International Society
ISCT
Cell & Gene Therapy®

Cell and Gene Therapy Global Regulatory Report

June 2023

Table of Contents

Overview of Report & Authors

Section 1

Overview of Report

Welcome to the first Cell and Gene Therapy Regulatory Report from ISCT and Citeline. This report provides a global overview of the cell and gene therapy regulatory landscape, including pipeline, late-stage (Phase III and pre-registration), and approved products. It covers Cell, Genetically-Modified Cell, and Gene Therapies.

Over the last few years, the regulatory agencies have been updating legislations and frameworks to keep up with the rapidly advancing cell and gene therapy space. As a result, ISCT and Citeline have collaborated to highlight some of these changes and offer commentary on the updates and their effects.

This report shows that year-over-year, cell therapies continue to make up the majority of all approved products (71%). However, the pipeline for genetically modified cell therapies has grown to include 1,150 therapies in development, compared to 839 non-genetically modified cell therapies and 920 gene therapies.

Meanwhile, ISCT continues to track regulatory changes and events and provide comments on Key Global Legislative/Framework Changes as well as international standards including WHO's approach towards the development of a global regulatory framework for cell and gene therapy products and FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product.

About the authors

- The International Society for Cell & Gene Therapy (ISCT) is a global society of clinicians, regulators, researchers, technologists, and industry partners with a shared vision to translate cell and gene therapy into safe and effective therapies to improve patients' lives worldwide.
- ISCT is the global leader focused on pre-clinical and translational aspects of developing cell and gene-based therapeutics, thereby advancing scientific research into innovative treatments for patients. ISCT offers a unique collaborative environment that addresses three key areas of translation: Academia, Regulatory, and Commercialization. Through strong relationships with global regulatory agencies, academic institutions, and industry partners, ISCT drives the advancement of research into a standard of care.
- Comprised of over 3,000 cell and gene therapy experts across five geographic regions and representation from over 60 countries, ISCT members are part of a global community of peers, thought leaders, and organizations invested in cell and gene therapy translation. For more information about the organization, visit ISCT.
- A special thanks to the ISCT Global Regulatory Task Force for their contribution. The ISCT GRTF works to address challenges and opportunities in established and evolving global regulatory environments

- Citeline powers a full suite of complementary business intelligence offerings to meet the evolving needs of life science professionals to accelerate the connection of treatments to patients and patients to treatments. These patient-focused solutions and services deliver and analyze data used to drive clinical, commercial, and regulatory related-decisions and create real-world opportunities for growth.
- Our global teams of analysts, journalists and consultants keep their fingers on the pulse of the pharmaceutical, biomedical and medtech industries, covering it all with expert insights: key diseases, clinical trials, drug R&D and approvals, market forecasts and more. For more information on one of the world's most trusted life science partners, visit Citeline.

Global Overview of Pipeline Products, Recent Approvals & Regulatory Reviews

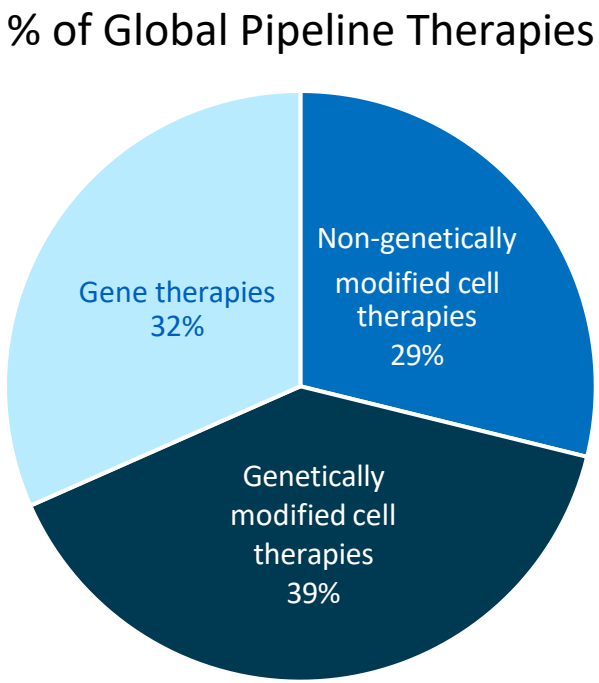
Section 2

Global Overview of Pipeline Products

Cell, Genetically Modified Cell, and Gene Therapies

Global Pipeline Overview – by category

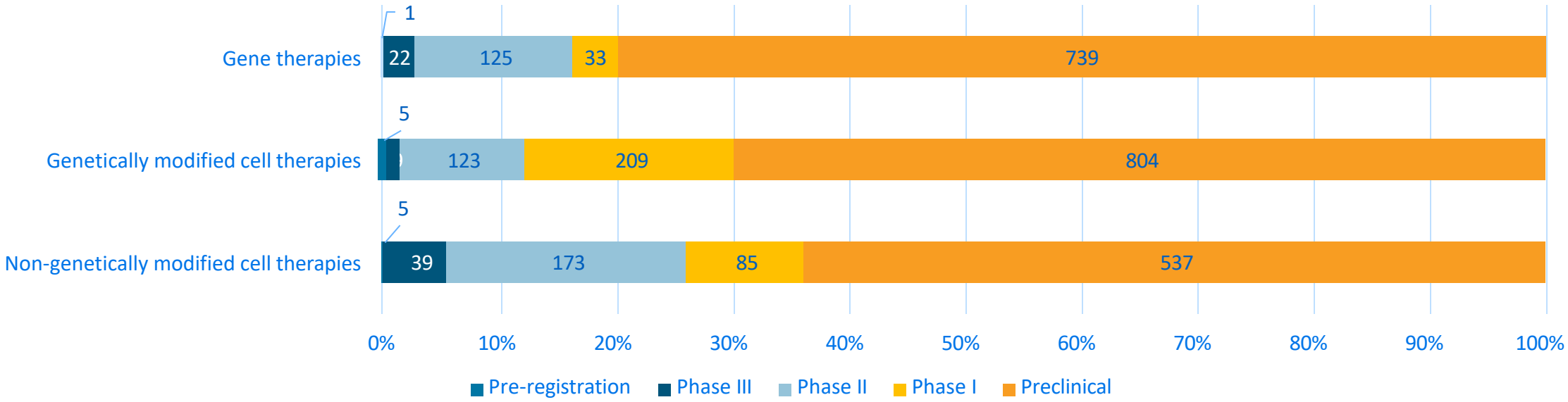
- As of June 1, 2023, of the 2,909 pipelines (from preclinical to preregistration phase) therapies, there are:
  - 839 non-genetically modified cell therapies
  - 1,150 genetically modified cell therapies
  - 920 gene therapies



