2013	- Official announcement on evaluation criteria of next generation medical devices and regenerative medicine products (Notification No. 0529-1, OMDE/ELD/PFSB/MHLW, 29 May 2013)	- Evaluation criteria on autologous iPS cell-based retinal pigment cells
2014	- Official announcement on evaluation criteria of next generation medical devices and regenerative medicine products (Notification No. 0912-2, MHLWSC/OMDE/ELD/PFSB/MHLW, 12 September 2014)	- Evaluation criteria on allogeneic iPS-like cell-based retinal pigment cells
2015	- Official announcement on evaluation criteria of next generation medical devices and regenerative medicine products (Notification No. 0630-1, MHLWSC/OMDE/ELD/PFSB/MHLW, 25 September 2015)	- Evaluation criteria on nasal cartilage regeneration
2016	- Official announcement on evaluation criteria of next generation medical devices and regenerative medicine products (Notification No. 0630-1, OMDE/ELD/PFSB/PSEHB/MHLW, 30 June 2016)	- Annex-1: Evaluation criteria on articular cartilage regeneration treated by human chondrocyte- or somatic stem cell-based products - Annex-2: Evaluation criteria on articular cartilage regeneration treated by allogeneic human iPS-like cell-based products
Quality		
1998	- Stability testing of Biologics such biotechnology applied products or biological-origin products (Notification No. 6, OEL/PAB/MHW, 6 January 1998)	- ICH-Q5C: Quality of Biotechnology products: Stability testing of Biotechnological/biological products
	- Analysis of the expression construct in cells used for production of recombinant DNA derived protein products (Notification No. 3, OEL/PAB/MHW, 6 January 1998)	- ICH-Q5B: Quality of Biotechnology products: Analysis of the expression construct in cells used for production of r-DNA derived protein products
2000	- Viral safety evaluation of biotechnology applied pharmaceuticals derived from cell lines of human or animal origin (Notification No. 329, OEL/PAB/MHW, 22 February 2000)	- ICH-Q5A: Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin
	- Origin, generation and characterization analysis of cell substrates used for production of biologics such biotechnology applied products or biological-origin products (Notification No. 873, OEL/PAB/MHW, 14 July 2000)	- ICH-Q5D: Derivation and characterization of cell substrates used for production of biotechnological/biological products
2001	- Setting specifications of acceptance criteria and test procedures of biologics such biotechnology applied products or biological-origin products (Notification No. 571, OMDE/ELD/PFSB/MHLW, 1 May 2001)	- ICH-Q6B: Specifications: Test procedures and acceptance criteria for biotechnological/biological products
2005	- Comparability evaluation of biotechnology applied products or biological-origin products subject to change in their manufacturing process (Notification No. 0426001, OMDE/ELD/PFSB/MHLW, 26 April 2005)	- ICH-Q5E: Comparability of biotechnological/biological products subject to change in their manufacturing process
No-clinical safety evaluation		
1989	- Guideline of mandatory toxicological testing for application dossier of pharmaceuticals (Notification No. 1-24, FERD/SERD/BD PAB/MHW, 11 September 1989)	- Annex: Guideline of toxicological testing for pharmaceuticals

2010	- Guidance of conducting nonclinical safety examinations prior to clinical trials and for application dossier of pharmaceuticals (Notification No. 0219-4, OMDE/ELD/PFSB/MHLW, 19 February 2010)	- Annex: Guidance of conducting nonclinical safety examinations prior to clinical trials and for application dossier of pharmaceuticals; ICH-M3 (R2): Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for Pharmaceuticals
2012	- Principal concept of essential biosafety evaluations for market application dossier of medical device (Notification No. 0301-20, OMDE/ELD/PFSB/MHLW, 1 March 2010)	- Annex: Principal concept of essential biosafety evaluations for market application dossier of medical device
	- Nonclinical safety examinations of biotechnology applied products (Notification No. 0323-1, OMDE/ELD/PFSB/MHLW, 23 March 2012)	- Annex: Nonclinical safety evaluation of biotechnology applied products or biological-origin products; ICH-S6(R1): Preclinical safety evaluation of biotechnology-derived pharmaceuticals
Conformity inspection (GLP/GCP/GCTP): Good Laboratory Practice (GLP)		
2014	- Ministerial ordinance on standards for conducting nonclinical safety studies of regenerative medicine products (MHLW ministerial ordinance No. 88, 30 July 2014)	- Ministerial ordinance of good laboratory practice (GLP)
	- Enforcement of ministerial ordinance on standards for conducting nonclinical safety studies of regenerative medicine products (Notification No. 0812-20, PFSB/MHLW, 12 August 2014)	- Enforcement of ministerial ordinance GLP
	- Handling of documents to be attached application for nonclinical safety studies of pharmaceuticals, medical devices, and regenerative medicines (Notification No. 1121-9, MHLWSC/OMDE/ELD/PFSB/MHLW; No. 1121-13, OMDE/ELD/PFSB/MHLW, 21 November 2014)	- Guideline of nonclinical safety studies of regenerative medicines
	- Procedure for conformity document review and GCP site inspection for clinical trial sites for application of regenerative medicine products (PMDA notification No. 1121010, 21 November 2014)	- Annex 5: Certification of Good Laboratory Practice compliance by test facilities (domestic sites) - Annex 6: Certification of Good Laboratory Practice compliance by test facilities (oversea sites)
Conformity inspection (GLP/GCP/GCTP): Good Clinical Practice (GCP)		
2014	- Ministerial ordinance on standards for conducting clinical trials of regenerative medicine products (MHLW ministerial ordinance No. 89, 30 July 2014)	- Ministerial ordinance of good clinical practice (GCP)
	- Enforcement of ministerial ordinance on standards for conducting clinical trials of regenerative medicine products (Notification No. 0812-16, PFSB/MHLW, 12 August 2014)	- Enforcement of ministerial ordinance of GCP
	- Guideline of GCP compliance site inspection of regenerative medicine products (Notification No. 1121-3, MHLWSC/OMDE/ELD/PFSB/MHLW, 21 November 2014)	- Guideline of GCP compliance site inspection of regenerative medicine products
	- Guideline of GCP compliance document review of regenerative medicine products (Notification No. 1121-10, MHLWSC/OMDE/ELD/PFSB/MHLW, 21 November 2014)	- Guideline of GCP compliance document review of regenerative medicine products
	- Procedure for conformity document review and GCP site inspection for clinical trial sites for application of regenerative medicine products (PMDA notification No. 1121010, 21 November 2014)	- Procedure for conformity document review and GCP site inspection for clinical trial sites of regenerative medicine products
Conformity inspection (GLP/GCP/GCTP): Good Gene, Cellular, and Tissue-based Products Manufacturing Practice (GCTP)		
2014	- Document to be attached the application for conformity inspection of regenerative medicine products (Administrative notification, OQM/PMDA, 11 November 2014)	- Annex 1: Outline of product(s) subject to inspection Annex 2: Outline of Manufacturing site subject to inspection (domestic manufacturing site) Annex 3: Outline of Manufacturing site subject to inspection (oversea manufacturing site)
2015	- Questions and answers on standards for manufacturing management and quality control of regenerative medicine products (0317-1, CND/PFSB/MHLW, 17 March 2015)	- Q&A of manufacturing management and quality control
	- Questions and answers on standards for manufacturing management and quality control of regenerative medicine products: No.3 (0629-1, CND/PFSB/MHLW, 29 June 2015)	- Q&A (No.3) of manufacturing management and quality control
	- Questions and answers on standards for manufacturing management and quality control of regenerative medicine products: No.2 (0728-4, CND/PFSB/MHLW, 28 July 2015)	- Q&A (No.2) of manufacturing management and quality control
Conformity inspection of Good Postmarketing Study Practice (GPSP)		
2014	- Ministerial ordinance on standards for conducting good post-marketing study practice of regenerative medicine products (MHLW ministerial ordinance No. 90, 30 July 2014)	- Ministerial ordinance of good post-marketing study practice (GPSP)
	- Enforcement of ministerial ordinance on standards for conducting good post-marketing study practice of regenerative medicine products of regenerative medicine products (Notification No. 0812-23, PFSB/MHLW, 12 August 2014)	- Enforcement of ministerial ordinance of GPSP
	- Guideline of GPSP compliance site inspection of regenerative medicine products (Notification No. 1121-7, MHLWSC/OMDE/ELD/PFSB/MHLW, 21 November 2014)	- Guideline of GPSP compliance site inspection

(*Continued*)

Table 5 (Continued)

Year	*Name of recommendations*	*Note*
	- Procedure for conformity document review and GPSP site inspection for application of approval review, re-review, and re-evaluation after conditional and time-limited approval of regenerative medicine products (PMDA notification No. 1121011, 21 November 2014)	- Procedure for conformity document review and GPSP site inspection of regenerative medicine products
2017	- Partial revision of ministerial ordinance on standards for conducting good post-marketing study practice of pharmaceuticals: Partial revision of ministerial ordinance on standards for conducting good post-marketing study practice of regenerative medicine products (MHLW ministerial ordinance No. 116, 26 October 2017)	- Partial revision of GPSP ministerial ordinance
	- Promulgation of partial revised ministerial ordinance on standards for conducting good post-marketing study practice of pharmaceuticals: Partial revision of ministerial ordinance on standards for conducting good post-marketing study practice of regenerative medicine products (Notification No. 1026-10, PFSB/MHLW, 26 October 2017)	- Promulgation of partially revised GPSP ministerial ordinance

PMDA, Pharmaceuticals and Medical Devices Agency; *PFSB*, Pharmaceutical and Food Safety Bureau; *MHLW*, Ministry of Health Labour Welfare; *MHLWSC*, Office of Evaluation and Licensing, Ministry of Health, Labor and Welfare Minister's Secretariat Counselor; *OMDE*, Office of Medical Devices Evaluation; *ELD*, Evaluation and Licensing Division; *PMSB*, Pharmaceutical and Medical Safety Bureau; *ORM*, Office of Review Management; *OS1*, Office of Safety 1; *PSEHB*, Pharmaceutical Safety and Environmental Health Bureau; *OEL*, Office of Evaluation and Licensing; *PAB*, Pharmaceutical Affairs Bureau; *FERD*, First Evaluation and Registration Division; *SERD*, Second Evaluation and Registration Division; *BD*, Biologics Division; *PAB*, Pharmaceutical Affairs Bureau; *MHW*, Ministry of Health and Welfare; *CND*, Compliance and Narcotics Division; *OQM*, Office of Quality Management, *ICH*, The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; *GLP*, Good Laboratory Practice; *GCP*, Good Clinical Practice; *GCTP*, Good Gene, Cellular, and Tissue-based Products Manufacturing Practice; *GPSP*, Good Post-Marketing Study Practice.

