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Cell, tissue and gene products with marketing authorization in 2018 worldwide

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Abstract

Cell and gene therapies (CGTs) are progressively entering into clinical practice in different parts of the world. The International Society for Cell & Gene Therapy (ISCT), a global scientific society, has been committed since 1992 to supporting and developing knowledge on clinical applications of CGTs. Considering the number of products that have been progressively approved and, in some cases, withdrawn in recent years, the ISCT would like to present a brief annual report on CGTs with marketing authorization (MA) in different regions. This article reflects the dynamic momentum around authorized CGTs coinciding with the parallel increase of unproven approaches where cells are delivered without appropriate and rigorous scientific and regulatory assessment and authorization. This is intended to be a living document with a yearly update linked to a dedicated section of the ISCT website for faster adjustments. The aim is to ultimately inform, by periodic snapshots, the scientific community, healthcare stakeholders and patient associations on authorized CGT products as a way to increase communication around the approved therapeutic approaches charged with heightened expectations.

Introduction

The International Society for Cell & Gene Therapy (ISCT) is committed to translating cellular therapy into safe and effective treatments to improve patients' lives while minimizing and balancing risks for patients. Being aware that many unproven or insufficiently proven cell-based treatments are commercially available for hopeful individuals seeking cures or health improvement for a variety of conditions, the ISCT created the ISCT Presidential Task Force (PTF) on the Use of Unproven Cellular Therapies (UCT) in 2014. The PTF-UCT strives to characterize unproven cellular interventions and promote safe and effective practices worldwide [1,2].

In line with the above goals, the PTF-UCT has launched several initiatives including providing updated information on approved cellular therapies. For a list of PTF-UCT–authored resources visit http://www.celltherapysociety.org/page/UCT. In this document the PTF-UCT has summarized cell, tissue and gene medicinal products authorized for commercialization by regions/countries, to help patients seeking safe and effective treatments. We have not included any products that are categorized as medical devices, even if they are cell-based. If a patient lives in one of the regions/countries

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included in the document and a healthcare professional or a business is offering a cell-based treatment not listed, they should ask whether they are going to receive the treatment as part of a clinical trial. If not, the ISCT recommends asking for more information about the "regulatory status" of the treatment they are going to receive to make an informed decision.

Definitions and principles

Human cell– or tissue-based products are highly heterogeneous and regulatory authorities will always apply their rulings on a case-by-case basis. Nevertheless, at present, most of the cell- and tissue-based products are considered biological medicinal products in those countries with more developed regulatory structures. The development of safe and effective "proven" cell therapies requires testing these medicinal products according to some general principles [3]. Before administration into humans, both biological activity and toxicity of the investigational medicinal product must be tested in relevant animal model(s). Researchers must then seek approval of an institutional review board (IRB) for all centers involved in the clinical trial as well as an authorization from the national regulatory agencies of the countries where patients will be recruited, irrespective of their nationalities. The sponsor's duties also include ensuring: (i) that there is an insurance policy in place to cover any liability, (ii) that recruitment of subjects is done after appropriate informed consent and (iii) that medicinal product batches for release conform to specifications. If the regulatory bodies determine that quality, safety and efficacy of a cell- or tissue-based medicinal product are sufficiently established through successful clinical phases (clinical trial phase 1, 2 and 3), then the next step is to apply for marketing authorization (MA). After that, the company that holds the MA can commercialize the medicinal product in the countries in which the product has been granted MA. In some cases, MA is provisional and post-marketing surveillance studies are required. Of note, some countries permit exceptions to this authorization rule depending on the nature of the medicinal product, be it industrial or otherwise. In any case, the use of a medicinal product has to be supervised by a regulatory body.

Identified cell and gene therapies with MA

We have identified and listed cell and gene therapies (CGTs) with MA based on available information, considering as a source of trustworthy information the regulatory body web resources, official press release by the interested companies or other source of data as indicated in Tables I–X where countries/regions are listed in alphabetical order. The list has been updated as of September 15, 2018, unless otherwise specified.

In Figure 1, we present the distribution of authorized CGT products by region. In addition, we have listed (Table XI) the CGT approaches that have received a Regenerative Medicine Advanced Therapy (RMAT) designation by the United States Food and Drug Administration (USFDA) [4] but have not been approved as of September 2018. In Figure 2, we have categorized CGT products with MA worldwide in three different ways, namely, by product, therapy and disease type. Finally, in Figure 3 we present CGT products according to the year in which they received MA.

Several products are currently available in different regions but have the same MA holder (YESCARTA, KYMRIAH, IMLYGIC, RMS Ossron/OSSGROW and Chondron/CARTIGROW). These products are taken into account only once in Figures 2 and 3, leading to a total number of 44 unique products.