Source: Pharmaprojects | Citeline, June 2023

Global Pipeline Overview – by phase

- As of June 1, 2023, the majority of therapies are in preclinical development
  - Non-genetically modified cell category has the most therapies under regulatory review with 44 therapies in Phase III or in pre-registration
  - Genetically modified cell category has the greatest absolute number of therapies in preclinical development (804 therapies), while the gene category has the greatest proportion of preclinical development (just over 80%)



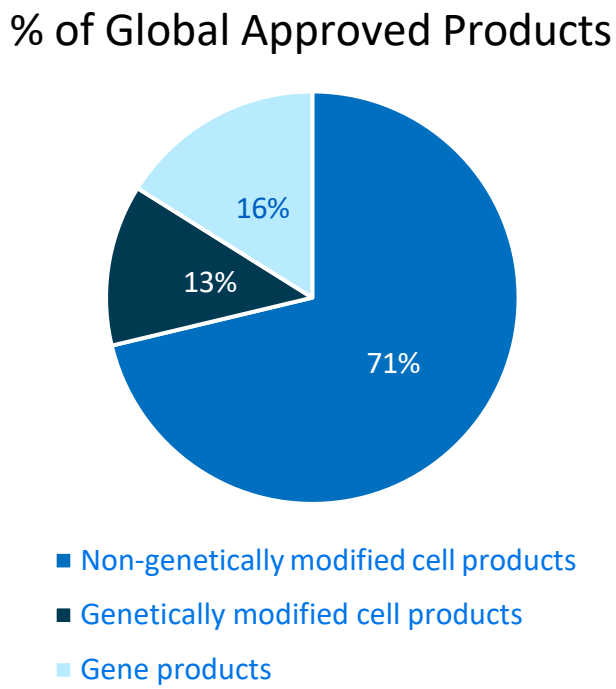
Source: Pharmaprojects | Citeline, June 2023

Approved Products

Cell, Genetically Modified Cell, and Gene Therapies

Overview of Approved Products – by category

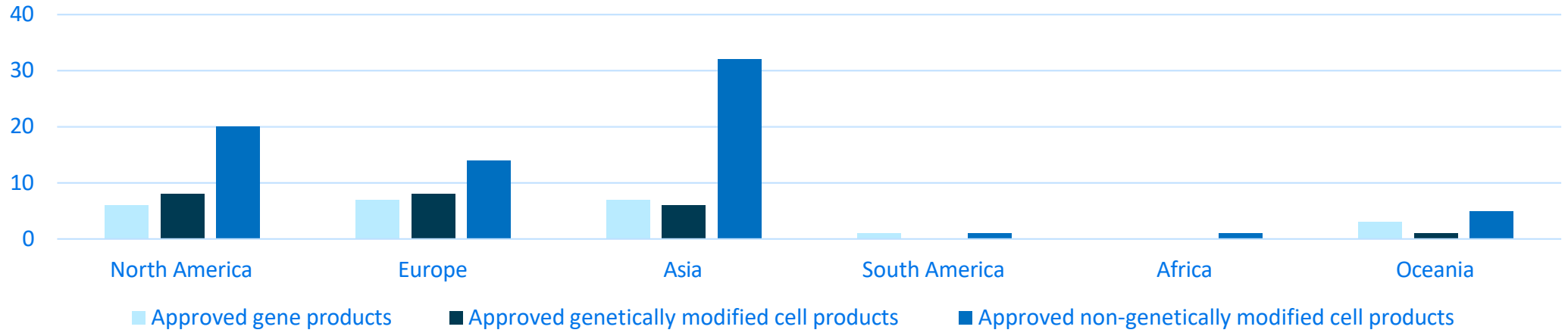
- As of June 1, 2023, 87 products are approved globally
  - 62 non-genetically modified cell products are approved
  - 11 genetically modified cell products are approved
  - 14 gene products are approved



Source: Pharmaprojects | Citeline, June 2023

Overview of Approved Products – by region*

- As of June 1, 2023, there is a similar approval distribution pattern among North America, Europe, and Asia
  - Non-genetically modified cell products – the most approved product category in all regions besides South America
  - Genetically modified cell products – the second most approved product category in North America and Europe. There is currently no approval in South America and Africa.
  - Gene products – the least approved product category in North America and Europe and the second most approved product category in Asia and Oceania. There is currently no approval in Africa.



**Approvals by regions do not necessarily represent the approvals from one or more countries in the regions.*
*****Oceania*** *includes Australia and New Zealand.*

Source: Pharmaprojects | Citeline, June 2023

Approved Non-Genetically Modified Cell Products (10-year period, June 2013–2023)

Product name	Generic name	Year first approved	Disease(s)	Locations approved	Originator company
Holoclar	autologous corneal epithelial cells	2015	Limbal stem cell deficiency	EU, UK	Holostem Terapie Avanzate
TCD-51073	autologous myoblast cell therapy	2015	Heart failure	Japan	Precigen
Stempeucel	allogeneic mesenchymal stem cells	2016	Ischemia, limb	India	Stempeutics
Apceden	autologous dendritic cells	2017	Cancer, colorectal; cancer, lung, non-small cell; cancer, ovarian; cancer, prostate	India	APAC Biotech
Alofisel	darvadstrocel	2018	Anal fistula, Crohn's disease	EU, Israel, Japan, UK	Takeda
Kyslecel	minimally manipulated autologous pancreatic islets	2018	Pancreatitis	US	Orgenesis
Stemirac	Stemirac	2018	Spinal cord injury	Japan	Nipro
CartiLife	autologous chondrocytes	2019	Arthritis, osteo	South Korea	Biosolution Co.
Nepic	autologous corneal epithelium cells	2020	Limbal stem cell deficiency	Japan	Teijin Pharma
Stratagraft	allogenic skin tissue cells	2021	Wound healing	US	Mallinckrodt
Ocural	autologous cultured oral mucosal epithelium	2021	Limbal stem cell deficiency	Japan	Teijin Pharma
Rethymic	allogeneic processed thymus tissue-agdc	2021	DiGeorge syndrome	US	Sumitomo Dainippon Pharma
Sakracy	autologous cultured oral mucosal epithelium	2022	Limbal stem cell deficiency	Japan	Hirosaki Lifescience Innovation
Tab-cel	tabelecleucel	2022	Post-transplant lymphoproliferative disorder	EU, UK	Atara Biotherapeutics
Vyznova	corneal endothelial cell therapy	2023	Corneal dystrophy	Japan	Aurion Biotech
Omisirge	omidubicel	2023	Stem cell engraftment	US	Gamida Cell

Source: Pharmaprojects | Citeline, June 2023

Approved Genetically-Modified Cell Products (10-year period, June 2013–2023)