Table 6 Approved allogeneic human cells and tissue products in the US, the EU, and Japan

Generic name (Trade name)	*Cell origin (Material)*	*Approval date*	*Marketing authorization holder*	*Authority*	*Indication*	*Category*
US						
Interactive wound and burn dressing (Formerly, Dermagraft-TC™, currently, TransCyte®)	Allogeneic fibroblasts (Extracellular matrix and bioabsorbable polyglactin mesh scaffold)	March 18, 1997 (PMA)	Advanced Tissue Science, La Jolla, CA, US (1997–2002)	FDA/CDRH	Use as 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 replacement	Medical device
		August 14, 1998 (PMA/ supplement)			Treatment of mid-dermal to indeterminate depth burn wounds not requiring autografting	
			Smith & Nephew, Jolla, CA, US (2002–2005)			
			Advanced BioHealing[1]), La Jolla, CA, US (2006–)			
			Organogenesis Inc., Canton, MA, US			
Living Skin Equivalent (LSE) Graftskin (Apligraf™)	Allogeneic fibroblasts and keratinocytes (Type I bovine collagen)	May 22, 1998 (PMA)	Organogenesis Inc., Canton, MA, US	FDA/CDRH	Use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy	Medical device
		June 20, 2000 (PMA/ supplement)			Treatment of diabetic foot ulcers	
Interactive wound and burn dressing (Composite Cultures Skin)	Allogeneic epidermal keratinocytes and dermal fibroblasts (Bovine collagen matrix)	February 21, 2001 (HDE)	Ortec International, Inc., New York City, NY, US	FDA/CDRH	Use in patients with mitten hand deformity due to Recessive Dystrophic Epidermolysis Bullosa (RDEB) as adjunct to standard autograft procedure (i.e., skin grafts and flaps) for covering wounds and donor sites created after the surgical release offhand contraction (i.e., mitten hand deformity)	Medical device
Interactive wound and burn dressing (Orcel™)	Allogeneic epidermal keratinocytes and dermal fibroblasts (Bovine collagen matrix)	August 31, 2001 (PMA)	Ortec International, Inc., New York City, NY, US	FDA/CDRH	Treatment of fresh, clean split thickness donor site wounds in burn patients.	Medical device
			Forticell Bioscience, New York, NY, US			

(*Continued*)

Table 6 (Continued)

Generic name (Trade name)	*Cell origin (Material)*	*Approval date*	*Marketing authorization holder*	*Authority*	*Indication*	*Category*
Interactive wound dressing (Dermagraft®)	Allogeneic fibroblasts (Extracellular matrix and bioabsorbable polyglactin mesh scaffold)	September 28, 2001 (PMA)	Advanced BioHealing, La Jolla, CA, US (2001–2002) Smith & Nephew, La Jolla, CA, US (2002–2006) Advanced BioHealing[1], La Jolla, CA, US (2006–) Organogenesis Inc., Canton, MA, US	FDA/CDRH	Use for treatment of full-thickness diabetic foot ulcers greater than six weeks duration which extend through the dermis, but without tendon, muscle, joint capsule or bone exposure	Medical device
Allogeneic cultured keratinocyte and fibroblast in bovine collagen (GINTUIT™)	Allogeneic fibroblasts and keratinocytes (Bovine-derived collagen biomaterial)	March 9, 2012 (BLA) September 3, 2014 June 29, 2017 (Notification by CBER) August 17, 2017 (Reply to CBER)	Organogenesis Inc., Canton, MA, US	FDA/CBER	Topical (non-submerged) application to surgically created vascular wound bed in the treatment of mucogingival conditions in adults *Discontinued list (Not being Marketed)* The FDA issued the "Notification of Non-compliance with PREA": the FDA's determination is that Organogenesis Inc. has failed to meet a posmarketing requirement (PMR) of PREA Organogenesis Inc. replied to the FDA "Response to PREA Non-compliance, Deferral Extension Required" which provided the reason(s) for delayed pediatric assessment and date by which the company expect to submit the assessment	Biologics
BCG Live (Intravesical) (TheraCys®)	*Bacillus Calmette–Guérin* (BCG)	November 8, 2012 March 23, 2018	Sanofi Pasteur Limited, West Toronto, Ontario, Canada	FDA/CBER	Treatment of non-muscle invasive bladder cancer *Discontinued list (Not being Marketed)*	Biologics
Talimogene laherparepvec (IMLYGIC)	A replication-competent, attenuated derivative of herpes simplex virus type 1 (HSV-1)	October 27, 2015	Amgen, Inc., Thousand Oaks, CA, US	FDA/CBER	Indicated for local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. *(Genetically modified live oncolytic herpes virus therapy)*	Biologics

Voretigene neparvovec-rzyl (LUXTURNA)	A recombinant adeno-associated virus serotype 2 (AAV2) vector expressing the gene for human retinal pigment epithelium 65 kDa 5 protein (hRPE65)	December 19, 2017	Spark Therapeutics, Inc., Philadelphia, PA, US	FDA/CBER	An adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s). *(Gene therapy)*	Biolpgics
EU						
Alipogene tiparvovec (Glybera)	A replication-deficient adeno-associated viral vector designed to deliver and express the human LPL gene variant LPLS447X	October 25, 2012 October 28, 2017	uniQure biopharma B.V., Amsterdam, The Netherlands	EMA/CAT	Treat adults with lipoprotein lipase deficiency who have severe or multiple attacks of pancreatitis (inflammation of the pancreas) despite maintaining a low-fat diet. *(Gene therapy product)* *(Marketing Authorization under exceptional circumstances: 5 years)* *Expiry of the marketing authorization in the European Union*	ATMP
Talimogene laherparepvec (IMLYGIC)	A replication-competent, attenuated derivative of herpes simplex virus type 1 (HSV-1)	December 16, 2015	Amgen Europe B.V., Breda Netherlands	EMA/CAT	Treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease *(Genetically modified live oncolytic herpes virus therapy)*	ATMP
Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) (Zalmoxis)	Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	August 18, 2016	MolMed SpA, Milan Italy	EMA/CHAMP	Adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies *Allogeneic T cells genetically modified with a retroviral vector* *(Conditional market authorization)*	ATMP
Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue (Alofisel)	Expanded adipose stem cells	December 14, 2017 (Positive opinion)	Tigenix, S.A.U., Madird Spain	EMEA/CHMP	Treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy	ATMP
Japan						
Human (allogeneic) bone marrow-derived mesenchymal stem cells (Temcell Inj®)	Allogeneic bone marrow-derived mesenchymal stem cells	September 18, 2015	JCR Pharmaceuticals Co., Ltd.	MHLW-PMDA/OCTP	Acute graft versus host disease following hematopoietic stem cell transplantation	RMP

PMA, Premarket Approval Application; *CA*, California; *US*, the United States; *FDA*, Food and Drug Administration; *CDRH*, Center for Devices and Radiological Health; *MA*, Massachusetts; *HDE*, Humanitarian Device Exemption; *NY*, New York; *DMSO*, Dimethyl Sulfoxide; *BLA*, Biologics License Applications; *CBER*, Center for Biologics Evaluation and Research; *PREA*, Pediatric Research Equity Act; *OCTP*, Office of Cellular and Tissue-based Products; *RMP*, Regenerative Medicine Product.
[1]Advanced BioHealing was acquired by Shire pharmaceuticals in 2011.

Table 7 Approved unrelated allogeneic placental/umbilical cord blood products in the United States

Generic name (trade name)	*Cell origin*	*Approval date*	*Marketing authorization holder*	*Authority*	*Indications and usage*[a]	*Category*
HEMACORD, HPC, Cord Blood (HEMACORD™)	Cord blood	November 10, 2011 (BLA)	New York Blood Center, Inc., New York, NY, USA	FDA/ CBER	Use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. The risk benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the disease, on characteristics of the graft, and other available treatment or types of hematopoietic progenitor cells.	Biologics
HPC, Cord Blood (None)	Cord blood	May 24, 2012 (BLA)	Clinimmune Labs, University of Colorado Cord Blood Bank, Aurora, CO, USA	FDA/ CBER		Biologics
HPC, Cord Blood (Ducord)	Cord blood	October 4, 2012 (BLA)	Duke University School of Medicine, Translation Cell Therapy Center, Carolinas Cord Blood Bank	FDA/ CBER		Biologics
HPC, Cord Blood (ALLOCORD)	Cord blood	May 30, 2013 (BLA)	SSM Cardinal Glennon Children's Medical Center, St. Louis, MO, USA	FDA/ CBER		Biologics
HPC, Cord Blood BLA 125432 (None)	Cord blood	June 13, 2013 (BLA)	LifeSouth Community Blood Center, Inc., Gaineville, FL, USA	FDA/ CBER		Biologics
HPC, Cord Blood (None)	Cord blood	January 28, 2016 (BLA)	Bloodworks, Seattle, WA, USA	FDA/ CBER		Biologics
HPC, Cord Blood (CLEVECORD)	Cord blood	September 1, 2016 (BLA)	Cleveland Cord Blood Center, Warrensville Heights, OH, USA	FDA/ CBER		Biologics
Sterile Cord Blood Collection Unit with Anticoagulant Citrate Phosphate Dextrose Solution USP (CPD) (None)	Non	December 21, 2016 (NDA)	MacoProductions S.A.S. Duluth, GA, USA	FDA/ CBER	The bags are indicated for the collection of 40–250 mL of umbilical cord blood from either vaginal birth or within the sterile field of a cesarean section	Biologics

BLA, Biologics license application; *NY*, New York; *US*, the United States; *FDA*, Food and Drug Administration; *CBER*, Center for Biologics Evaluation and Research; *CO*, Colorado; *MO*, Missouri; *FL*, Florida; *WA*, Washington; *OH*, Ohio.
[a]Indications and usage are same as all seven HPCs, Cord Blood.

Table 8 Approved autologous human cells and tissue products in the US, EU, and Japan

Generic name (Trade name)	*Cell origin*	*Approval date*	*Marketing authorization holder*	*Authority*	*Indication*	*Category*
US						
Autologous cultured chondrocytes (Carticel™)	Autologous chondrocytes	August 22, 1997	Genzyme Tissue Repair, Cambridge, MA, US	FDA/CBER	Repair of clinically significant, systematic, cartilaginous defects of the femoral condyle caused by acute or repetitive trauma In 2000, the indication has been changed to narrow that "in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure"	Biologics
		September 26, 2017			*Discontinued list (Not being Marketed)*	
Cultured epidermal autografts (Epicel®)	Autologous epidermis	October 25, 2007	Genzyme Biosurgery, Cambridge, MA, US	FDA/CDRH	Use in patients who have deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%	Medical device
		February 18, 2016	Vericel Corporation Cambridge, MA, US		Humanitarian Device Exemption (HDE) Supplement: Use in adult and pediatric patients who have deep dermal or full thickness burns comprising a total body surface area greater than or equal to 30%	
Sipuleucel-T (Provenge®)	Autologous peripheral blood mononuclear cells	April 29, 2010	Dendreon Co., Seattle, WA, US	FDA/CBER	Treatment of asymptomatic or minimally symptomatic metastatic hormone refractory prostate cancer	Biologics
Azficel-T (Laviv®)	Autologous fibroblasts	June 21, 2011	Fibrocell Science Inc., Boulder, CO, US	FDA/CBER	Improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults	Biologics
Autologous Cultured Chondrocytes on a Porcine Collagen Membrane (MACI)	Autologous Cultured Chondrocytes	December 13, 2016	Vericel Corporation, Cambridge, MA, US	FDA/CBER	Indicated for the repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults. MACI is an autologous cellularized scaffold product	Biologics
Tisagenlecleucel (KYMRIAH)	CD19-directed genetically modified autologous T cell	August 30, 2017	Novartis Pharmaceuticals Corporation, East Hanover, NJ, US	FDA/CBER	Indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. *(Cell-based gene therapy)*	Biologics
		May 1, 2018			Indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma	
Axicabtagene ciloleucel (YESCARTA)	CD19-directed genetically modified autologous T cell	October 18, 2017	Kite Pharma, Incorporated, Santa Monica, CA, US	FDA/CBER	A CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. *(Cell-based gene therapy)*	Biologics