Discussion and conclusions

The goal of this article is to provide a quick reference for anyone interested in a snapshot, to be updated annually, of the CGT landscape worldwide. This list may not be exhaustive and additional CGT products

Table I. List of cell/tissue/gene products with MA in Australia by TGA.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
Chondrocytes - T - Ortho-ACI (Orthocell Pty Ltd)	Autologous cultured chondrocytes for use in treatment of cartilage lesions associated with the knee, patella and ankle	Cell therapy product	26-Mar-2017	Still in market	Click here for link to TGA website

TGA, Therapeutic Goods Administration.

Table II. List of cell/tissue/gene products with MA in Canada by Health Canada (March 2018).

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
KYMRIAH (NOVARTIS PHARMACEUTICALS CANADA INC)	CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of pediatric and young adult patients 3–25 y with B-cell ALL who are refractory, have relapsed after allogeneic SCT or are otherwise ineligible for SCT, or have experienced second or later relapse and for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma.	Gene therapy product	05-Sep-2018	In market	Click here for link to Health Canada website
Prochymal (MESOBLAST INTERNATIONAL SARL)	Allogeneic *ex vivo*–cultured adult human mesenchymal stromal cells for the management of aGvHD in pediatric patients	Cell therapy product	02-May-2015	The product was never marketed in Canada	Click here for link to Health Canada website

ALL, acute lymphoblastic leukemia; SCT, stem cell transplantation; DLBCL, diffuse large B-cell lymphoma; aGVHD, acute graft-versus-host disease.

Table III. List of cell/tissue/gene products with MA in China by CSFDA.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
Gendicine (Shenzhen SiBiono GeneTech Co. Ltd.)	Recombinant adenovirus expressing p53 for treatment of head and neck squamous cell carcinoma	Gene therapy product	Oct-2003	Still in market	Click here

CSFDA, Chinese Food and Drug Administation.

with MA will be included in future updates. To our knowledge, no cell/tissue/gene products have been authorized for marketing in Brazil, Hong Kong, Israel, Malaysia, Singapore and Taiwan as of September 2018.

We have identified 44 unique products, 37 of them are cell and tissue therapies (84%) and mainly autologous (55%) (Figure 2). As far as targeted diseases are concerned, more than one third of the products are intended for the treatment of oncological or hematologic diseases.

As shown in Figure 3, the number of products with MA has increased in recent years. For example, those authorized from 2015 to September 2018 represent 45%. Unfortunately, there has been a parallel increase in the number of businesses offering unproven and unlicensed cell-based interventions [5,6].

Even though the distribution of authorized CGTs shows important differences among countries or regions, it is not our intention to debate the complex financial, societal and scientific reasons behind these differences or the impact of different regulatory systems on the number of marketed products. As members of the ISCT PTF-UCT, our main objective is to help patients make informed decisions before receiving a cell or gene treatment so that they can avoid being exposed to unproven and unlicensed cell interventions. For that purpose, we aim to provide a reliable, up-to-date resource where patients or professionals can check whether a cell or gene therapy has been approved by a regulatory/medicine agency.

As mentioned before, the ISCT recommends asking for information about the "regulatory status" of the treatment patients are going to receive to make

Table IV. List of Cell/Tissue/Gene Products with MA in the European Union by EMA.

Name (MA holder)	Product description and indication(s)	ATMP	Date of MA	Current status	Additional information
YESCARTA (Kite Pharma EU B.V.)	CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory DLBCL and PMBCL, after two or more lines of systemic therapy	GTMP	23-Aug-2018	Details of MA conditions not displayed at EMA website as of 31-Aug-2018	Click here for link to EMA website
KYMRIAH (Novartis Europharm Limited)	CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of pediatric and young adult patients up to 25 y of age with B-cell ALL that is refractory, in relapse post-transplantation or in second or later relapse, and for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy	GTMP	27-Aug-2018	Details of MA conditions not displayed at EMA website as of 31-Aug-2018	Click here for link to EMA website
ALOFISEL (Takeda Pharma A/S)	Expanded allogeneic adipose stem cells as a suspension for injection for the treatment of complex perianal fistulas in patients with Crohn's disease	SCTMP	27-Mar-2018	The company will complete a study to continue to collect information on the effectiveness and safety	Click here for link to EMA website
SPHEROX (CO. DON AG)	Spheroids of human autologous matrix-associated chondrocytes for knee-repairing cartilage defects	TEP	10-Jul-2017	MA under several obligations (post-authorization long-term efficacy and safety study, prospective process validation study and re-validation of the potency assay)	Click here for link to EMA website
ZALMOXIS (MolMed SpA)	Donor's T lymphocytes genetically modified with a suicide gene as a control mechanism for GVHD after haploidentical bone marrow transplantation	GTMP	18-Aug-2016	Granted MA under conditional approval	Click here for link to EMA website
STRIMVELIS (GSK Trading Services Limited)	Autologous CD34+ cells transduced with a retroviral vector that encodes for the human ADA cDNA sequence for severe combined immunodeficiency due to ADA deficiency	GTMP	26-May-2016	Granted MA under additional monitoring until 2037	Click here for link to EMA website
IMLYGIC (Amgen Europe B.V.)	Oncolytic immunotherapy derived from a herpex simplex virus-1 genetically engineered to infect and replicate within melanoma cells and to produce GM-CSF for unresectable melanoma	GTMP	16-Dec-2015	Granted MA under additional monitoring	Click here for link to EMA website
HOLOCLAR (Chiesi Farmaceutici S.p.A.)	*Ex vivo*—expanded autologous human corneal epithelial cells containing stem cells for severe limbal stem cell deficiency	SCTMP	17-Feb-2015	Granted MA under conditional approval	Click here for link to EMA website