Product name	Generic name	Year first approved	Disease(s)	Locations approved	Originator company
Strimvelis	autologous CD34+ enriched cells	2016	Adenosine deaminase deficiency	EU, UK	GSK
Kymriah	tisagenlecleucel-t	2017	Cancer, leukemia, acute lymphocytic; Cancer, lymphoma, B-cell, diffuse large; Cancer, lymphoma, follicular	US, EU, UK, Japan, Australia, Switzerland, Canada, South Korea	Novartis
Yescarta	axicabtagene ciloleucel	2017	Cancer, lymphoma, B-cell, diffuse large; Cancer, lymphoma, follicular	Japan, China, Canada, EU, US, UK, Australia	Gilead Sciences
Zynteglo	betibeglogene autotemcel	2019	Thalassaemia	EU*, US	bluebird bio
Tecartus	brexucabtagene autoleucel	2020	Cancer, leukaemia, acute lymphocytic, Cancer, lymphoma, mantle cell	EU, UK, US, Australia	Gilead Sciences
Libmeldy	atidarsagene autotemcel	2020	Leukodystrophy, metachromatic	EU, UK	GSK
Breyanzi	lisocabtagene maraleucel	2021	Cancer, lymphoma, B-cell, diffuse large; Cancer, lymphoma, follicular	EU, UK, US, Japan, Canada, Switzerland	Bristol-Myers Squibb
Abecma	idecabtagene vicleucel	2021	Cancer, myeloma	US, EU, UK, Canada, Japan	bluebird bio
Skysona	elivaldogene autotemcel	2021	Adrenoleukodystrophy	EU*, US	bluebird bio
Benoda	relmacabtagene autoleucel	2021	Cancer, lymphoma, B-cell, diffuse large; Cancer, lymphoma, follicular	China	JW Therapeutics
Carvykti	ciltacabtagene autoleucel	2022	Cancer, myeloma	US, EU, UK, Japan, Australia	Legend Biotech

**The first approval dates for these 2 products relates to their approval in the EU. However, bluebird bio had requested to withdraw them due to commercial reasons.*

Source: Pharmaprojects | Citeline, June 2023

Approved Gene Products (10-year period, June 2013–2023)

Product name	Generic name	Year first approved	Disease(s)	Locations approved	Originator company
Imlygic	talimogene laherparepvec	2015	Melanoma	US, EU, UK, Australia	Amgen
Luxturna	voretigene neparvovec	2017	Leber's congenital amaurosis; retinitis pigmentosa	US, EU, UK, Australia, Canada, South Korea	Roche
Zolgensma	onasemnogene abeparvovec	2019	Spinal muscular atrophy	US, EU, UK, Japan, Australia, Canada, Brazil, Israel, Taiwan, South Korea	Regenxbio
Collategene	beperminogene perplasmid	2019	Ischaemia, limb	Japan	AnGes
Delytact	teserpaturev	2021	Brain cancer	Japan	Daiichi Sankyo
Upstaza	eladocagene exuparvovec	2022	Aromatic L-amino acid decarboxylase (AADC) deficiency	EU, UK	PTC Therapeutics
Roctavian	valoctocogene roxaparvovec	2022	Haemophilia A	EU, UK	BioMarin
Hemgenix	etranacogene dezaparvovec	2022	Haemophilia B	US, EU, UK	uniQure
Adstiladrin	nadofaragene firadenovec	2022	Bladder cancer	US	Merck
Vyjuvek	beremagene geperpavec	2023	Epidermolysis bullosa	US	Krystal Biotech

Source: Pharmaprojects | Citeline, June 2023

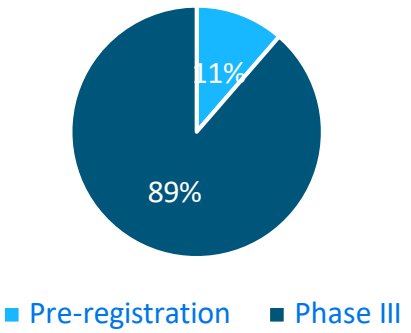
Products Under Regulatory Review (Pre-registration and Phase III)

Cell, Genetically Modified Cell, and Gene Therapies

Non-Genetically Modified Cell Therapies Under Regulatory Review

- 44 non-genetically modified cell therapies are under regulatory review (pre-registration or Phase III clinical trials)
  - 5 non-genetically modified cell therapies are in pre-registration, accounting for 11% of late-stage non-genetically modified cell therapies
  - 39 non-genetically modified cell therapies are in Phase III clinical trials, accounting for 89% of late-stage non-genetically modified cell therapies

% of non-genetically modified cell therapies in late-stage development



Non-genetically modified cell therapies in pre-registration

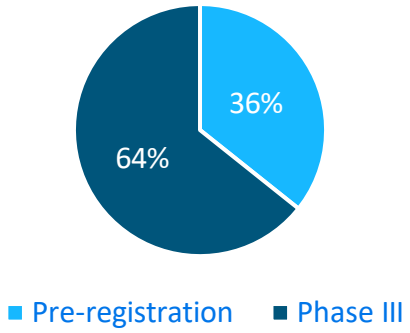
Drug Name	Generic Drug Name	Cell Type	Disease	Company	Reviewer Agency
ACE-02	autologous cultured epidermis with melanocytes	Skin cells	Piebaldism; Vitiligo	Teijin Pharma	MHLW (Japan)
Sitoiganap	ERC-1671	Glioma-derived cell lysates and irradiated cells	Brain cancer	Epitopoietic Research	EMA (EU and UK)
Lantidra	donislecel	Pancreatic cells (Islet cells)	Diabetes, Type 1	CellTrans	FDA (US)
Astrostem	stem cell therapy, autologous	Connective tissue cells (Adipocytes)	Arthritis, osteo	K-StemCell	MFDS (South Korea)
SB-623	vandefitemcel	Mesenchymal stem cells (bone marrow)	Traumatic brain injury	SanBio	MHLW (Japan)

Source: Pharmaprojects | Citeline, June 2023

Genetically Modified Cell Therapies Under Regulatory Review

- 14 genetically modified cell therapies are under regulatory review (pre-registration or Phase III clinical trials)
  - 5 genetically modified cell therapies are in pre-registration, accounting for 36% of late-stage genetically-modified cell therapies
  - 9 genetically modified cell therapies are in Phase III clinical trials, accounting for 64% of late-stage genetically-modified cell therapies