(*Continued*)

Table 8 (Continued)

Generic name (Trade name)	*Cell origin*	*Approval date*	*Marketing authorization holder*	*Authority*	*Indication*	*Category*
EU						
Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins (ChondroCelect®)	Autologous chondrocytes	October 5, 2009	Tigenix NV, Leuven, Belgium	EMEA/CHMP	Repair of single symptomatic cartilaginous defects of the femoral condyle of the knee (ICRS grade III or IV) in adults	ATMP (Drug)
		November 30, 2016			*Withdrawal of the marketing authorization in the European Union*	
Matrix-applied haracterized autologous cultured chondrocytes (MACI)	Autologous chondrocytes	June 27, 2013	Genzyme Biosurgery ApS, Kastrup, Denmark	EMEA/CHMP	Repair of symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale) of 3-20 cm^2 in skeletally mature adult patients	ATMP (Drug)
		September 5, 2014			*Unavailable in the EU once the European manufacturing site has close*	
Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (Sipuleucel-T) (Provenge)	Autologous peripheral blood mononuclear cells	September 6, 2013	Dendreon UK Ltd., London, UK	EMEA/CHMP	Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated	ATMP (Drug)
		May 6, 2015			*Withdrawal of the marketing authorization in the European Union*	
Ex vivo expanded autologous human corneal epithelial cells containing stem cells (Holoclar)	Autologous human corneal epithelial cells	February 17, 2015	Chiesi Farmaceutici S.p. A., Parma Italy	EMEA/CHMP	Treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1–2 mm^2 of undamaged limbus is required for biopsy *(Conditional approval)*	ATMP (Drug)
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence from human haematopoietic stem/progenitor (CD34+) cells (Strimvelis)	Autologous CD34+ enriched cell	May 26, 2016	GlaxoSmithKline Trading Services Limited, County Cork Ireland	EMEA/CHMP	Treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available *(New gene therapy)*	ATMP (Drug)

Spheroids of human autologous matrix-associated chondrocytes (Spherox)	Autologous matrix-associated chondrocytes	July 10, 2017	CO.DON AG, Teltow, Germany	EMEA/CHMP	Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Repair Society [ICRS] grade III or IV) with defect sizes up to 10 cm2 in adults	ATMP (Drug)
Japan						
Other surgical/ orthopedic materials; autologous cultured epidermis (JACE)	Autologous epidermis	October 29, 2007	Japan Tissue Engineering Co., Ltd., Gamagori, Japan	MHLW-PMDA/OB	*Severe burns:* Use in patients with serious, extensive burns when sufficient donor sites for autologous skin graft are not available and the total area of deep dermal and full-thickness burns is 30% or the total of surface area	Medical device
		August 6, 2014			Changed the category of Regenerative Medicine Product	RMP
		September 29, 2016		MHLW-PMDA/ OCTP	*Giant Congenital Melanocytic Nevus:* Use in patient after excised Giant Congenital Melanocytic Nevus for wound closure	
Human autologous cells and tissues (JACC)	Autologous chondrocytes	July 27, 2012	Japan Tissue Engineering Co., Ltd., Gamagori, Japan	MHLW-PMDA/OB	An autologous cultured cartilage to alleviate clinical symptoms by implanting it in the affected site of traumatic cartilage deficiency and osteochondritis dissecans (excluding knee osteoarthritis) in the knee joints with a cartilage defective area of 4 cm^2 or more for which there are no other options	Medical device
		August 6, 2014			Changed the category of Regenerative Medicine Product	RMP
Human autologous skeletal myoblast-derived cell sheet (HeartSheet)	Autologous skeletal myoblast-derived cell	September 18, 2015	Terumo Corporation, Tokyo, Japan	MHLW-PMDA/ OCTP	Treatment of patients with severe heart failure due to ischemic heart disease unresponsive to standard treatments including drug and invasive therapies who meet all the following criteria. Eligibility criteria: ● NYHA class III or IV heart failure; ● Resting left ventricular ejection fraction $\leq$35%	RMP

US, the United States; *EU,* the European Union; *MA*, Massachusetts; *FDA*, Food and Drug Administration; *CBER*, Center for Biologics Evaluation and Research; *CDRH*, Center for Devices and Radiological Health; *MHLW*, Ministry of Health, Labour and Welfare; *PMDA*, Pharmaceuticals Medical Device Administration; *OB*, Office of Biologics; *EMEA*, European Medicines Agency; *CHMP*, Committee for Human Medicinal Products; *AMTP*, Advanced Therapy Medicinal Products; *WA*, Washington; *CO*, Colorado; *UK*: United Kingdom; *OCTP*: Office of Cellular and Tissue-based Products; *RMP*: Regenerative Medicine Product.

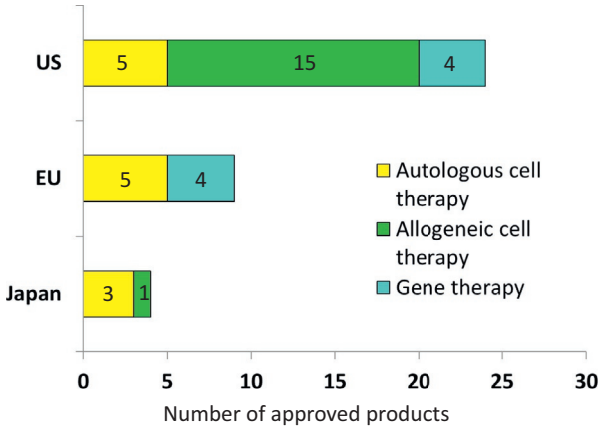

Fig. 4 Number of approved human cell-based products in the United States, the European Union, and Japan. As of December 2017, 24 human cell-based products and gene therapy products which are 5 autologous human cell-based products, 15 allogeneic human cell-based products, and 4 gene therapy products as well as cell-based gene therapies were approved in the United States. In the European Union, nine human cell-based products and gene therapy products which are five autologous human cell-based products, and four gene therapy products were approved. No allogeneic human cell-based product was approved, however, an allogeneic human cell-based product was granted a positive opinion from CHMP on December 14, 2017. In Japan, four human cell-based products which are three autologous human cell-based products, and an allogeneic human cell-based product were approved.

A product which is not a HPC but is a sterile cord blood collection unit, described as a "Sterile Cord Blood Collection Unit with Anticoagulant Citrate Phosphate Dextrose Solution USP (CPD), (No-Trade name)" was approved as a product related to HPCs in 2016 (Table 7).

Cell-based products as regenerative medicine products

In Japan, Temcell Inj was approved for the indication of acute graft versus host disease following hematopoietic stem cell transplantation in 2015 (Table 6) after it was categorized as a Regenerative Medicine Product under the PMDA Act.

Advanced therapy medicine products

In the EU, no ATMP has been approved as of 2017 as an allogeneic human cell-based product. However, Alofisel was granted a positive opinion from CHMP for the treatment of complex perianal fistulas in adult patients with nonactive/mildly active luminal Crohn's disease, on December 14, 2017 (Tables 6).

Approved Autologous Human-Cell Based Products

Biologics and medical devices

In the United States, Carticel was approved for repair of cartilaginous defect of the femoral condyle in 1997 but placed on the discontinued list on September 26, 2017 (Table 8). Epicel was approved in 2007 for use in adult patients who have deep dermal or full thickness burns under a Humanitarian Device Exemption, and was also approved for use in pediatric patients (Table 8). Provenge was approved for the treatment of hormone refractory prostate cancer in 2010 (Table 8). Laviv was approved for improvement of the appearance of wrinkles in adults in 2011 (Table 8). MACI was approved for cartilage defects of knee in 2016 (Table 8).

Advanced therapy medicine products

In the EU, ChondroCelect was approved for the repair of cartilaginous defects of the femoral condyle of the knee in 2009, and was withdrawn from the market for commercial reasons in 2016 (Table 8). MACI was approved for the repair of cartilaginous defects of the knee in 2013, but the marketing authorization holder closed the EU manufacturing site for the medicine for commercial reasons in 2014 (Table 8). Provenge was approved for treatment of castrate resistant prostate cancer in 2013 but the market authorization was abandoned for commercial reasons in 2015 (Table 8). After being granted orphan designation in 2008, Holoclar was approved for treatment of adult patients with limbal stem cell deficiency under a conditional approval in 2015 (Table 8). Spherox was approved for repair of articular cartilage defects of the femoral condyle and the patella of the knee in 2017 (Table 8).

Medical devices and regenerative medicine products

In Japan, JACE was approved as medical device for use in patients with serious, extensive burns in 2007 and recategorized as a regenerative medicine product in 2014. The product was also approved for use in patients whose giant congenital melanocytic nevus has been treated by excision in 2016 (Table 8). JACC was approved as a medical device to repair cartilage deficiency and osteochondritis dissecans in the knee in 2012, and reclassified as a regenerative medicine product in 2014 (Table 8).