EMA, European Medicines Agency; ATMP, Advanced Therapy Medicinal Product; PMBCL, primary mediastinal large B-cell lymphoma; ADA, Adenosine deaminase; cDNA, complementary DNA; TEP, Tissue Engineered Product; GTMP, Gene Therapy Medicinal Product; SCTMP, Somatic Cell Therapy Medicinal Product; EC, European Commission.

Table V. List of cell/tissue/gene products with MA withdrawn or suspended in the European Union by EMA.

Name (MA holder)	Product description and indication(s)	ATMP	Date of MA	Current status	Additional information
PROVENGE (Dendreon)	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor for metastatic prostate cancer	SCTMP	6-Sep-2013	Granted MA under additional monitoring. Withdrawn: company announced bankruptcy in 2015	Click here for link to EMA website
MACI (Aastrom Biosciences, Inc.)	Matrix applied characterized autologous cultured chondrocytes for repairing knee cartilage defects	TEP	27-Jun-2013	Granted MA under additional monitoring. MA suspended: 25-Sep-2014	Click here for link to EMA website
GLYBERA (uniQure biopharma BV)	Alipogene tiparvovec (human lipoprotein lipase gene variant in a adeno-associated viral vector) for adult patients with familiar lipoprotein lipase deficiency	GTMP	25-Oct-2012	Granted MA under additional monitoring. Withdrawn: MA expired on 25-Oct-2017. The company did not apply for renewal due to the lack of demand	Click here for link to EMA website
CHONDROCELECT (TiGenix NV)	Characterized viable autologous cartilage cells expanded *ex vivo* for repairing knee cartilage defects	TEP	5-Oct-2009	The product was reimbursed in 3 countries. Withdrawn: 30-Nov-2016. Requested by the company for commercial reasons	Click here for link to EMA website

Table VI. List of cell/tissue/gene products with MA in India by DCGI.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
CARTIGROW™ (Chondron ACI) (RMS Regrow)	Autologous cultured cartilage cells for treatment of articular cartilage defects	Cell therapy product	Apr-2017	Conditional approval, post-market surveillance study required (50 subjects)	Click here
OSSGROW™ (Ossron ABI) (RMS Regrow)	Autologous cultured osteoblasts for avascular necrosis of hip	Cell therapy product	Apr-2017	Conditional approval, post-market surveillance study required (50 subjects)	
APCEDEN (APAC Biotech)	Autologous monocyte-derived mature dendritic cells for treatment of prostate, ovarian, colorectal and non-small cell lung carcinoma	Cell therapy product	Mar-2017	Conditional approval, post-market surveillance study required	Click here
Stempeucel® (Stempeutics Research)	*Ex vivo*—cultured adult allogeneic mesenchymal stromal cells for treatment of critical limb ischemia due to Thromboangiitis Obliterans (Buerger's disease)	Cell therapy product	May-2016	In market, limited release (200 patients on a cost recovery basis), post-market surveillance study required	Click here

DCGI, Drug Controller General of India.

an informed decision. This is particularly relevant for patients living in one of the regions/countries included in the document who seek safe and effective treatments, should a healthcare professional or a business offer a CGT that is neither listed nor part of a clinical trial.

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Table VII. List of cell/tissue/gene products with MA in Japan by PMDA.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information (In Japanese)
Temcell HS (JCR Pharmaceuticals Co. Ltd.)	Allogeneic mesenchymal stromal cells for treatment of aGVHD	Cell therapy product	Sep-2015	In market	Click here for link to PMDA website
HeartSheet (Terumo Corporation, Ltd.)	Autologous skeletal myoblast sheet product for the treatment of severe heart failure	Tissue engineered product	Sep-2015	Conditional approval	Click here for link to PMDA website
JACC (J-TEC)	Autologous cultured cartilage	Tissue engineered product	Jul-2012	Still in market, previous authorization was as medical device	Click here for link to PMDA website
JACE (J-TEC)	Autologous cultured epidermis for treatment of severe burns	Tissue engineered product	Oct-2007	Still in market, previous authorization was as medical device	Click here for link to PMDA website

PMDA, Pharmaceuticals and Medical Devices Agency.