% of genetically modified cell therapies in late-stage development



Genetically modified cell therapies in pre-registration

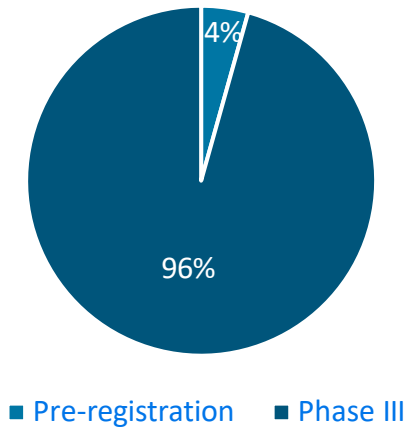
Drug Name	Generic Drug Name	Cell Type	Disease	Company	Reviewer Agency
CT-053	autologus BCMA-CAR-T cells	T cells	Cancer, myeloma	CARsgen Therapeutic	NMPA (China)
IB-1326	equecabtagene autoleucel	T cells	Cancer, myeloma	Nanjing IASO Biotherapeutics	NMPA (China)
Exa-cel	exagamglogene autotemcel	Hematopoietic stem and progenitor cells	Anemia, sickle cell; Thalassaemia	CRISPR Therapeutics	FDA (US); EMA (EU and UK)
CNCT-19	inaticabtagene autoleucel	T cells	Cancer, leukemia, acute lymphocytic	Juventas Cell Therapy	NMPA (China)
Lovo-cel	lovotibeglogene autotemcel	Hematopoietic stem and progenitor cells	Anemia, sickle cell	bluebird bio	FDA (US)

Source: Pharmaprojects | Citeline, June 2023

Gene Therapies Under Regulatory Review

- 23 gene therapies are under regulatory review (pre-registration or Phase III clinical trials)
  - 1 gene therapy is in pre-registration, accounting for 4% of late-stage gene therapies
  - 22 gene therapies are in Phase III clinical trials, accounting for 96% of late-stage gene therapies

% gene therapies in late-stage development



Gene therapies in pre-registration

Drug Name	Generic Drug Name	Cell Type	Disease	Company	Reviewer Agency
SRP-9001	delandistrogene moxeparvovec	Other/Unknown/ NA	Dystrophy, Duchenne's muscular	Sarepta Therapeutics	FDA (US)

Source: Pharmaprojects | Citeline, June 2023

Select Regulatory Review

Cell, Genetically Modified Cell, and Gene Therapies

Select Regulatory Review – Product Overview

Vyjuvek

First therapeutic approved by US FDA for Epidermolysis Bullosa

Vyjuvek (beremagene geperpavec)

Company:	Krystal Biotech, Inc.
Current phase:	US FDA Approval
Indication:	Epidermolysis Bullosa
Target:	Collagen
Formulation/dosing:	Viral gene therapy; topical gel of non-integrating, replication-incompetent HSV-1 expressing the human collagen VII protein
Designations:	Fast Track, Orphan, PRIME, Rare Disease, RMAT
Upcoming regulatory events:	CHMP Opinion from 9/1/23–3/31/24

Pivotal Study	GEM-3 (Update: 2/17/23)
Patient inclusion	≥ 6 months old and older at the time of Informed Consent with Dystrophic Epidermolysis Bullosa confirmed by genetic testing, including COL7A1, and 2 cutaneous wounds matching the criteria
Study design	Interventional, Randomized, Parallel Assignment, Quadruple Blind
Primary focus	Safety and efficacy
Trial efficacy data	The pivotal GEM-3 trial met its primary endpoint of complete wound healing at six months and its secondary endpoint of complete wound healing at three months.
Trial safety data	B-VEC was well tolerated, with no drug-related serious adverse events or discontinuations due to treatment.

Supporting clinical studies	Gem-1/2 (Completion date: 12/2019)
Patient inclusion	2 years of age and older with Dystrophic Epidermolysis Bullosa and at least one wound matching the criteria
Study design	Interventional, Randomized, Parallel Assignment
Primary focus	Treatment
Study status	Complete
Study results	Repeat topical applications of B-VEC were associated with durable wound closure, full-length cutaneous type VII collagen (COL7) expression, and anchoring fibril assembly with minimal reported adverse events

Source: Pharmaprojects | Citeline, June 2023

Select Regulatory Review – Large Impact Events

Vyjuvek – Regulatory Insights

Regulatory overview	
Expected event	CHMP Opinion
Expected event date	9/1/2023 – 3/31/2024
MAA filing date	12/14/22
Designations	Fast Track, Orphan, PRIME, Rare Disease, RMAT
Previous regulatory decision	FDA regulatory approval (US)

Summary of regulatory outcomes

- On May 19, 2023, the US FDA approved Vyjuvek for the treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene
- Krystal Biotech filed the marketing authorization application (MAA) for beremagene geperpavec (B-VEC) with the European Medicines Agency (EMA) and is currently working closely with the EMA through the MAA validation process

Additional notes Regulatory Decision	Comments
▪ Submission for CHMP Opinion	▪ Based on an internal analysis of the centralized European approval procedure, it is estimated the European marketing authorization for this drug for this indication will be granted in approximately 11-17 months. As the approval decision is normally issued 67 days from adoption of a positive Committee for Medicinal Products for Human Use (CHMP) opinion, it is estimated the CHMP opinion to occur between September 2023 and March 2024.
▪ US FDA Approval	▪ The safety and effectiveness of Vyjuvek was established primarily in a Phase III, randomized, double-blinded, placebo-controlled study (GEM-3) involving a total of 31 subjects with DEB, including 30 subjects with RDEB and one subject with DDEB. ▪ In addition, in a different Phase III clinical study, two young patients with RDEB (6 and 7 months of age, respectively) received topical Vyjuvek weekly without any new safety findings.

Source: Pharmaprojects | Citeline, June 2023

Select Regulatory Review – Product Overview

Exa-cel

Potential to be first gene-edited therapy approved

Exa-cel
(exagamglogene autotemcel)

Company:	Vertex Pharmaceuticals Incorporated & CRISPR Therapeutics
Current phase:	BLA
Indication:	Sickle Cell Anemia
Target:	BCL11A|CRISPR/CRISPR-Cas9
Formulation/dosing:	Non-viral gene therapy; single-dose infusion CTX001 (autologous CD34+ hHSPCs modified with CRISPR-Cas9 at the erythroid lineage-specific enhancer of the BCL11A gene)
Designations:	Fast Track, Orphan, PRIME, Rare Disease, RMAT
Upcoming regulatory events:	Approval Decision (UK) from 7/1/23–9/30/23 CHMP Results from 9/1/23–3/31/24

Pivotal Study	CLIMB-SCD-121 (Update: 12/10/22)
Patient inclusion	12 to 35 years of age with severe SCD and a history of ≥2 VOCs per year in the previous 2 years
Study design	Interventional, Single Group Assignment, Open Label
Primary focus	Safety and efficacy
Trial efficacy data	Data from 31 patients showed a single dose of Exa-cel leads to early increases in HbF and total HB that are durable up to nearly 3 years. All patients were free of VOCs.
Trial safety data	Safety profile is consistent with that of busulfan myeloablation and autologous HSCT. No patients with SCD had Exa-cel related SAEs.