Appendix 1 Classification of advanced therapy medicines products in the EU

Year	Name of recommendations	Note
Scientific Recommendation on Classification of Advanced Therapy Medicinal Products (Allogenic Cell Therapy)		
2009	- Substantially modified human allogeneic fibroblasts and keratinocytes administered in conjunction with fibrin as structural component (June 2009)	- Dermatology: intended for treatment of chronic venous leg ulcers; Somatic cell therapy medicinal product
	- Advanced therapy medicinal product containing substantially modified cytotoxic T-cells of human origin (August 2009)	- Oncology: intended for treatment of ovarian cancer; Somatic cell therapy medicinal product
	- Haploidentical donor T lymphocytes genetically modified to express HSV-Tk gene (October 2009)	- Oncology: intended as adjunctive treatment post bone marrow transplantation in patients with high risk acute leukemia; Somatic cell therapy medicinal product
	- A combination of lysates of tumor cells (autologous and allogenic) and living cells of a glioblastoma cell line (October 2009)	- Oncology: intended for treatment of glioblastoma; Somatic cell therapy medicinal product
2010	- Allogeneic cultured corneal epithelial cell sheet in amniotic membrane scaffold (January 2010)	- Intended for the treatment of ocular diseases; Tissue engineered product
	- Allogeneic natural killer cells activated with a lysate from a cell line which is established from a patient with acute monoblastic leukemia (January 2010)	- Intended for treatment of acute myeloid leukemia; Somatic cell therapy medicinal product
	- Allogeneic human dermal fibroblasts (March 2010)	- Intended for treatment of dystrophic epidermolysis bullosa; Tissue engineered product
	- Allogeneic T cells encoding an exogenous TK gene (March 2010)	- Intended as adjunct treatment in hematopoietic stem cell transplantation; Somatic cell therapy medicinal product
	- Hollow fiber cartridges populated with the C3A cells to be used with ancillar y support equipment (July 2010)	- Intended for treatment of acute or chronic hepatitis; Somatic cell therapy medicinal product - combined
	- Frozen, cultured allogeneic keratinocytes on a silicone dressing material (August 2010)	- Intended the treatment of acute burn wounds; Tissue engineered product - not combine
	Umbilical cord blood cells expanded ex vivo using allogeneic mesenchymal precursor cells (August 2010)	- Intended treatment of diseases in hematology-oncology therapeutic area; Tissue engineered product
	- Allogeneic mesenchymal precursor cells (August 2010)	- Intended for treatment of cardiovascular disease; Tissue engineered product
	- Allogeneic human placenta-derived, culture-expanded, mesenchymal-like cell population (October 2010)	- Intended for treatment of chronic inflammatory diseases such as Crohn's disease, multiple sclerosis, rheumatoid arthritis and the treatment of ischemic stroke; Somatic cell therapy product
	- Allogeneic human aortic endothelial cells cultured in a porcine gelatin matrix (October 2010)	- Intended for treatment of vascular injury; Somatic cell therapy medicinal product - not combined
2011	- Allogeneic human fibroblasts cultured onto a biodegradable matrix (April 2011)	- Dermatology; Tissue engineered product - combined
	- Heterologous human adult liver-derived progenitor cells (May 2011)	- Intended for treatment of inborn errors of liver metabolism; Somatic cell therapy medicinal product - not combined
	- Allogeneic bone-marrow derived osteoblastic cells (July 2011)	- Intended for treatment of nonunion, delayed union or other bone fractures; Tissue-engineered product - not combine
	- Mixture of porcine beta cell and their accompanying endocrine cell populations embedded in an alginate matrix (July 2011)	- Endocrinology: intended for treatment of diabetes; Somatic cell therapy medicinal product - not combined
2012	- Allogeneic human dermal fibroblasts (May 2012)	- Intended for treatment of dermal scars, hypertrophic scars and contractures; Tissue-engineered product
	- Allogenic and autologous haptenized and irradiated cells and corresponding cell lysates derived from the tumor mass of patients diagnosed with Glioblastoma multiforme (May 2012)	- Intended for treatment of glioblastoma multiforme; Somatic cell therapy medicinal product
2013	- Allogeneic Mesenchymal Precursor Cells (MPCs) (January 2013)	- Intended for treatment of rheumatoid arthritis; Somatic cell therapy medicinal product
	- Alginate encapsulated porcine pancreatic islet cells (February 2013)	- Intended for treatment of type 1 diabetes mellitus; Somatic cell therapy medicinal product - combined
	- EBV-specific T cells in suspension in human albumin (March 2013)	- Intended for the treatment of prophylactic or curative adoptive immunotherapy of EBV-associated malignant diseases (Somatic cell-therapy medicinal product)
	- Naturally-occurring allogeneic donor lymphocytes (derived from a leukapheresis, bone marrow or a whole blood product) that are enriched for antigen-specific CD4+ and CD8+ T cells using the Cytokine Capture system (IFN-gamma) (April 2013)	- Intended for treatment of therapy-refractory infectious and infection-related diseases and pre-emptive and prophylactic treatment of infectious and infection-related diseases; Somatic cell therapy medicinal product
	- Allogeneic bone marrow derived mesenchymal cells (MSCs) expanded ex vivo in synthetic media (April 2013)	- Intended for treatment of patients with acute graft-versus-host disease grades III and IV resistant to first line treatment; Somatic cell therapy medicinal product
	- Human dermal fibroblasts cultured on bioresorbable polyglactin mesh (July 2013)	- Intended for treatment of wounds and ulcers; Tissue engineered product

(*Continued*)

Appendix 1 (Continued)

Year	*Name of recommendations*	*Note*
2014	- Retinal pigment epithelium cells derived from human induced pluripotent stem cells (January 2014)	- Intended for treatment of retinal degenerative diseases associated with dystrophic or dysfunctional retinal pigment epithelium cells; Tissue-engineered product
	- Allogeneic activated leukocytes (January 2014)	- Intended for treatment of chronic lower extremity ulcers in adult diabetic patients; Somatic cell-therapy medicinal product
	- Allogeneic peripheral blood mononuclear cells induced to an early apoptotic state (July 2014)	- Intended for the treatment of glioblastoma; Somatic cell therapy medicinal product
	- Human retinal pigment epithelial cells derived from human embryotic stem cell (October 2014)	- Intended for the treatment of age-related macular degeneration and Stargardt's macular dystrophy; Tissue-engineered product
	- Allogeneic, human Wharton's jelly derived mesenchymal stem cells (November 2014)	- Intended for the treatment of cerebral palsy; Tissue engineered product
	- Allogeneic, human Wharton's jelly derived mesenchymal stem cells (November 2014)	- Intended for the treatment of cartilage lesions; Tissue engineered product
	- Allogeneic, human Wharton's jelly derived mesenchymal stem cells (November 2014)	- Intended for the treatment acute and chronic Graft-versus-Host Disease; Somatic cell therapy medicinal product
	- Allogeneic, human Wharton's jelly derived mesenchymal stem cells (November 2014)	- Intended for the treatment of Amyotrophic lateral sclerosis (ALS); Somatic cell therapy medicinal product
	- Allogeneic cord blood cells, ex vivo modulated with 16,16 dimethyl prostaglandin E2 (November 2014)	- Intended for the treatment of patients undergoing an hematopoietic stem cell transplantation; Tissue-engineered product
2015	- Adult stem cell population, prepared from human skeletal muscle (March 2015)	- Treatment of Duchenne Muscular Dystrophy (DMD); Tissue engineered product
	- Allogeneic ex-vivo expanded placental mesenchymal-like adherent stromal cells (April 2015)	- Treatment of Peripheral Arterial Occlusive Disease (PAOD); Tissue-engineered product
	- Irradiated plasmacytoid dendritic cell line loaded with peptides from tumor antigens (May 2015)	- Treatment of metastatic cancer; Somatic cell therapy medicinal product
	- Allogeneic (human Wharton's jelly derived) mesenchymal stem cells (October 2015)	- Intended for the treatment of amyotrophic lateral sclerosis (ALS); Somatic cell therapy product
	- Viable hepatocyte-like human embryonic stem cell-derived cells (October 2015)	- Intended for the treatment of inborn liver metabolic diseases like Crigler-Naijar syndrome 1 and for drug-induced acute liver failure such as paracetamol intoxication; Tissue-engineered product
	- Allogeneic mesenchymal precursor cells (October 2015)	- Intended for the treatment of chronic lumbar back pain; Tissue engineered product
	- Adipose derived regenerative cells encapsulated in hyaluronic acid (November 2015)	- Treatment of articular cartilage and bone defects including osteoarthrosis or osteochondral lesions; Tissue-engineered medicinal product - combined
2016	- Human amniotic membrane mesenchymal stem cells as a sheet (January 2016)	- Intended for the treatment of burns, scars, nonhealing wounds; Tissue-engineered product
	- Human amniotic membrane mesenchymal stem cells in suspension (January 2016)	- Intended for the treatment of burns, scars, nonhealing wounds; Tissue-engineered product
	- Human amniotic membrane mesenchymal stem cells seeded on acellular amniotic matrix (January 2016)	- Intended for the treatment of burns, scars, nonhealing wounds; Tissue-engineered product
	- Human amniotic membrane mesenchymal stem cells seeded on acellular dermal matrix (January 2016)	- Intended for the treatment of burns, scars, nonhealing wounds; Tissue-engineered product
	- Co-culture of keratinocytes and hAMMSCs as seeded on acellular dermal matrix (January 2016)	- Intended for the treatment of burns, scars, nonhealing wounds; Tissue-engineered product
	- Allogeneic human keratinocytes and human umbilical cord mesenchymal stem cells (January 2016)	- Intended for the treatment of burns and nonhealing wounds; Tissue-engineered product
	- Allogeneic human keratinocytes and human umbilical cord mesenchymal stem cells (January 2016)	- Intended for the treatment of burns and nonhealing wounds; Tissue-engineered product
	- Mesenchymal stem cells isolated from umbilical cord seeded onto acellular dermal matrix (January 2016)	- Intended for the treatment of burns, nonhealing wounds; Tissue-engineered product
	- Mesenchymal stem cells isolated from umbilical cord seeded acellular amniotic matrix (January 2016)	- Intended for the treatment of burns, nonhealing wounds; Tissue-engineered product
	- Mesenchymal stem cells isolated from umbilical cord (January 2016)	- Intended for the treatment of burns, nonhealing wounds; Tissue-engineered product
	- Human amniotic membrane mesenchymal stem cells (hAMMSCs), allogeneic or autologous keratinocytes, co-cultured (January 2016)	- Intended for the treatment of burns, scars, nonhealing wounds; Tissue-engineered product
	- Human adult allogenic mesodermal progenitor cells (January 2016)	- Intended for the treatment of incomplete revascularisation as an adjunct to CABG in patients with congenital coronary artery malformations; Tissue-engineered product
	- Allogeneic Epstein-Barr Virus Cytotoxic T Lymphocyte (May 2016)	- Intended for the treatment of Epstein-Barr Virus-associated Post Transplant Lymphoproliferative Disorder; Somatic cell therapy medicinal product

Appendix 1 (Continued)