Table VIII. List of cell/tissue/gene products with MA in New Zealand by MEDSAFE.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
Prochymal (Osiris Therapeutics Incorporated)	Allogeneic *ex vivo*–cultured adult human mesenchymal stromal cells indicated for the rescue of patients NLT 6 mo to 17 y of age with aGVHD, refractory to treatment with systemic corticosteroid therapy or other immunosuppressive agents	Cell therapy product	14-Jun-2012	Approval lapsed	Click here for link to MEDSAFE website

MEDSAFE, Medicines and Medical Devices Safety Authority; NLT, Not Lower Than.

Table IX. List of cell/tissue/gene products with MA in South Korea by MFDS.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
KeraHeal-Allo™ (Biosolution Co., Ltd.)	Composite cell product (allogeneic skin-derived keratinocytes suspended in a thermosensitive hydrogel) for deep 2nd degree burns	Cell therapy product	16-Oct-2015	Still in market	Click here for link to MFDS website
NEURONATA-R® (Corestem, Inc.)	Autologous bone marrow mesenchymal stromal cell therapy for Amyotrophic Lateral Sclerosis	Cell therapy product	30-Jul-2014	Orphan product	Click here for link to MFDS website
Cupistem® (Anterogen)	Autologous adipose tissue–derived mesenchymal stromal cell for Crohn's fistula	Cell therapy product	18-Jan-2012	Covered by insurance as of Jan-2014, orphan product	Click here for link to MFDS website
CARTISTEM® (Medipost Co., Ltd.)	Human umbilical cord blood–derived mesenchymal stromal cells for the treatment of knee articular cartilage defects in patients with osteoarthritis (ICRS grade IV)	Cell therapy product	18-Jan-2012	Still in market	Click here for link to MFDS website

(*continued*)

Table IX. (*Continued*).

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
Cellgram®-AMI (Pharmicell Co., Ltd.)	Autologous bone barrow–derived mesenchymal stromal cells for acute myocardial infarction patients (improvement of LVEF)	Cell therapy product	1-Jul-2011	Name at time of approval was Heart-icellgram®-AMI, still in market	Click here for link to MFDS website
CureSkin Inj. (S. Biomedics Co., Ltd.)	Autologous dermal fibroblasts (depressed acne scar)	Cell therapy product	11-May-2010	Still in market	Click here for link to MFDS website
Queencell® (Anterogen)	Autologous adipose tissue–derived adipose cell by minimal manipulation for subcutaneous tissue defect	Cell therapy product	26-Mar-2010	Still in market	Click here for link to MFDS website
Kaloderm® (Tego Science, Inc)	Allogeneic keratinocytes (cell sheet) for deep 2nd degree burn or diabetic foot ulcer	Tissue engineered product	21-Mar-2005 (2nd degree burn) 24-Jun-2010 (Diabetic foot ulcer)	Still in market	Click here for link to MFDS website
RMS OssronTM (Sewon Cellontech Co., Ltd.)	Cultured autologous osteoblasts for focal bone formation, can be used with or without fibrin glue	Cell therapy product	26-Aug-2009	Still in market	Click here for link to MFDS website
Immuncell-LC (GC Cell Corp.)	Autologous activated T cell for liver cancer (hepatocellular carcinoma)	Cell therapy product	6-Aug-2007	Currently in market for hepatocellular carcinoma and in clinical trials for newly diagnosed glioblastoma (phase 3, completed) advanced pancreatic cancer (phase 2, completed)	Click here for link to MFDS website
CreaVax-RCC® (JW CreaGene Corporation)	Autologous dendritic cells for metastatic renal cell carcinoma	Cell therapy product	15-May-2007	Received tentative approval in 2007 and product manufacture license as export product in 2013 from MFDS	Click here for link to MFDS website
KeraHeal® (Biosolution Co., Ltd.)	Autologous skin-derived keratinocytes for deep 2nd degree burns that cover >30% of TBSA and 3rd degree burns that cover >10% of TBSA	Cell therapy product	3-May-2006	Still in market	Click here for link to MFDS website
Holoderm® (Tego Science, Inc)	Autologous keratinocytes for deep 2nd degree burns that cover >30% of TBSA and 3rd degree burns that cover >10% of TBSA	Tissue engineered product	10-Dec-2002	Still in market, reimbursed by insurance	Click here for link to MFDS website
ChondronTM (Sewon Cellontech Co., Ltd.)	Cultured autologous chondrocytes for focal cartilage defect of knee, can be used with or without fibrin glue	Cell therapy product	30-Jan-2001	Still in market	Click here for link to MFDS website

MFDS, Ministry of Food and Drug Safety; ICRS, International Cartilage Regeneration & Joint Preservation Society; LVEF, left ventricular ejection fraction; TBSA, Total Burn Surface Area.