Supporting clinical studies	CLIMB-151 (Update: 1/25/23)
Patient inclusion	2 to 11 years of age with severe SCD and a history of ≥2 VOCs per year in the previous 2 years
Study design	Interventional, Single Group Assignment, Open Label
Primary focus	Safety and efficacy
Study status	Actively recruiting

Source: Pharmaprojects | Citeline, June 2023

Select Regulatory Review – Large Impact Events

Exa-cel - Regulatory Insights

Regulatory overview	
Expected event	Approval Decision (UK)
Expected event date	7/1/23–9/30/23
MHRA filing date	01/24/23
Designations	Fast Track, Orphan, PRIME, Rare Disease, RMAT
Previous regulatory decision	PDUFA for BLA - First Review (US)

Summary of regulatory outcomes

- Vertex announced that the Exa-cel filing for approval (UK) and MAA submissions were completed in the fourth quarter of 2022 in EU and UK for SCD
- April 3, 2023, Vertex Pharmaceuticals announced the completion of the rolling Biologics License Applications (BLAs) to the US Food and Drug Administration (FDA) for the investigational treatment exagamglogene autotemcel (exa-cel) for sickle cell disease (SCD)
- June 8, 2023, US Food and Drug Administration (FDA) accepted the Biologics License Applications (BLAs) for the investigational treatment exagamglogene autotemcel (exa-cel) for severe sickle cell disease (SCD) and transfusion-dependent beta thalassemia (TDT).

Additional notes Regulatory Decision	Comments
▪ Submission for CHMP Opinion (EU)	▪ Based on an internal analysis of the centralized European approval procedure, it is estimated the European marketing authorization for this drug for this indication will be granted in approximately 11–17 months. As the approval decision is normally issued 67 days from adoption of a positive Committee for Medicinal Products for Human Use (CHMP) opinion, we then estimate the CHMP opinion to occur between September 2023 and March 2024.
▪ Submission for Approval Decision (EU)	▪ The MHRA offers a 150-day assessment timeline for marketing authorization applications (MAAs) for new active substances and biosimilar products or existing active substances in the UK. Under this process, the MHRA will evaluate the application for marketing authorization and reach its opinion on approvability within 150 days of submission of a valid application. The assessment procedure also includes a stopped-clock period of up to 60 days for the applicant to address any questions from the MHRA. As such, a decision is expected between July 2023 and September 2023.
▪ BLA Submission (US)	▪ The FDA has granted Priority Review for SCD and Standard Review for TDT and assigned Prescription Drug User Fee Act (PDUFA) target action dates of December 8, 2023, and March 30, 2024, respectively.

Source: Pharmaprojects | Citeline, June 2023

Select Regulatory Review – Product Overview

SRP-9001

Potential to be the first gene therapy U.S. FDA approved for Duchenne Muscular Dystrophy

SRP-9001 (delandistrogene moxeparvovec)

Company:	Sarepta Therapeutics, Inc.
Current phase:	BLA
Indication:	Duchenne Muscular Dystrophy (DMD)
Target:	Microdystrophin
Formulation/dosing:	Viral gene therapy; single intravenous infusion of SRP-9001
Designations:	Fast Track, Orphan, Rare Disease
Upcoming regulatory events:	PDUFA/Approval Decision (U.S.) from 5/23–6/23

Pivotal Study	ENDEAVOR (Update: 7/6/22)
Patient inclusion	4 to 7 years of age, ambulatory male at birth with DMD confirmed by documented clinical findings and prior genetic testing. Participant will have had a stable dose equivalent of oral corticosteroids for at least 12 weeks and rAAVrh74 antibody titers are not elevated as per protocol requirements
Study design	Interventional, Single Group Assignment, Open Label
Primary focus	Safety and efficacy
Trial efficacy data	Across multiple new analyses, SRP-9001 treated patients showed statistically significant and clinically meaningful benefit versus propensity-matched external controls.
Trial safety data	The safety and tolerability profile of SRP-9001 is similar to past reports. The most common treatment-related adverse event was vomiting.

Supporting clinical studies	EMBARK (Update: 12/22)
Patient inclusion	4 to 7 years of age, ambulatory with DMD confirmed by documented clinical findings and prior genetic testing; participant will have had a stable dose equivalent of oral corticosteroids for at least 12 weeks and rAAVrh74 antibody titers are not elevated as per protocol requirements
Study design	Interventional, Randomized, Parallel Assignment, Quadruple Blind
Primary focus	Safety and efficacy
Study status	Enrolled

Source: Pharmaprojects | Citeline, June 2023

Select Regulatory Review – Large Impact Events

SRP-9001 – Regulatory Insights

Regulatory overview	
Expected event	PDUFA for BLA – First Review (US)
Expected event date	5/29/23
NDA/BLA filing date	9/29/22
Designations	Fast Track, Orphan, Rare Disease
Previous regulatory decision	Priority Review (US)

Summary of regulatory outcomes

- On May 24, 2023, Sarepta Therapeutics announced that the FDA has informed Sarepta that it requires modest additional time to complete the review of the company's BLA for SRP-9001 for the treatment of ambulant individuals with Duchenne muscular dystrophy (DMD) who have a confirmed mutation of the DMD gene, including final label negotiations and post-marketing commitment discussions, and that it anticipates that the review will be complete by June 22, 2023.
- On May 12, 2023, the U.S. Food and Drug Administration (FDA) Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) voted 8 to 6 in support of accelerated approval of SRP-9001 (delandistrogene moxeparvovec) for the treatment of ambulatory patients with Duchenne muscular dystrophy with a confirmed mutation in the DMD gene,

Additional notes Regulatory Decision	Comments
▪ MAA Submission (EU)	▪ Roche plans to file for approval of RG6356 for the treatment of DMD in 2024.
▪ J-NDA Filing (Japan)	▪ Chugai plans to file for approval of SRP-9001 for the treatment of DMD in Japan in 2024.
▪ Cellular, Tissue, and Gene Therapies Advisory Committee Meeting (US FDA)	▪ On May 12, 2023, the committee met in an open session to discuss the Biologics License Application (BLA) 125781 from Sarepta Therapeutics, Inc. for delandistrogene moxeparvovec with the requested indication for the treatment of ambulatory patients with Duchenne Muscular Dystrophy (DMD) with a confirmed mutation in the DMD gene. The meeting was open for the public. ▪ Despite the FDA's highly negative tone in the briefing document, the advisory committee narrowly voted in favor of accelerated approval for Sarepta's gene therapy, SRP-9001. Panelists appreciated the risk/benefit profile for SRP-9001, as well as the importance of time in an indication such as this. However, a key concern among panelists was the inability to complete the pivotal Phase III EMBARK trial before approval, which would mean an approval based on insufficient evidence of efficacy. Sarepta managed to convince many that accelerated approval would not cause the trial to lose its integrity, and also noted that very few patients would be treated commercially with SRP-9001 before the completion of EMBARK. Data from the trial are expected by the end of 2023.