Year	*Name of recommendations*	*Note*
	- Heterologous human adult liver-derived progenitor cells (July 2016)	- Intended for the treatment of fibro-inflammatory liver diseases; Tissue-engineered product
	- *Ex-vivo* cultured and expanded human cord blood progenitor cells (July 2016)	- Intended for the treatment of patients undergoing hematopoietic stem cell transplantation; Tissue-engineered product
	- Wharton jelly derived allogeneic mesenchymal stem cells, cultured in vitro (October 2016)	- Intended for the treatment of acute myocardial infarction, chronic ischemic heart failure, no-option critical limb ischemia; Tissue engineered product
	- Allogeneic bone marrow derived mesenchymal stem cells (November 2016)	- Intended for the treatment of acute myocardial infarction, chronic ischemic heart failure, no-option critical limb ischemia; Tissue engineered product
	- Bone Marrow derived lineage negative heterogenic stem and progenitor cells (December 2016)	- Intended for the treatment of the acute Graft versus Host Disease grades III and IV resistant to the first line of treatment; Somatic cell therapy medicinal product
2017	- Allogeneic cytomegalovirus-specific cytotoxic T lymphocytes (January 2017)	- Intended for the treatment of Cytomegalovirus-associated viraemia or disease after allogeneic hematopoietic cell transplant or solid organ transplant after failure of at least two different antiviral therapies; Somatic cell therapy medicinal product
	- Allogeneic bone marrow derived mesenchymal stem cells (January 2017)	- Intended for the treatment of the acute Graft versus Host Disease grades III and IV and extensive chronic GvHD resistant to the first line of treatment; Somatic cell therapy medicinal product
	- Banked allogenic leukocytes (March 2017)	- Intended for the treatment of metastatic Pancreatic Ductal Adeno Carcinoma; Somatic cell therapy medicinal product
	- Allogeneic human mesenchymal stem cells derived from umbilical cord (March 2017)	- Intended for the treatment of intervertebral disc degeneration; Tissue engineered medicinal product
	- Allogeneic haptenized, stimulated and irradiated nonproliferative colorectal tumor whole cells derived from 3 colorectal cell lines (May 2017)	- Intended for the treatment of colorectal cancer; Somatic cell therapy medicinal product
	- Human cultured dermal fibroblasts and human epidermal keratinocytes embedded in/on collagen hydrogel (June 2017)	- Intended for the treatment of partial deep dermal and full thickness burn wounds; Tissue engineered product
	- Allogeneic suspension of unexpanded and uncultured human amniotic fluid-derived cells (June 2017)	- Intended for the treatment of chronic, nonhealing wounds; Tissue engineered product
	- Cultured allogenic Wharton's jelly derived mesenchymal stem cells (June 2017)	- Intended for the treatment of myotrophic lateral sclerosis
	- Allogeneic human mesenchymal stem cells derived from Wharton's jelly tissue of umbilical cord (June 2017)	- Intended for the treatment of Chronic obstructive pulmonary disease (COPD); Tissue engineered product
	- Human umbilical cord blood-derived mesenchymal stem cells (June 2017)	- Intended for treatment of atopic dermatitis; Somatic cell therapy medicinal product
	- Viable chondrocytes cultured within a 3D hydrogel (September 2017)	- Intended for the treatment of articular cartilage defects of the knee; Tissue engineered product (combined)
	- Allogeneic human glial-restricted precursors (September 2017)	- Intended for the treatment of amyotrophic lateral sclerosis; Tissue engineered medicinal product
	- Allogeneic human glial-restricted precursors (September 2017)	- Intended for the treatment of spinal cord injuries (four-limb paralysis, paresis); Tissue engineered medicinal product
	- Cultured dental pulp stem cells (October 2017)	- Intended for regeneration of soft and hard tissues of temporomandibular joints; Tissue engineered product
	- Full-thickness human skin substitute composed of an epidermal layer of fully-stratified human keratinocytes and a collagen-rich dermal equivalent containing human dermal fibroblasts (October 2017)	- Treatment of patients with acute complex skin loss; Tissue engineered product
	- Allogenic adipose-derived stem cells (ADSC) differentiated in vitro towards the cardiovascular lineage (October 2017)	- Intended to restore cardiac function post myocardic infarction; Tissue engineered product (combined)
Scientific Recommendation on Classification of Advanced Therapy Medicinal Products (Autologous Cell Therapy)		
2009	- Immunotherapeutic medicinal product composed of autologous tumor cells (August 2009)	Oncology: intended for treatment of colon cancer; Somatic cell therapy medicinal product
	- Suspension of expanded autologous skeletal muscle derived cells (myoblasts) (October 2009)	- Urology/gynecology: intended for regeneration of the external urethral sphincter muscle (rhabdosphincter) in patients suffering from various levels of stress urinary incontinence; Tissue engineered product - not combined
	- Autologous tolerogenic dendritic cells derived from peripheral blood monocytes (October 2009)	- Intended for treatment of rheumatoid arthritis; Somatic cell therapy medicinal product. Not combined
2010	- Autologous cell therapy product (January 2010)	- Intended for treatment of Crohn's disease; Somatic cell therapy medicinal product
	- Autologous cultured chondrocytes integrated in a scaffold (January 2010)	- Intended for repair of symptomatic cartilage defects in joints such as the knee and ankle; Tissue engineered medicinal product - combined

(*Continued*)

Appendix 1 (Continued)

Year	*Name of recommendations*	*Note*
	- Buffy coat of centrifuged autologous bone marrow containing hematopoietic and mesenchymal stem cells (January 2010)	- Intended for treatment of incomplete and complete chronic traumatic spinal cord injury; Advanced therapy medicinal product
	- Autologous osteoprogenitor cells, isolated from bone marrow and expanded in vitro, incorporated, as an integral part, with 3D biodegradable scaffold (January 2010)	- Intended for repairing and regenerating and replacing bone defects in odontostomatology and maxillofacial surgery; Tissue engineered product - combined
	- Autologous *ex-vivo* pulsed dendritic cell (July 2010)	- Intended for treatment of ovarian cancer; Somatic cell therapy medicinal product
	- Autologous human keratinocytes (August 2010)	- Intended for treatment of superficial, partial and full thickness burns; Tissue engineered product - not combined
	- Autologous bone marrow-derived progenitor cells (October 2010)	- Intended for treatment of patients with failed left ventricular recovery despite successful reperfusion therapy postacute myocardial infarction, chronic ischemic heart disease, peripheral vascular diseases and Buerger's disease; Tissue engineered product
	- Adult skeletal muscle derived cells	- Intended for treatment of female stress urinary incontinence; Tissue engineered product - not combined
	- Layer of autologous corneal epithelium containing stem cells (December 2010)	- Intended for treatment of extended corneal lesions; Tissue engineered product - not combined
2011	- Autologous mesenchymal stem cells (MSC)(July 2011)	- Intended for treatment of chronic heart failure symptoms by improvement in exercise capacity of NYHA class II and III chronic heart failure patients receiving standard therapy; Tissue-engineered product - not combined
	- Autologous dendritic cell immunotherapy consisting of autologous mature DCs co-electroporated with autologous RCC IVT RNA and synthetic CD40L IVT RNA (October 2011)	- Intended for the treatment of advanced renal cell carcinoma; Somatic cell therapy medical product
	- Concentrate of autologous bone marrow-derived mononuclear cells (BM-MNC) (October 2011)	- Intended for improvement of heart function (LVEF) and quality of life in patients with ischemic postacute MI and in chronic heart disease; Tissue-engineered product
	- Autologous bone marrow-derived CD133+ stem cells (November 2011)	- Intended for improvement of heart function (LVEF) and quality of life in patients with ischemic heart disease postacute MI and in chronic iscaemic heart disease and after MI; Tissue-engineered product
	- Autologous CD4+ T cells targeted to cells presenting class II restricted epitopes (November 2011)	- Intended for autoimmune diseases with MHC restricted specific immunity e.g. multiple sclerosis, type I diabetes or graft rejection; Somatic cell therapy medicinal product
2012	- A mixture of autologous dendritic cells (DCs) pulsed with a Nonstructural 3 (NS3) protein fragment of Hepatitis C Virus (HCV) and activated T-cells (February 2012)	- Intended for treatment of patients with chronic HCV infection; Somatic cell therapy medicinal product
	- Bone marrow-derived autologous CD34+ cells (March 2012)	- Intended for improvement of heart function in patients with refractory angina and chronic myocardial ischemia; Tissue-engineered product
	- Autologous oral mucosa cells seeded onto a membrane (March 2012)	- Intended for treatment of urethral stricture; Tissue engineered product - combined
	- Bone marrow derived autologous suspensions of hematopoietic and mesenchymal stem cells depleted from erythrocytes and lymphocytes (July 2012)	- Intended for treatment of complete or incomplete traumatic spinal cord injury; Tissue-engineered product
	- Autologous skeletal muscle-derived-cells (November 2012)	- Intended for repair of deficient external anal sphincter in patients suffering from faecal incontinence; Tissue-engineered product
	- Autologous Mesenchymal Stromal Cells secreting NeuroTrophic Factors (December 2012)	- Intended for treatment of amyothropic lateral sclerosis; Somatic cell therapy medicinal product
	- Concentrate of autologous bone marrow (December 2012)	- Intended for increase new bone formation in critical area of atrophic nonunion; Tissue engineered medicinal product, combined ATMP
	- Tissue like combination of osteogenic cells and demineralized bone matrix (Three-dimensional structure of demineralized bone matrix and autologous adipose-derived and differentiated osteogenic cells) (December 2012)	- Intended for treatment of bone defects; Tissue engineered medicinal product
2013	- Human autologous tumor-infiltrating lymphocytes (TIL) (April 2013)	- Intended for regeneration, repair, or replacement of weakened or injured subcutaneous tissue
	- Autologous expanded CD34+ stem cells (May 2013)	- Intended for treatment of stage III melanoma with one invaded lymph node; Somatic cell therapy medicinal product
	- Adipose derived mesenchymal stem cells combined with beta-tricalcium phosphate (June 2013)	- Intended for treatment of accute myocardial infarction (AMI) via regeneration of damaged tissue; Tissue-engineered product
	- Autologous dendritic cells activated with autologous oncolysate (July 2013)	- Intended for treatment of bone defects; Tissue-engineered medicinal product – combined
	- Mesenchymal stem cells extraction from Bone (Ilium) marrow, cultured and pretreated by melatonin (July 2013)	- Intended for treatment of glioma; Somatic cell therapy medicinal product

Appendix 1 (Continued)

Year	*Name of recommendations*	*Note*
	- Cultured mesenchymal stem cells suspension extracted from bone (Ilium) marrow (July 2013)	- Intended for treatment of chronic myocardial ischemia with left ventricular dysfunction; Tissue-engineered medicinal product
	- Ex-vivo expanded autologous human corneal epithelium containing stem cells (December 2013)	- Intended for treatment of limbal stem cell deficiency; Tissue-engineered product
2014	- Ex vivo expanded autologous skeletal myoblasts (January 2014)	- Intended for treatment of oculopharyngeal muscular dystrophy; Tissue-engineered product
	- Viable, autologous keratinocytes and melanocytes grown on AS210 matrix. The active component of tissue engineered dermis consists of viable, autologous fibroblasts (January 2014)	- Intended for wound healing; Tissue-engineered product
	- Autologous Lymphoid Effector Cells Specific against Tumor-cell (February 2014)	- Intended for treatment of solid tumors; Somatic cell-therapy medicinal product
	- Viable autologous adipose tissue-derived mesenchymal stem cells (May 2016)	- Intended for the treatment of degenerative arthritis, osteoarthritis (OA), articular cartilage defects in the knee, ankle or hip joints; Tissue engineered product
	- Autologous antigen-specific regulatory T lymphocytes suspended in a cryopreservation medium (May 2014)	- Intended for the treatment of inflammatory eyes diseases and inflammatory articular diseases; Somatic cell therapy medicinal product
	- Tracheal scaffold seeded with autologous bone marrow derived mononuclear cells (May 2014)	- Intended for reconstruction of trachea subsequent to damage or stenosis due to cancer, injury or infection; Tissue-engineered product - combined
	- Autologous bone marrow cell aspirate in autologous plasma (May 2014)	- Intended for treatment of osteoarthrosis and osteochondral lesion; Tissue-engineered product
	- Autologous bone marrow aspirate enriched in autologous mesenchymal stromal cells (June 2014)	- Intended for treatment in the field of regenerative medicine: bone damaged by disease (e.g. osteonecrosis), fracture or age-related loss of bone function; Tissue-engineered product
	- Autologous mature dendritic cells pulsed with tumor antigen-derived synthetic peptides (July 2014)	- Intended for the treatment of glioblastoma; Somatic cell therapy medicinal product
	- Autologous differentiated adipocytes derived from the subcutaneous adipose tissue (November 2014)	- Intended for the treatment of primary perianal fistula; Tissue-engineered product
	- Cultured autologous chondrocytes in fibrin based excipient of human origin (December 2014)	- Intended for the treatment of focal nonarthritic cartilage defects of Outerbridge Classification Grade III or IV of the femoral condyle including the trochlea; Tissue-engineered product
2015	- Ex vivo expanded adipose-derived stem cell suspension (January 2015)	- Autoimmune diseases (rheumatoid arthritis and systemic lupus erythematosus); Somatic cell therapy medicinal product
	- Living, autologous, melanoma-derived lymphocytes (CD3+) (January 2015)	- Therapeutic treatment of metastatic melanoma in patients pre-conditioned with chemotherapy and undergoing concomitant interleukin-2 (IL-2) treatment; Somatic cell therapy medicinal product
	- Ex vivo expanded human umbilical tissue-derived cells (February 2015)	- Thromboangiitis obliterans (Buerger's disease); Somatic cell therapy medicinal product
	- Autologous dendritic cells loaded with autologous irradiated tumor stem cells (April 2015)	- Treatment of melanoma; Somatic cell therapy medicinal product
	- Ex vivo expanded human umbilical tissue-derived cells (April 2015)	- Improvement of visual acuity in patients with vision loss from geographic atrophy secondary to age-related macular degeneration; Somatic cell therapy medicinal product
	- Autologous mononuclear cells derived from human cord blood (April 2015)	- Pediatric brain damage, hypoxic-ischemic encephalopathy, and cerebral palsy; Tissue-engineered product
	- Autologous expanded viable chondrocytes combined with three dimensional structure (biphasic collagen scaffold) (May 2015)	- Articular cartilage defect of the knee; Tissue-engineered product(combined ATMP)
	- Autologous human gamma-delta T lymphocytes (July 2015)	- Chronic Lymphocytic Leukemia, Acute Lymphoblastic Leukemia; Somatic cell therapy medicinal product
	- Peripheral blood monocytes-derived suppressive cells (July 2015)	- Treatment of acute Graft-versus-Host Disease refractory to first-line treatment; Somatic cell therapy medicinal product
	- Autologous bone marrow mononuclear cells (BM-MNC) (July 2015)	- To improve limb perfusion/restore blood flow to previously ischemic tissue, and improve the mobility and quality of life (QoL) of patients with peripheral artery disease and critical limb ischemia; Tissue-engineered product
	- Autologous bone marrow derived mesenchymal stem cells (October 2015)	- Intended for the treatment of amyotrophic lateral sclerosis (ALS); Somatic cell therapy product
	- Autologous adipose tissue derived mesenchymal stem cells (October 2015)	- Intended for the treatment of amyotrophic lateral sclerosis (ALS); Somatic cell therapy product
	- Autologous expanded mesenchymal cells seeded onto an allogeneic human decellularized trachea scaffold (October 2015)	- Intended for the reconstruction of trachea subsequent to damage or stenosis due to cancer, injury, infection or congenital deformities; Tissue-engineered product
	- Autologous expanded viable chondrocytes embedded in a cross linked hydrogel (October 2015)	- Intended for the treatment of articular cartilage defect; Tissue-engineered product(combined)