Table X. List of cell/tissue/gene products with MA in the United States by USFDA.

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
HPC, Cord Blood (MD Anderson Cord Blood Bank)	For 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	Cell therapy product	06-Jun-2018	Still in market	Click here for link to FDA website
LUXTURNA (voretigene neparvovec-rzyl) (Spark Therapeutics, Inc.)	Adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy	Gene therapy product	19-Dec-2017	Still in market	Click here for link to FDA website
YESCARTA (axicabtagene ciloleucel) (Kite Pharma, Incorporated)	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 DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma	Gene therapy product	18-Oct-2017	Still in market	Click here for link to FDA website
KYMRIAH (tisagenlecleucel) (Novartis Pharmaceuticals Corporation)	CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of patients up to 25 y of age with B-cell precursor ALL that is refractory or in second or later relapse	Gene therapy product	30-Aug-2017	Still in market	Click here for link to FDA website
MACI (Vericel Corporation)	Autologous cultured chondrocytes on a porcine collagen membrane for the repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults	Tissue engineered product	13-Dec-2016	Still in market	Click here for link to FDA website
Clevecord (HPC, Cord Blood) (Cleveland Cord Blood Center)	For 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	Cell therapy product	1-Sep-2016	Still in market	Click here for link to FDA website
HPC, Cord Blood (Bloodworks)	For 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	Cell therapy product	28-Jan-2016	Still in market	Click here for link to FDA website
IMLYGIC (talimogene laherparepvec) (Amgen Inc.)	Genetically modified oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial surgery	Gene therapy product	27-Oct-2015	Still in market	Click here for link to FDA website
HPC, Cord Blood (LifeSouth	For use in unrelated donor hematopoietic progenitor cell transplantation	Cell therapy product	13-Jun-2013	Still in market	

(*continued*)

Table X. (*Continued*).

Name (MA holder)	Product description and indication(s)	Product category	Date of MA	Current status	Additional information
Community Blood Centers, Inc.)	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				Click here for link to FDA website
ALLOCORD (SSM Cardinal Glennon Children's Medical Center)	For 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	Cell therapy product	30-May-2013	Still in market	Click here for link to FDA website
Ducord (HPC, Cord Blood) (Duke University School of Medicine)	For 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	Cell therapy product	4-Oct-2012	Still in market	Click here for link to FDA website
HPC, Cord Blood (Clinimmune Labs, University of Colorado Cord Blood Bank)	For 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	Cell therapy product	24-May-2012	Still in market	Click here for link to FDA website
GINTUIT (Organogenesis, Inc.)	Allogeneic cultured keratinocytes and fibroblasts in bovine collagen (cellular sheets) for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults	Tissue engineered product	9-Mar-2012	Still in market	Click here for link to FDA website
Hemacord (HPC, Cord Blood) (New York Blood Center, Inc.)	For 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	Cell therapy product	1-Nov-2011	Still in market	Click here for link to FDA website
Laviv® (Azficel-T) (Fibrocell Technologies, Inc.)	Autologous fibroblasts for improvement of the appearance of moderate-to-severe nasolabial fold wrinkles in adults	Cell therapy product	21-Jun-2011	Still in market	Click here for link to FDA website
PROVENGE (sipuleucel-T) (Dendreon Corporation)	Autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer	Cell therapy product	29-Apr-2010	Still in market	Click here for link to FDA website