Source: Pharmaprojects | Citeline, June 2023

Select Regulatory Review – Product Overview

Lumevoq

Potential to be the first gene therapy U.S. FDA approved for Leber's Hereditary Optic Neuropathy

Lumevoq
(GS-010)

Company:	GenSight Biologics S.A.
Current phase:	Phase III
Indication:	Leber's Hereditary Optic Neuropathy (LHON)
Target:	Mitochondrial Electron Transport Chain|NADPH: Quinone Oxidoreductase-1 (NQO1)
Formulation/dosing:	Viral gene therapy; single dose of GS010 (recombinant adeno-associated viral vector serotype 2 (rAAV2/2) containing the wild-type ND4 gene (rAAV2/2-ND4))
Designations:	Orphan, Rare Disease, SPA
Upcoming regulatory events:	Product launch (EU) from 9/1/2023 – 12/31/2023

Pivotal Study	**REFLECT, RESCUE, REVERSE (Update: 3/23)**
Patient inclusion	18+ years of age with onset of vision loss based on medically documented history or subject testimony, in both eyes for 181 and ≤365 days in duration and documented results of genotyping showing the presence of the G11778A mutation in the ND4 gene and the absence of the other primary LHON-associated mutations (ND1 or ND6) in the subject's mitochondrial DNA
Study design	Interventional, Randomized, Parallel Assignment, Quadruple Blind
Primary focus	Safety and efficacy
Trial safety and efficacy data	The results show sustained efficacy and favorable safety for bilateral intravitreal injection of the gene therapy with a statistically significant visual acuity improvement from baseline in both treated eyes, showing an additional benefit of a bilateral injection compared to a unilateral injection.

Supporting clinical studies	**REVEAL (Completion date: 6/20)**
Patient inclusion	18+ years of age with LHON based on a genetic test confirming the presence of the G11778A mutation in the mitochondrial ND4 and visual acuity ≤ 1/10 of the less functional eye
Study design	Interventional, Safety Study, Single Group Assignment, Open Label
Primary focus	Safety
Trial safety data	Well tolerated with a good safety profile during 5 years of follow-up and may offer meaningful lasting improvements in vision for this LHON population

Source: Pharmaprojects | Citeline, June 2023

Select Regulatory Review – Large Impact Events

Lumevoq – Regulatory Insights

Regulatory overview	
Expected event	Product launch (EU)
Expected event date	9/1/23–12/31/23
MAA filing date	09/15/20
Designations	Orphan, Rare Disease, SPA
Previous regulatory decision	MAA Withdrawal

Summary of regulatory outcomes

- On April 20, 2023, GenSight Biologics announced that the Committee for Advanced Therapies (CAT) of the Committee Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) assessed the data presented during the oral explanation on LUMEVOQ European regulatory dossier. Following interactions with the CAT indicating that the data provided thus far would not be sufficient to support a positive opinion of the marketing authorization of LUMEVOQ by EMA, GenSight decided to withdraw its application ahead of a final opinion by the CAT.
- GenSight submitted the MAA for LUMEVOQ to the EMA in September 2022 based on the benefit-risk balance established by results from a Phase-I/IIa study (CLIN-01), two pivotal Phase-III efficacy studies (CLIN-03A: RESCUE, and CLIN-03B: REVERSE and the long-term follow up study of RESCUE and REVERSE (CLIN 06 – readout at Year 3 post-injection).

Additional notes Regulatory Decision	Comments
▪ MAA Withdrawal	▪ The decision to withdraw the MAA enables the Company to discuss the best possible path forward for LUMEVOQ with the EMA in the coming weeks, aiming at submitting a new application addressing remaining objections as soon as possible, in Europe and other countries. The company is exploring options including generating new clinical data, which may induce material delays and additional costs. ▪ GenSight confirms that the manufacturing validation campaign is on track with its partner in the United-States, as planned, with a product released for human use by the end of 2023.
▪ FDA response to a Type-C meeting (US)	▪ The FDA provided feedback in January 2022 recommending that the company conduct an additional placebo-controlled trial to bolster the demonstration of LUMEVOQ efficacy in view of the unexpected bilateral effect observed in unilaterally treated patients in the Phase III RESCUE, REVERSE and REFLECT trials. This feedback from the FDA is in response to a Type-C meeting with the company held in December 2021.

Source: Pharmaprojects | Citeline, June 2023

Upcoming Regulatory Events, Highlights of Key Global Legislative/Framework Changes, Recent or Upcoming Standards & Highlights of the Latest Approved Products

Section 3

Upcoming Regulatory Events

Upcoming Regulatory Events

START DATE	END DATE	EVENT DESCRIPTION	TYPE OF EVENT	NAME OF AGENCY
March 17, 2023	June 20, 2023	Guidance document: Pharmacogenomic Data Submissions	Public consultation	CBER-FDA
April 3, 2023	July 3, 2023	Guidance document: Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions	Public consultation	CBER-FDA
April 5, 2023	July 5, 2023	Guidance document: Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making	Public consultation	CBER-FDA
April 21, 2023	Sept. 30, 2023	Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorization	Public consultation	CAT-EMA
May 17, 2023	July 17, 2023	Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act Guidance for Industry	Public consultation	CBER-FDA
17 May 2023	17 July 2023	Guidance for Industry: Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations	Public consultation	CBER-FDA
May 19, 2023	Vary*	E6(R2) Guideline “Good Clinical Practice” (GCP)	Public consultation	ICH
May 24, 2023	July 24, 2023	Guidance for Industry: Generally Accepted Scientific Knowledge in Applications for Drug and Biological Products: Nonclinical Information	Public consultation	CBER-FDA
May 30, 2023	Aug. 1, 2023	Guidance document: Decentralized Clinical Trials for Drugs, Biological Products, and Devices	Public consultation	CBER-FDA
June 14, 2023	June 16, 2023	Committee for Advanced Therapies (CAT) Meeting	Meeting	CAT-EMA
June 26, 2023	June 27, 2023	Multi-stakeholder workshop on Real-world Data (RWD) quality and Real-World Evidence (RWE) use	Workshop	EMA
12 July 2023	14 July 2023	Committee for Advanced Therapies (CAT) Meeting	Meeting	CAT-EMA
Sept.1, 2023	Sept. 1, 2023	Advisory Committee on Biologicals (ACB) Meeting #20	Meeting	TGA
TBD	TBD	Guidance for Industry and Staff: Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies	Public consultation	CBER-FDA
TBD	TBD	Draft Guidance for Industry: Considerations for the Use of Human- and Animal- derived Materials and Components in the Manufacture of Cell and Gene Therapy and Tissue-Engineered Medical Products	Public consultation	CBER-FDA
TBD	TBD	Draft Guidance for Industry: Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products	Public consultation	CBER-FDA
TBD	TBD	Draft Guidance for Industry: Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)	Public consultation	CBER-FDA
TBD	TBD	Draft Guidance for Industry: Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products	Public consultation	CBER-FDA

**The public consultation deadline varies depending on the regulatory agency partners, click here to find out more.*

Highlights of Key Global Legislative/Framework Changes

ICH – E6(R3) Draft Guideline: Good Clinical Practice[1,2]

About the guideline

- This is a revision of the E6(R2) Guideline “Good Clinical Practice” (GCP), it is because, since the development of E6(R2), clinical trials have continued to evolve with new designs and technological innovations.
- The proposed revision to ICH E6 would likely primarily benefit innovators who typically conduct clinical trials, such as those in the pharmaceutical and biotech sectors.