(*Continued*)

Appendix 1 (Continued)

Year	*Name of recommendations*	*Note*
	- Autologous cells of stromal vascular fraction of adipose tissue (November2015)	- Intended for the treatment of nonhealing wounds and scarred tissue; Tissue-engineered product
	- Autologous cells of stromal vascular fraction of adipose tissue (November 2015)	- Intended for the treatment of pain associated with joint osteoarthritis; Somatic cell therapy medicinal product
	- Pro-inflammatory dendritic cells (November 2015)	- Intended for the treatment of metastatic renal cell carcinoma; Somatic cell therapy medicinal product
	- Bone marrow-derived autologous nonhematopoietic stem cells (December 2015)	- Intended for the treatment of type I diabetes; Somatic cell therapy medicinal product
	- Bone marrow-derived autologous nonhematopoietic stem cells (December 2015)	- Intended for the treatment of type II diabetes; Somatic cell therapy medicinal product
	- Bone marrow-derived autologous nonhematopoietic stem cells (December 2015)	- Intended for the treatment of patients after myocardial infarction; Tissue-engineered product
	- Bone marrow-derived autologous nonhematopoietic stem cells (December 2015)	- Intended for the treatment of patients after ischemic stroke; Tissue-engineered product
	- Bone marrow-derived autologous nonhematopoietic stem cells (December 2015)	- Intended for the treatment of rheumatoid arthritis; Somatic cell therapy medicinal product
	- Human hepatoblastoma cells (HepG2) encapsulated in alginate, expanded to competence and maintained in a fluidized bed bioreactor (December 2016)	- Intended for the treatment of acute liver failure; Somatic cell therapy medicinal product - combined
2016	- Cultured epithelial autografts (CEA); cultured fibroblasts (January 2016)	- Intended for the treatment of deep and extensive burns, chronic wounds, skin donor sites; Tissue-engineered product
	- Autologous fibroblasts and keratinocytes co-culture seeded on transgenic porcine acellular dermal matrix (January 2016)	- Intended for the treatment of deep and extensive burns, chronic wounds, skin donor sites; Tissue-engineered product - combined
	- *Ex vivo* expanded adipose-derived stem cell suspension in a pre-filled syringe for autologous application (January 2016)	- Autoimmune diseases (rheumatoid arthritis and systemic lupus erythematosus); Somatic cell therapy medicinal product
	- Mesenchymal stem cells isolated from umbilical cord suspended in autologous platelet rich plasma (January 2016)	- Intended for the treatment of burns, nonhealing wounds; Tissue-engineered product
	- Autologous blood-derived cells which are filtered to remove other blood components (January 2016)	- Intended for the treatment of critical limb ischemia (CLI); Tissue-engineered product
	- *Ex vivo* expanded autologous Epstein-Barr Virus specific T-cells derived from peripheral blood mononuclear cells (March 2016)	- Intended for the treatment of Epstein-Barr Virus (EBV) positive malignancies; Somatic cell therapy medicinal product
	- MSCs derived from human burn eschar and debrided adipose tissue cells and keratinocytes (March 2016)	- Intended for the treatment of deep and extensive burns, chronic wounds and skin donor sites; Tissue-engineered product
	- Human autologous stromal vascular fraction (SVF) cells and human autologous adipose-derived mesenchymal stem cells (ADSC) cells (March 2016)	- Intended for the treatment of keloid scars; Tissue-engineered product
	- Viable autologous adipose-derived regenerative cells (April 2016)	- Autologous dermal filling; Not determined its classification
	- Autologous human mesenchymal stem cells present in bone marrow cells suspension (April 2016)	- Treatment of type 2 *Diabetes Mellitu*; Somatic cell therapy medicinal product
	- Autologous stromal vascular fraction (April 2016)	- Autologous lipofilling; Not determined the classification it
	- Autologous ex vivo expanded polyclonal CD4+CD25+CD127lo/-FOXP3+ regulatory T cells (April 2016)	- Treatment of type 1 *Diabetes Mellitus*; Somatic cell therapy medicinal product
	- Human autologous stromal vascular fraction cells and human autologous adipose-derived mesenchymal stem cells (September 2016)	- Intended for treatment of *cutis laxa senilis;* Tissue engineered product
	- Bone marrow-derived autologous nonhematopoietic stem cells (October 2016)	- Intended for the treatment of multiple sclerosis; Tissue engineered product
	- Autologous human adipose mesenchymal stromal cells, expanded in culture (October 2016)	- Intended for cardiac repair; Tissue engineered product
	- Autologous skin cell suspension (October 2016)	- Intended for burn wound treatment, donor site treatment; Tissue engineered product
2017	- Autologous tumor-infiltrating lymphocytes (February 2017)	- Intended for the treatment of metastatic melanoma; Somatic cell therapy medicinal product
	- Autologous bone marrow derived mesenchymal stem cell (March 2017)	- Intended for the treatment of coma (traumatic brain injury, stroke); Somatic cell therapy medicinal product
	- Human autologous adipose-derived stromal/stem cells (ADSCs) (June 2017)	- Intended for the treatment of articular cartilage and bone defects; Tissue engineered medicinal product
	- Human autologous stromal vascular fraction (SVF) (June 2017)	- Intended for the treatment of articular cartilage and bone defects; Tissue engineered medicinal product
	- Cultured autologous Wharton's jelly derived mesenchymal stem cells (June 2017)	- Intended for the treatment of amyotrophic lateral sclerosis; Tissue engineered medicinal product
	- Cultured autologous adipose derived mesenchymal stem cells (June 2017)	- Intended for the treatment of autoimmune drug resistant epilepsy; Somatic cell therapy medicinal product

Appendix 1 (Continued)

Year	Name of recommendations	Note
	- Cultured autologous adipose derived regenerative mesenchymal stem cells (June 2017)	- Intended for the treatment of autoimmune drug resistant epilepsy; Somatic cell therapy medicinal product
	- Autologous adipose derived mesenchymal stem cells, freshly isolated (June 2017)	- Intended for the treatment of autoimmune drug resistant epilepsy; Somatic cell therapy medicinal product
	- Stromal vascular fraction cells (June 2017)	- Indicated to relieve symptoms of osteoarthritis; Somatic cell therapy medicinal product
	- Human autologous keratinocytes (June 2017)	- Intended for the treatment of burns and chronic, severe wounds; Tissue engineered medicinal product
	- Human autologous chondrocytes (June 2017)	- Intended for repair of single symptomatic cartilage defect of the knee or ankle; Tissue engineered product
	- Autologous adipose tissue-derived mesenchymal stem cells (July 2017)	- Intended for chronic wounds healing (venous leg ulcers, post-traumatic wounds); Somatic cell therapy medicinal product
	- Viable chondrocytes cultured within a 3D hydrogel (September 2017)	- Intended for the treatment of articular cartilage defects of the knee; Tissue engineered product (combined)
	- Autologous dental pulp stem cells (October 2017)	- Intended for regeneration of soft and hard tissues of temporomandibular joints; Tissue engineered product
	- Freshly isolated autologous CD34+ (October 2017)	- Intended for regeneration of soft and hard tissues of temporomandibular joints; Tissue engineered product
Scientific Recommendation on Classification of Advanced Therapy Medicinal Products (Gene Therapy)		
2009	- Adeno-associated virus (AAV) vector containing a gene coding for N-sulfoglucosamine sulfohydrolase (December 2009)	- Intended for treatment of congenital, hereditary, and neonatal diseases and abnormalities; Gene therapy medicinal product
	- Lentiviral vector expressing the ABCA4 gene, packaged into infectious VS virus envelope	- Intended for the treatment of retinal disorders; Gene therapy medicinal product
	- Lentiviral vector expressing the human MYO7A gene (December 2009)	- Intended for the treatment of retinitis pigmentosa; Gene therapy medicinal product
2010	- *Salmonella typhi* strain genetically modified to secrete a fusion protein of the prostate specific antigen (PSA) and a protein leading to an increased antigenicity (January 2010)	- Oncology: intended for treatment of prostate cancer; Gene therapy medicinal product
	- Adenovirus encoding vascular endothelial growth factor C (VEGF-C) (January 2010)	- Intended for treatment of secondary lymphoedema associated with the treatment of breast cancer; Gene therapy medicinal product
	- Genetically modified *Lactococcus lactis* secreting human interleukin-10 (February 2010)	- Intended for treatment of inflammatory bowel disease; Gene therapy medicinal product
	- Lentiviral vector expressing the truncated form of human tyrosine hydroxylase (TH), human aromatic L-amino-acid decarboxylase (AADC), human GTP-cyclohydrolase 1 (CH1) (March 2010)	- Intended for treatment of Parkinson's disease; Gene therapy medicinal product
	- DNA plasmid encoding for the human fibroblast growth factor type 1 (FGF 1) (May 2010)	- Intended for treatment of critical limb ischemia; Gene therapy medicinal product
	- Nonintegrative vector including a gene coding for an anti-HSV-1 meganuclease for the *ex-vivo* transduction of human cornea (October 2010)	- Intended for prevention of infectious diseases in cornea grafted patients; Gene therapy medicinal product
	- Lentiviral vector expressing the naturally occurring human anti-angiogenic proteins endostatin and angiostatin (November 2010)	- Intended for treatment of age-related macular degeneration; Gene therapy medicinal product
2011	- Medicinal product composed of living, genetically modified *Lactococcus lactis* bacteria, containing the human trefoil factor 1 (hTFF1) gene (February 2011)	- Intended for prevention and treatment of chemotherapy-induced and/or radiotherapy-induced oral mucositis in patients with cancer of the head and the neck; Gene therapy medicinal product
	- Human islets of Langerhans (July 2011)	- Intended for: Autologous: Post pancreatectomy for benign pancreatic pathologies Allogeneic: Treatment of severe forms of type 1 diabetes; Not a ATMP
	- Autologous CD34+ hematopoietic stem cells (HSCs) transduced with lentiviral vector Lenti-D encoding the human ABCD1 cDNA (December 2011)	- Intended for treatment of childhood cerebral adrenoleukodystrophy (CCALD); Gene therapy medicinal product
	- Autologous CD34+ hematopoietic stem cells (HSCs) transduced with lentiviral vector LentiGlobin encoding the human βA-T87Q-globin gene (December 2011)	- Intended for treatment of beta-thalassemia major and intermedia, sickle cell anemia; Gene therapy medicinal product
2012	- Recombinant Herpes Simplex Virus type 1 (HSV-1) containing the gene encoding human granulocyte macrophage colony-stimulating factor (GM-CSF) (August 2012)	- Intended for treatment of adults with unresectable or metastatic melanoma; Gene therapy medicinal product
	- Human ciliary neurotrophic factor (CNTF) (October 2012)	- Intended for reducing photoreceptor loss associated with degeneration of the cells of the retina
	- Aqueous suspension of attenuated Salmonella typhi Ty21a strain transfected with a plasmid vector encoding for the human vascular endothelial growth factor receptor 2 (November 2012)	- Intended for treatment of solid malignancies with or without metastases; Gene therapy medicinal product