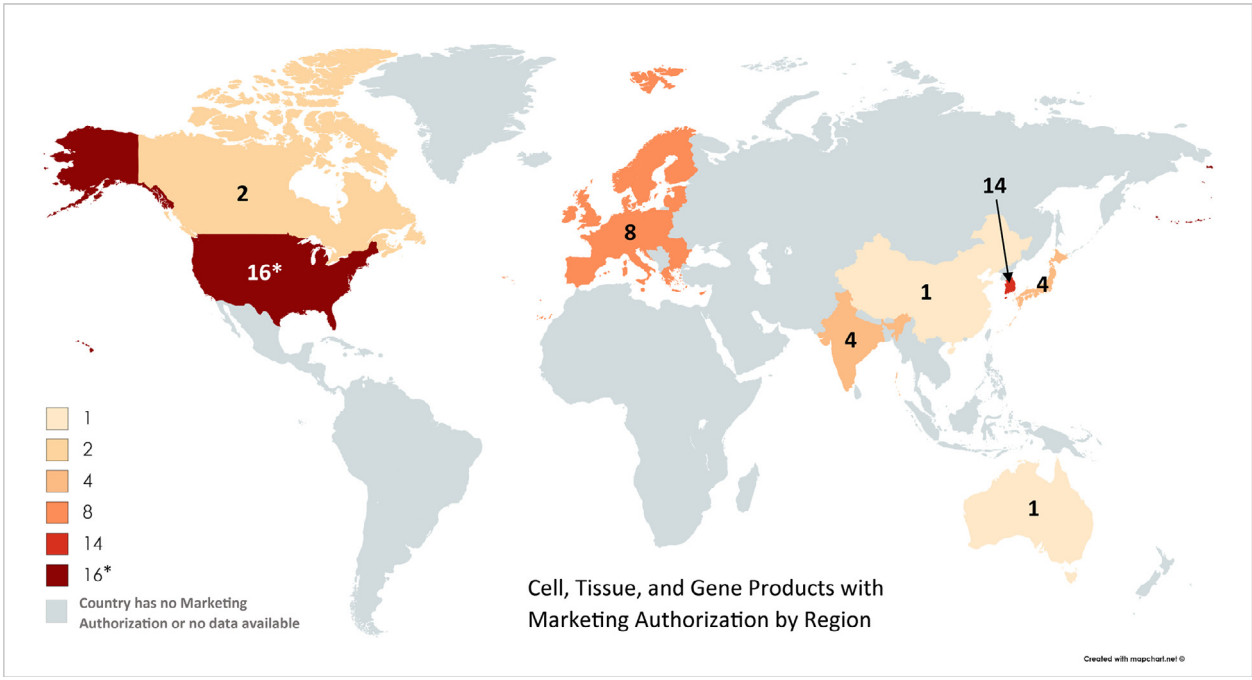

Figure 1. Number of cell, tissue and gene products with MA per region. *Eight products based on cord blood hematopoietic progenitors for unrelated donor hematopoietic progenitor cell transplantation have been included in the US's total number. These hold a MA license only in the US. Similar products are available in most countries as cell transplants and not as marketed products. The number of products presented in this figure does not include either products with Regenerative Medicine Advanced Therapy (RMAT) designation (United States Food and Drug Administration [USFDA]) or products with suspended MA.

Table XI. List of cell/tissue/gene products with RMAT Designation [4] in the United States by USFDA (Sep-2018).

Name (MA holder)	Product description and indication (s)	Product category	Date of RMAT designation	Additional designations	Additional information
AT132 (Audentes Therapeutics, Inc.)	AAV-mediated gene therapy for the treatment of XLMTM, a rare monogenic disease caused by mutations in the MTM1 gene	Gene therapy product	21-Aug-2018	Rare pediatric disease; fast track; orphan drug	Press release
Romyelocel-L (Cellerant Therapeutics, Inc.)	Off-the-shelf human myeloid progenitor cells for the prevention of serious bacterial and fungal infections in patients with *de novo* AML undergoing induction chemotherapy	Cell therapy product	02-Jul-2018		Press release
VY-AADC (Voyager Therapeutics, Inc.)	AAV-mediated gene therapy for the treatment of Parkinson's disease in patients with motor fluctuations that are refractory to medical management	Gene therapy product	21-Jun-2018		Press release
CLBS14-RfA (Caladrius Biosciences, Inc.)	CD34+ cell therapy program for the treatment of refractory angina	Cell therapy product	19-Jun-2018		Press release
NSR-REP1 (Nightstar Therapeutics plc)	AAV-mediated gene therapy for the treatment of choroideremia, a rare, degenerative, genetic retinal disorder that leads to blindness	Gene therapy product	14-Jun-2018		Press release
ABO-102 (Abeona Therapeutics Inc.)	AAV-mediated gene therapy for the treatment of Sanfilippo syndrome Type A (MPS IIIA), a rare autosomal-recessive lysosomal storage disease	Gene therapy product	23-Apr-2018		Press release

(*continued*)

Table XI. (*Continued*).