Scope and application

- Addressing the application of GCP principles to the increasingly diverse trial types and data sources being employed to support regulatory and healthcare-related decision-making on drugs and provide flexibility whenever appropriate to facilitate the use of technological innovations in clinical trials.

European Health Union – Commission Proposal to Reform EU Pharmaceutical Legislation[3]

About the proposal

- The Commission is proposing to revise the EU's pharmaceutical legislation — the largest reform in over 20 years
- The revision will make medicines more available, accessible, and affordable. It will support innovation and boost the competitiveness and attractiveness of the EU pharmaceutical industry, while promoting higher environmental standards.
- The revision includes proposals for a new directive and a new regulation, which revise and replace the existing pharmaceutical legislation, including the legislation on medicines for children and for rare diseases.

6 key elements of the proposal

- Better access to innovative and affordable medicines for patients and national health systems
- Promoting innovation and competitiveness through an efficient and simplified regulatory framework
- Effective incentives for innovation
- Addressing shortages of medicines and ensuring security of supply
- Stronger protection of the environment
- Tackling antimicrobial resistance (AMR)

FDA – Distributed Manufacturing and Point-of-Care Manufacturing of Drugs | Discussion Paper[4]

About the paper

- This discussion paper presents areas associated with Distributed Manufacturing (DM) and Point-of-Care (POC) manufacturing that FDA has identified for consideration as FDA evaluates our existing risk-based regulatory framework as it applies to these technologies.

Scope and application

- The discussion paper considers relevant background, including terminology, to the FDA's regulation of DM and POC, identifies challenges presented by DM and POC, and poses key questions to facilitate public comment.
- The discussion paper does not constitute guidance; instead, its purpose is to gather feedback from the public to inform future policy development.

FDA – draft guidance on Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products[5]

About the guidance

- This guidance provides recommendations to sponsors and investigators considering the use of externally controlled clinical trials to provide evidence of the safety and effectiveness of a drug and biological product.

Scope and application

- This guidance focuses on the use of patient-level data from other clinical trials or from real-world data (RWD) sources, such as registries as well as electronic health records (EHRs) and medical claims.

Health Canada – Draft guidance on advanced therapeutic products framework[6]

About the guidance

- The guidance document provides an overview of how Health Canada designates and regulates advanced therapeutic products (ATPs) under sections 21.9 to 21.96 of the Food and Drugs Act.

Scope and application

- This guidance applies to:
  - All ATPs that are or may be set out in Schedule G of the act
  - The following activities related to ATPs:
    - manufacture, prepare, preserve, package, label, test, store, import, advertise, sell

MHRA – UK to introduce first-of-its-kind framework to make it easier to manufacture innovative medicines at the point of care[7]

About the framework

- The framework is specifically designed to create and regulate a step change in the range of manufacturing options to enable the supply and increase the availability of innovative new medicinal products to patients.
- This new manufacturing and supply system in the UK healthcare system will benefit patients that currently have no or few treatment options by improving the availability of innovative medicines.

Scope and application

- The aim is to support increased manufacture of point-of-care products whilst ensuring these products attain the same assurance of safety, quality and efficacy currently in place for more conventional medicinal products.

TGA – Update to the Manufacturing Principles for Medicines, APIs & Sunscreens[8]

About the guidance

- TGA adopted the PIC/S Guide to Good Manufacturing Practice for Medicinal Products (PE009-15) that was issued on May 1, 2021, as the Manufacturing Principles for medicines, active pharmaceutical ingredients and sunscreens.
- This adoption of the PIC/S Guide commenced on July 1, 2022, from which point, GMP inspectors will use the new Guide to GMP during inspections.

Summary of change(s)

- The changes in version 15 relate to Annex 2 - Biological Medicines, which has been split into two sub-annexes:
  - Annex 2A “Manufacture of advanced therapy medicinal products for human use”; and
  - Annex 2B “Manufacture of biological medicinal substances and products for human use.”

New Zealand Ministry of Health – Therapeutic Products Bill

About the bill[9]

- The bill will replace the Medicines Act 1981 that is currently the main legislation for enabling access to safe medicines and medical devices. The bill would repeal most provisions of the Medicines Act, except those relating to pharmacy ownership, and revoke the regulations made under the act. It would also revoke the Dietary Supplements Regulations.
- Changes that the bill proposes include:
  - requiring therapeutic products to receive a market authorization before they could be imported into, exported from, or supplied in New Zealand
  - providing for the regulation of a range of controlled activities
  - establishing a Therapeutics Products Regulator

ISCT general comments

- Although there is a good coverage of amendments to national legislation within the bill, a separate document explaining the implications for those required to adhere to other pieces of legislation or regulations would be useful and since this bill has not covered topics regarding unproven stem cell therapies, provisions about it should be included.
- In addition, it is important to provide explanation on the scheme and how it is similar to, and differs from, other regulatory schemes internationally, and how it articulates with other national legislation (e.g., Human Tissue Act 2008) and the types of amendments made to other national legislation to accommodate it.

WHO – Approach Towards the Development of a Global Regulatory Framework for Cell and Gene Therapy Products

About the white paper[10]

- Publication of this early draft is to provide information about the proposed document- WHO approach towards the development of a global regulatory framework for cell and gene therapy products, to a broad audience and to ensure the transparency of the consultation process.

ISCT general comments

- WHO to establish a platform to whom each state (independently from the level of experience of its own regulatory body) may refer to. Use of certain established networks, such as those already working in Asia or Africa, will likely have limited effect upon the direction of global harmonization.
- WHO to consider a centralized organization that functions as reference body and establishes the basic guidelines for manufacturing, control, shipping, indication, application, and surveillance of ATMPs, for example, as ICH has done to foster alignment on multiple topics including analytics, etc. The number of countries aligning to ICH standards continues to grow.

Recent or Upcoming Standards

FACT-JACIE International Standards for HCT Product Collection, Processing and Administration – 9th edition

About the standards

- These standards represent the basic fundamentals of cellular therapy that can be applied to any cell source or therapeutic application and are intended to be used throughout product development and clinical trials.

Publication timeline

- The new edition of this standard will be published in early 2025.