(*Continued*)

Appendix 1 (Continued)

Year	*Name of recommendations*	*Note*
2013	- Adult Autologous Regenerative Cells in Autologous Cell-Enriched Matrix for Subcutaneous Administration	- Intended for regeneration, repair, or replacement of weakened or injured subcutaneous tissue; Not a ATMP
	- Adult Autologous Regenerative Cells for Subcutaneous Administration (February 2013)	- Intended for regeneration, repair, or replacement of weakened or injured subcutaneous tissue; Not a ATMP
	- Pseudomonas aeruginosa bacteria genetically modified to secrete oncoproteins of Merkel cell carcinoma (April 2013)	- Intended for treatment of merkel cell carcinoma; Gene-therapy medicinal product
	- Genetically modified adenovirus coding for human granulocyte-macrophage colony stimulating factor (GM-CSF) (December 2013)	- Intended for treatment of cancer; Gene-therapy medicinal product
2014	- Allogeneic engineered Chimeric Antigen Receptor (CAR+) T-cells (May 2014)	- Intended for treatment of acute lymphoblastic leukemia and chronic lymphocytic leukemia; Gene-therapy medicinal product
	- Double-stranded naked DNA plasmid encoding an inactive human telomerase reverse transcriptase protein fused to ubiquitin (June 2014)	- Intended for the treatment of various malignancies and the prevention of tumor relapse; Gene therapy medicinal product
	- Plasmid encoding a mutation-inactivated E7-E6 fusion protein from Human Papillomavirus 16 linked to the human chemokine hMIP-1α via a dimerization module derived from human IgG3 (June 2014)	- Intended for prevention and treatment of HPV16 induced pre-malignancies and malignancies; Gene therapy medicinal product
	- Viral solution for injection of HSV-1 derived oncolytic virus (July 2014)	- Intended for the treatment of advanced pancreatic cancer and / or unresectable hepatocellular carcinoma; Gene therapy medicinal product
	- Adeno-Associated Viral Vectors derived from wild-type AAV2/5. The expression cassettes contain DNA encoding an RNA interference (RNAi) suppressor molecule, designed to suppress both mutant and wild-type rhodopsin gene transcripts (July 2014)	- Intended for the treatment of autosomal dominant rhodopsin-linked retinitis pigmentosa; Gene therapy medicinal product
	- Medicinal product composed of living, genetically modified Lactococcus lactis bacteria, containing the gene for anti-human tumor necrosis factor-alpha protein (October 2014)	- Intended for the reduction of signs and symptoms, and induction and maintenance of clinical remission in patients with moderately active ulcerative colitis (UC); Gene therapy medicinal product
	- AAV vector carrying an expression cassette for photoactivable enhanced halorhodopsin protein from Natronomonas pharaonis (eNpHR) (October 2014)	- Intended for the treatment of Retinitis Pigmentosa; Gene therapy medicinal product
2015	- Autologous engineered anti-CD19 Chimeric Antigen Receptor (CAR+) T-cells (July 2015)	- Treatment of various types of cancer; Gene therapy medicinal product
	- Adeno-associated virus vector serotype rh10 encoding human factor IX (July 2015)	- Treatment of hemophilia B; Gene therapy medicinal product
	- Suspension of live-attenuated, double-deleted Listeria monocytogenes expressing human mesothelin (September 2015)	- Treatment of malignant pleural mesothelioma; Gene therapy medicinal product
	- Encapsulated allogeneic cells secreting GM-CSF and Irradiated Autologous tumor cells. (September 2015)	- Intended for the treatment of malignant solid tumors; Gene therapy medicinal product(combined)
	- Adeno-associated virus serotype 8 vector encoding human ornithine transcarbamylase (December 2015)	- Intended for the treatment of ornithine transcarbamylase deficiency; Gene therapy medicinal product
2016	- Adeno-associated virus serotype 2 based vector containing the human RPE65 gene expression cassette (January 2016)	- Intended for the treatment of inherited retinal degeneration due to autosomal recessive RPE65 gene mutations; Gene therapy medicinal product
	- Two irradiated allogeneic pancreatic tumor cell lines, genetically engineered to secrete human granulocyte macrophage-colony stimulating factor (GM-CSF) (March 2016)	- Intended for the treatment of pancreatic cancer; Gene therapy medicinal product
	- Intended for cardiac repair - DNA plasmid encoding for the extracellular domain of human TNFα p55 receptor linked to the human IgG1 Fc domain (April 2016)	- Intended for the treatment of refractory chronic noninfectious uveitis; Gene therapy medicinal product
	- Recombinant adeno-associated viral vector serotype 2 encoding the human aromatic L-amino acid decarboxylase gene (July 2016)	- Intended for the treatment of Parkinson's disease; Gene therapy medicinal product
	- Recombinant adeno-associated viral vector serotype 8 (AAV8) encoding human glucose-6- phosphatase-α (G6Pase or G6PC) (July 2016)	- Intended for the treatment of glycogen storage disease type Ia (von Gierke disease); Gene therapy medicinal product
	- Living, genetically modified Lactobacillus reuteri bacteria, with a plasmid containing the gene for human CXCL12-1a with an inducible promoter; and an activating peptide (September 2016)	- Intended for treatment of chronic skin wounds in diabetic patients; Gene therapy medicinal product
	- Tumor selectively replicating oncolytic adenovirus expressing tumor necrosis factor alpha (TNFα) and interleukin 2 (IL2) (September 2016)	- Intended for treatment of metastatic melanoma and other solid tumors; Gene therapy medicinal product
	- Autologous T-cells expressing a chimeric NKG2D receptor (September 2016)	- Intended for treatment of various tumor types; Gene therapy medicinal product
	- The product includes two active substances i.e. two plasmids encoding for synthetic, nonfunctional consensus E6 and E7 antigens of human papilloma virus types 16 and 18 (September 2016)	- Intended for treatment of HPV-16 and -18 related high-grade squamous intraepithelial lesions (HSIL) of the cervix and vulva; Gene therapy medicinal product
	- Autologous anti-BCMA CAR-T cells (October 2016)	- Intended for the treatment of multiple myeloma and B cell lymphoma; Gene therapy medicinal product

Appendix 1 (Continued)

Year	Name of recommendations	Note
	- A recombinant replicating vaccinia viral vector (rilimogene galvacirepvec) and a recombinant nonreplicating fowlpox viral vector (rilimogene glafolivec), both expressing a modified human Prostate Specific Antigen (PSA) and three human costimulatory molecules (LFA-3, ICAM-1, and B7.1) (October 2016)	- Intended for treatment of metastatic, castrate-resistant prostate cancer; Gene therapy medicinal product
	- Recombinant modified vaccinia virus ankara (MVA) containing genetic sequences coding for the human mucin 1 and the human interleukin 2 (October 2016)	- Intended for the treatment of advanced nonsquamous nonsmall cell lung cancer (NSCLC); Gene therapy medicinal product
2017	- mRNA sequence encoding the wild type human OX40L protein (January 2017)	- Intended for the treatment of solid tumors; Gene therapy medicinal product
	- *In vitro* transcribed mRNA sequences encoding six nonsmall cell lung cancer (NSCLC) associated antigens (January 2017)	- Intended for the treatment of nonsmall cell lung cancer; Gene therapy medicinal product
	- Genetically engineered AAV8 that lacks all of the viral protein-coding sequences and encodes a human MTM1 complementary DNA (January 2017)	- Intended for the treatment of X-linked Myotubular Myopathy; Gene therapy medicinal product
	- Viable genetically engineered ARPE-19 cells of human origin secreting glucose-binding fluorescent biosensor protein (March 2017)	- Intended for adjunct glucose monitoring in diabetes patients; Gene therapy medicinal product
	- nonreplicating recombinant Adeno associated virus (rAAV8), expressing the human UGT1A1 gene (March 2017)	- Intended for the treatment of Crigler–Najjar syndrome; Gene therapy medicinal product
	- Genetically modified oncolytic adenovirus coated with oligopeptide-end modified Poly (β-amino) esters (March 2017)	- Intended for the treatment of pancreatic cancer; Gene therapy medicinal product
	- Natural killer cells derived from human induced pluripotent stem cells transduced to express highaffinity noncleavable CD16 (hnCD16) Fc receptor (April 2017)	- Intended for the treatment of advanced solid tumor malignancies that have failed available approved therapies; Gene therapy medicinal product
	- Recombinant adeno-associated virus (AAV) pseudotyped with viral capsid from serotype 5 which holds a construct that contains two guide ribonucleic acids (gRNAs) sequences (CEP290-64 and CEP290-323) driven by human U6 promoter elements and the clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (Cas9) gene (June 2017)	- Intended for the treatment of patients aged 3 years and older with Leber Congenital Amaurosis type 10 (LCA10) caused by a homozygous or compound heterozygous intron 26 mutation, c.2991 + 1655 A > G, in the CEP290 gene; Gene therapy medicinal product
	- Replication incompetent adenoviral vector encoding Interleukin 12 with activator ligand (June 2017)	- Intended for the treatment of patients with recurrent or progressive glioblastoma multiforme; Gene therapy medicinal product
	- Autologous human adipose perivascular stromal cells genetically modified to secrete soluble TRAIL ligand (AD-PC-sTRAIL) (June 2017)	- Intended for the treatment of TRAIL-sensitive cancers such as Ewing sarcoma and pancreatic ductal adenocarcinoma; Gene therapy medicinal product
	- Messenger RNAs (mRNAs) encoding immunostimulatory proteins caTLR4, CD40L and CD70 and tumor associated antigens (TAA) tyrosinase, gp100, MAGE A3, MAGE C2 and PRAME (September 2017)	- Intended for the treatment of melanoma; Gene therapy medicinal product
	- Adeno-associated viral vector serotype 8 containing the human low-density lipoprotein receptor (LDLR) gene (October 2017)	- Intended for treatment of homozygous familial hypercholesterolemia caused by mutations in the LDLR gene; Gene therapy medicinal product
	- Recombinant adeno-associated virus serotype 2/1 vector encoding human β-hexosaminidase alpha and beta subunits (October 2017)	- Intended for treatment of Tay-Sachs disease and Sandhoff disease; Gene therapy medicinal product
Scientific Recommendation on Classification of Advanced Therapy Medicinal Products (Not ATMP)		
2009	- Fresh and freeze - dried thrombocytes isolated from autologous or allogeneic blood (November 2009)	- Intended for wound healing in orthopedic and dental surgery; Not a ATMP
	- Mesenchymal stem cell-derived microvesicles (containing receptors, proteins, lipids, mRNA and microRNA) (December 2009)	- Intended for treatment of renal diseases; Not a ATMP
2010	- Product consisting of naturally occurring antigen-specific CD8 + donor lymphocytes isolated with streptamers (January 2010)	- Intended for treatment of infectious diseases; Not a ATMP
2011	- Live recombinant lentiviral vectors encoding HIV epitopes to be used for therapeutic HIV vaccination of HIV-1 infected patients (May 2011)	- Infectious disease: HIV-1; Not a ATMP
2012	- Suspension of oncolytic adenovirus (March 2012)	- Intended for treatment of colorectal cancer; Not a ATMP
	- Autologous collagen (AC) derived from human adipose tissue (May 2012)	- No medical or therapeutic claims pursued. Cosmetic dermal filling; Not ATMP
	- Autologous cells of Stromal Vascular Fraction (SVF) of adipose tissue (May 2016)	- Not medical or therapeutic claims pursued. Cosmetic lipofilling in combination with fresh lipoaspirate; Not a ATMP
	- Autologous, nonmanipulated lipoaspirate containing adipocytes and stromal vascular fraction (May 2012)	- No medical or therapeutic claims pursued. Autologous lipofiller; Not a ATMP
2013	- Adenoviral vector expressing the nonstructural region of hepatitis C virus (HCV) in which a mutation has been introduced (July 2013)-	- Intended for prevention and treatment of HCV and HCV-induced hepatocellular carcinoma; Not a ATMP
	- Concentrate of autologous, uncultured, custom-prepared bone marrow aspirate (July 2013)	- Intended for treatment of avascular necrosis e.g. of the femur head; Not a ATMP