Name (MA holder)	Product description and indication (s)	Product category	Date of RMAT designation	Additional designations	Additional information
AmnioFix® (MiMedx)	Allogeneic micronized dehydrated human amnion/chorion membrane for use in the treatment of OA of the knee	Tissue engineered product	9-Mar-2018		Press release
CAP-1002 (Capricor Therapeutics)	Allogeneic cell therapy (cardiosphere-derived cells) that is currently in clinical development for the treatment of Duchenne muscular dystrophy	Cell therapy product	5-Feb-2018	Orphan drug; rare pediatric disease	Press release
EB-101 (Abeona Therapeutics Inc.)	Gene-corrected autologous cell therapy product for patients with RDEB	Gene therapy product	29-Jan-2018	Breakthrough therapy; orphan drug; rare pediatric disease	Press release
MPC therapy (Mesoblast Limited)	MPC therapy in the treatment of patients with heart failure with left ventricular systolic dysfunction and LVADs	Cell therapy product	21-Dec-2017		Press release
CEVA101 (Cellvation)	Autologous bone marrow–derived stem cells for the treatment of traumatic brain injury	Cell therapy product	8-Nov-2017		Press release
Multistem (Athersys)	Proprietary stem cell product for the treatment of ischemic stroke	Cell therapy product	5-Oct-2017		Press release
AST-OPC1 (Asterias Biotherapeutics)	Oligodendrocyte progenitor cells manufactured from pluripotent embryonic stem cells for treatment of patients with spinal cord injury	Cell therapy product	2-Oct-2017		Press release
LentiGlobin® BB305 (Bluebird Bio)	*Ex vivo* modified autologous hematopoietic stem cells for treatment of transfusion-dependent β-thalassemia (also known as β-thalassemia major) and severe SCD	Gene therapy product	1-Oct-2017		Press release
ATIR101™ (Kiadis Pharma)	Adjunctive immunotherapeutic on top of allogeneic HSCT	Cell therapy product	20-Sep-2017		Press release
StrataGraft (Mallinckrodt plc)	Autologous skin cell product for the treatment of deep partial thickness burns	Tissue engineered product	18-Jul-2017		Press release
Ixmyelocel-T (Vericel)	Autologous expanded multicellular (mesenchymal cells, monocytes and alternatively activated macrophages) product for the treatment of patients with advanced heart failure due to ischemic dilated cardiomyopathy	Cell therapy product	10-May-2017		Press release
jCell (jCyte)	Adult retinal progenitor cells for the treatment of RP	Cell therapy product	2-May-2017		Press release
RVT-802 (Enzyvant)	Allogeneic thymic tissue for the treatment of primary immune deficiency resulting from cDGS	Cell therapy product	17-Apr-2017	Breakthrough therapy, rare pediatric disease, orphan drug	Press release
HUMACYL® (Humacyte)	HAV for patients undergoing hemodialysis	Tissue engineered product	20-Mar-2017		Press release
JCAR017 (Juno Therapeutics)	Treatment of r/r aggressive large B-cell non-Hodgkin lymphoma	Cell therapy product			

AAV, adeno-associated virus; XLMTM, X-linked Myotubular Myopathy; AML, acute myeloid leukemia; OA, osteoarthritis; RDEB, recessive dystrophic epidermolysis bullosa; MPC, mesenchymal precursor cell; LVADs, left ventricular assist devices; SCD, sickle cell disease; HSCT, hematopoietic stem cell transplantation; RP, retinitis pigmentosa; cDGS, complete diGeorge Syndrome; HAV, human acellular vessel.

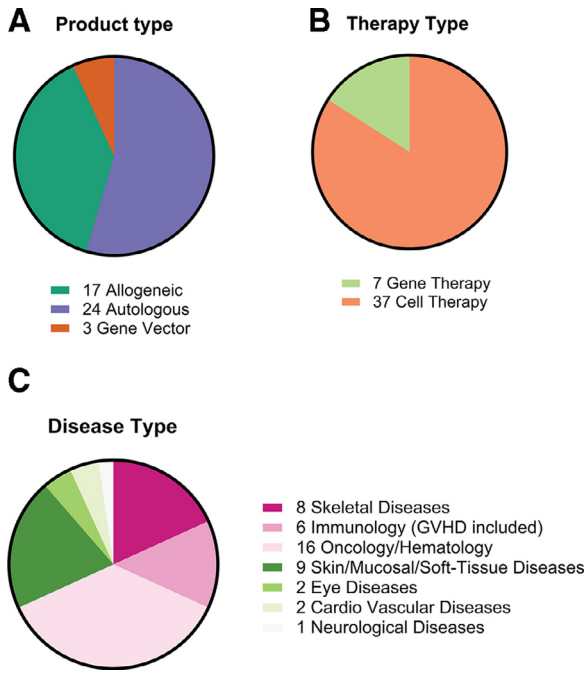

Figure 2. Cell, tissue and gene products with MA worldwide (44 unique products) organized by (A) product type, (B) therapy type and (C) disease type. "Cell Therapy" products in (B) also include tissue engineered products. Eight products based on cord blood hematopoietic progenitors for unrelated donor hematopoietic progenitor cell transplantation have been included in the total number. These hold a MA license only in the US. Similar products are available in most countries as cell transplants and not as marketed products. The number of products presented in this figure does not include either products with RMAT designation (USFDA) or products with suspended MA. GVHD, graft-versus-host disease.