(*Continued*)

Appendix 1 (Continued)

Year	*Name of recommendations*	*Note*
2014	- Killed spores of Bacillus subtilis incorporating a nontoxic antigen of *Clostridium difficile* (September 2014)	- Intended for the prevention of *Clostridium difficile* infections in elderly patients; Not a ATMP
	- *In vitro* derived platelet (November 2014)	- Hematology; Not a ATMP
2015	- Human extracellular matrix proteins (mainly Collagen I and glycosaminoglycans) and residual absorbable polymer, supplied as a lyophilized (dry) and ethyleneoxide sterilized product (February 2015)	- Surgical or interventional treatment of congenital heart defects, thereby correcting anatomic malformations; Not a ATMP
	- Hematopoietic progenitor cells, facilitating cells and $\alpha\beta$ T cells from mobilized peripheral blood mononuclear cells (October 2015)	- Intended for the treatment of the prophylaxis of organ rejection; Not a ATMP
2016	- Decellularized porcine dermal matrix (January 2016)	- Intended for the treatment of various skin injuries; Not a ATMP
	- Adenovirus serotype 5 expressing the Core protein, the Polymerase protein and selected domains of the Envelope protein of Hepatitis B Virus (March 2016)	- Intended for the treatment of chronic hepatitis B; Not a ATMP
2017	- Resorbable, viscoelastic matrix (June 2017)	- Matrix prior to combination with the cells; Not a ATMP
	- Nuclease resistant, synthetic double-stranded small interfering RNA (siRNA) (September 2017)	- Intended for the treatment of hepatic fibrosis; Not a ATMP

HeartSheet was approved for treatment of patients with severe heart failure under the conditional and time-limited approval pathway in 2015 (Table 8).

Approved Gene Therapy Products

Autologous cell-based gene therapy products

In the United States, KYMRIAH was approved as a cell-based gene therapy for treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia in 2017, and for adult patients with relapsed or refractory large B-cell lymphoma in 2018 (Table 8). YESCARTA was approved as cell-based gene therapy for treatment of adult patients with large B-cell lymphoma in 2017 (Table 8).

In the EU, after being granted orphan designation in 2005, Strimvelis was approved as a cell-based gene therapy to treat patients with severe combined immunodeficiency due to adenosine deaminase deficiency in 2016 (Table 8).

Gene therapy products

In the United States, IMLYGIC was approved as a genetically modified live oncolytic herpes virus therapy for the local treatment of melanoma in 2015 (Table 6). LUXTURNA was approved as an adeno-associated virus vector-based gene therapy for treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy in 2017 (Table 6).

In the EU, Glybera was approved as the first gene therapy product in the world for treatment of adults with lipoprotein lipase deficiency who have severe or multiple attacks of pancreatitis under the pathway identified as "Marketing Authorization Under Exceptional Circumstances" in 2012, whose system was time-limited to market authorization for 5 years, so its expiration occurred in the EU in 2017 (Table 6). IMLYGIC was approved as first oncolytic immunotherapy for treatment of adults with unresectable melanoma in 2015 (Table 6).

After orphan designation in 2003, Zalmoxis was approved as a genetically modified allogenic cell-based therapy for adjunctive treatment in haploidentical hematopoietic stem cell transplantation of adult patients with high-risk hematological malignancies under the Conditional Market Authorization in 2016 (Table 6).

Conclusions

We reviewed current regulations of human cell-based products and gene therapy products and approved products in the United States, the EU and Japan. The regulations of cell-based products among the United States, the EU and Japan are already well-established and the supporting systems for developers and manufacturers facilitate their development and market approval. We have a primary focus on allogeneic human cell-based products because such products are capable of producing large-sized lots of product with well-controlled quality at a reasonable price.

In the United States, many guidance documents were issued not only for autologous cell-based products, but also allogeneic cell-based products as well as gene therapy products. More recently, a new designation system for RMAT products and an expedited approval system for such products promise to facilitate their development. In the EU, developers or researchers can take advantage of the ATMP classification system that includes somatic-cell therapy medicines, gene therapy medicine products, or tissue-engineered medicines. The many guidelines and reflection papers of EMA are helpful to develop these types of products. A series

of pathways, including traditional marketing authorization systems as well as conditional market authorization, market authorization under exceptional circumstances, and reexamination by CHMP, foster ATMP development.

In Japan, systems have been introduced so that developers of regenerative medicine products have access to multiple types of consultations at early development stages and during and after conducting clinical trials. Standards for biological raw materials, standards for ensuring of quality and safety of medical products when submitting a market application, and information about evaluation are useful to facilitate the market approval. Of particular value may be five standards for ensuring the quality and safety of medical products that have been published in English.

The numbers of approved products are rising although some of these products appear to have difficulties in assuring commercial viability. In the United States, 24 human cell-based products and gene therapy products were approved: 5 autologous cell-based products, 15 allogeneic cell-based products, and 4 gene therapy products. In the EU, nine human cell-based products and gene therapy products were approved: 5 autologous human cell-based products, and 4 gene therapy products. In Japan, 4 human cell-based products were approved: 3 autologous human cell-based products, and an allogeneic human cell-based product. However, 3 products (GINTUIT, Carticel, TheraCys) in the United States and 4 products (Chondrocelect, MACI, Provenge, Glybera) in the EU were on the discontinued list, withdrawn or allowed to have the market authorization expire. Allogeneic cell-based products, including 15 products in the United States, and a single product in Japan have been marketed. In the EU, none of products has been marketed yet, however, one product has been granted a positive opinion from CAT.

Further Reading

Coppens DGM, De Bruin ML, Leufkens HGM, and Hoekman J (2018) Global regulatory differences for gene- and cell-based therapies: Consequences and implications for patient access and therapeutic innovation. *Clinical Pharmacology & Therapeutics* 103(1): 120–127. https://doi.org/10.1002/cpt.894.

Cossu G, Birchall M, Brown T, et al. (2018) Lancet commission: Stem cells and regenerative medicine. *Lancet* 391(10123): 883–910. https://doi.org/10.1016/s0140-6736(17)31366-1.

European Parliament and the Council of the European Union (2007) 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. *Official Journal of the European Union* L324: 121–137.

Halioua-Haubold CL, Peyer JG, Smith JA, et al. (2017) Regulatory considerations for gene therapy products in the US, EU, and Japan. *Yale Journal of Biology and Medine* 90(4): 683–693.

Hara A, Sato D, and Sahara Y (2014) New governmental regulatory system for stem cell-based therapies in Japan. *Therapeutic Innovation & Regulatory Science* 48(6): 681–688.

Hayakawa T, Aoi T, Umezawa A, et al. (2015) A study on ensuring the quality and safety of pharmaceuticals and medical devices derived from processing of allogeneic human induced pluripotent stem(-like) cells. *Regenerative Therapy* 2: 95–108. https://doi.org/10.1016/j.reth.2015.06.004.

Okada K, Koike K, and Sawa Y (2015) Consideration of and expectations for the pharmaceuticals, medical devices and other therapeutic products act in Japan. *Regenerative Therapy* 1: 80–83.

Watanabe N, Yano K, Tsuyuki K, Okano T, and Yamato M (2015) Re-examination of regulatory opinions in Europe: Possible contribution for the approval of the first gene therapy product Glybera. *Molecular Therapy Methods & Clinical Development* 2: 14066.

Yano K, Tsuyuki K, Watanabe N, Kasanuki H, and Yamato M (2013) The regulation of allogeneic human cells and tissue products as biomaterials. *Biomaterials* 34(13): 3165–3173. Epub 2013 Feb 12.

Yano K, Watanabe N, Tsuyuki K, et al. (2015) Regulatory approval for autologous human cells and tissue products in the United States, the European Union, and Japan. *Regenerative Therapy* 1: 45–56.

Relevant Websites

Public Law 114-125 114th Conress (2016) An Act to accelate the discovery, development, and delivery of 21st century cures, and for other purposes: Short title cited as "21st Century Cures Act". Retrieved from: https://www.congress.gov.

The Food and Drug Administration (2018a) Code of Federal Regulation Title 21, Part 1271 Human, Tissue, and Cellular and Tissue-Based Products. Retrieved from: https://www.accessdata.fda.gov.

The Food and Drug Administration (2018b) Regenerative Medicine Advanced Therapy Designation. Retrieved from: https://www.fda.gov.

The Ministry of Health Labour and Welfare (2018) Act on Ensuring the Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, and Other Products. Retrieved from: http://wwwhourei.mhlw.go.jp (in Japanese).