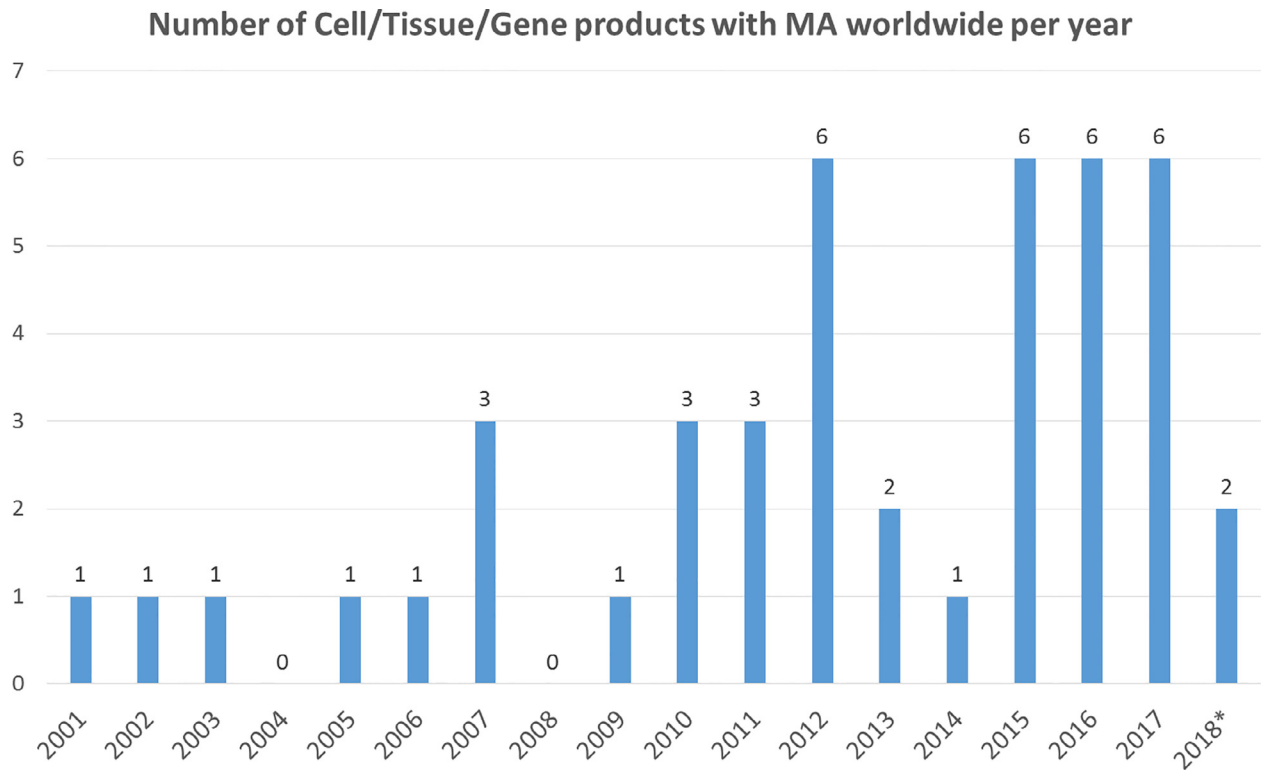

Figure 3. Cell, tissue and gene products with MA worldwide (44 unique products) organized by year of MA. Eight products based on cord blood hematopoietic progenitors for unrelated donor hematopoietic progenitor cell transplantation have been included in the total number. These hold a MA license only in the US. Similar products are available in most countries as cell transplants and not as marketed products. The number of products presented in this figure does not include either products with RMAT designation (USFDA) or products with suspended MA.

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References

[1] Dominici M, Nichols K, Srivastava A, Weiss DJ, Eldridge P, Cuende N, et al. Positioning a Scientific Community on Unproven Cellular Therapies: The 2015 International Society for Cellular Therapy Perspective. Cytotherapy 2015;17:1663–6.

[2] Srivastava A, Mason C, Wagena E, Cuende N, Weiss DJ, Horwitz EM, et al. Part 1: Defining unproven cellular therapies. Cytotherapy 2016;18:117–9.

[3] Cuende N, Izeta A. Clinical translation of stem cell therapies: a bridgeable gap. Cell Stem Cell 2010;6:508–12.

[4] Marks P, Gottlieb S. Balancing safety and innovation for cell-based regenerative medicine. N Engl J Med 2018;378:954–9.

[5] Berger I, Ahmad A, Bansal A, Kapoor T, Sipp D, Rasko JEJ. Global distribution of businesses marketing stem cell-based interventions. Cell Stem Cell 2016;19:158–62.

[6] Knoepfler PS, Turner LG. The FDA and the US direct-to-consumer marketplace for stem cell interventions: a temporal analysis. Regen Med 2018;13:19–27.