FACT Standards for Immune Effector Cells – The Second Edition

About the standards

- These standards promote quality practice in immune effector cell therapies and apply to a wide range of immune effector cells used to modulate an immune response for therapeutic intent, whether genetically modified or not. This includes, but is not limited to, dendritic cells, natural killer cells, T cells, B cells, genetically engineered chimeric antigen receptor T cells (CAR-T cells), and therapeutic vaccines.

Publication timeline

- The final standards will be published in November 2023 and will become effective in February 2024.

Highlights of the Latest Approved Products

First Gene Therapy to Treat Adults with Hemophilia B – Hemgenix®[11-18]

About the product

- Hemgenix® is an adeno-associated viral (AAV5) vector-based gene therapy that encodes factor IX. Patients with hemophilia B have mutations (changes) in a gene which the body needs to make the clotting protein Factor IX, resulting in either a partial or complete lack of its activity.

Approval history

- August 2022 – was granted orphan designation by the TGA
- Nov. 22, 2022 – received FDA BLA approval
- Feb. 20, 2023 – received EU Conditional Marketing Approval
- March 27, 2023 – received conditional marketing authorization from UK MHRA
- April 5, 2023 – was granted an OGTR license

First therapy to Treat Transplant Patients with Post-transplant Lymphoproliferative Disease – Ebvallo™[19-22]

About the product

- The first therapy to treat transplant patients with post-transplant lymphoproliferative disease
- A medicine used to treat adults and children from 2 years of age who, after receiving an organ- or a bone marrow-transplantation, develop a blood cancer called Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD)

Approval history

- Dec. 16, 2022 – the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization under exceptional circumstances

First Topical Gene Therapy for Treatment of Wounds in Patients with Dystrophic Epidermolysis Bullosa – Vyjuvek™[23]

About the product

- Vyjuvek™, a herpes-simplex virus type 1 (HSV-1) vector-based gene therapy, for the treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene.
- Vyjuvek™ is a genetically modified (engineered in a laboratory) herpes-simplex virus used to deliver normal copies of the COL7A1 gene to the wounds.

Approval history

- May 19, 2023 – received FDA BLA approval

Cell Therapy for Patients with Blood Cancers to Reduce Risk of Infection Following Stem Cell Transplantation – Omisirge®[24]

About the product

- Omisirge® (omidubicel-onlv), a substantially modified allogeneic (donor) cord blood-based cell therapy to quicken the recovery of neutrophils (a subset of white blood cells) in the body and reduce the risk of infection.
- The product is intended for use in adults and pediatric patients 12 years and older with blood cancers planned for umbilical cord blood transplantation following a myeloablative conditioning regimen (treatment such as radiation or chemotherapy).

Approval history

- April 17, 2023 – received FDA BLA approval

Cell Therapy for Patients with Relapsed or Refractory Multiple Myeloma – Carvykti®[25-30]

About the product

- Ciltacabtagene autoleucel is a B-cell maturation antigen (BCMA)-directed genetically modified autologous chimeric antigen receptor (CAR) T-cell therapy.
- Each dose is customized using a patient's own T-cells, which are collected and genetically modified, and infused back into the patient.

Approval History

- Feb. 28, 2022 – received FDA BLA approval
- May 25, 2022 – received EMA conditional marketing authorization
- Designated as an orphan drug by UK MHRA until Jan. 4, 2033
- Sept. 27, 2022 – received PMDA approval
- 22 February 2023 – received FDA supplement approval
- 6 June 2023 – received TGA approval

Disclaimer

Disclaimer

Although the information provided in this report has been produced from sources believed to be reliable, no warranty, express or implied, is made by the publishers regarding the accuracy, adequacy, completeness, legality, reliability or usefulness for any particular purpose.

The publishers provide this information on an “as is” basis and disclaim any and all warranties, express and implied, including, but not limited to, any warranties of accuracy, reliability, title, merchantability, fitness for a particular purpose, freedom from contamination by computer viruses (if provided digitally) and non-infringement of proprietary rights.

In no circumstances will the publishers be liable for any trading, investment, commercial or other decisions based on or made in reliance on the report. Changes may periodically be made to the information included in the report and these changes may or may not be incorporated in any new version of the report. Data can also quickly become out of date.

In no event shall the publishers be liable for any special, indirect, or consequential damages or any damages whatsoever, whether direct, indirect, consequential, incidental, or special, or any claim for attorney’s fees arising out of or in connection with the information provided in the report.

**The publishers: ISCT and Citeline*

References, Methodology, Glossary of Key Terms

References

1. ICH, Public Consultations, https://www.ich.org/page/public-consultations, accessed 12 June 2023.
2. ICH, Draft Guideline – Good Clinical Practice (GCP) E6(R3), https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf, accessed 12 June 2023.
3. European Commission, Press release - European Health Union: Commission proposes pharmaceuticals reform for more accessible, affordable and innovative medicines, https://ec.europa.eu/commission/presscorner/detail/en/IP_23_1843, published 26 April 2023, accessed 4 May 2023.
4. US FDA, Distributed Manufacturing and Point-of-Care Manufacturing of Drugs | Discussion Paper, https://www.fda.gov/about-fda/reports-budgets-cder/distributed-manufacturing-and-point-care-manufacturing-drugs-discussion-paper, published 18 October 2022, accessed 05 April 2023.
5. US FDA, Draft guidance: Considerations for the design and conduct of externally controlled trials for drug and biological products, https://www.fda.gov/media/164960/download, published February 2023, accessed 29 March 2023.
6. Government of Canada, Draft guidance on advanced therapeutic products framework: Overview, https://www.canada.ca/en/health-canada/programs/consultation-draft-guidance-advanced-therapeutic-products-framework/overview.html, published 28 December 2022, accessed 29 March 2023.
7. Press Release, UK to introduce first-of-its-kind framework to make it easier to manufacture innovative medicines at the point of care, https://www.gov.uk/government/news/uk-to-introduce-first-of-its-kind-framework-to-make-it-easier-to-manufacture-innovative-medicines-at-the-point-of-care, published 25 January 2023, accessed 05 April 2023.
8. Australia TGA, Update to the Manufacturing Principles for medicines, APIs & sunscreens, https://www.tga.gov.au/news/notices/update-manufacturing-principles-medicines-apis-sunscreens-0, published 25 August 2022, accessed 30 March 2023.
9. New Zealand Parliament, Therapeutic Products Bill, https://www.parliament.nz/en/pb/sc/make-a-submission/document/53SCHE_SCF_BILL_130084/therapeutic-products-bill, published 7 February 2023, accessed 29 March 2023
10. World Health Organization, WHO approach towards the development of a global regulatory framework for cell and gene therapy products, https://cdn.who.int/media/docs/default-source/biologicals/bs2424_cgtp-document-for-2nd-public-consultation.pdf?sfvrsn=11a0c885_1, accessed 05 April 2023
11. EMA, Hemgenix, https://www.ema.europa.eu/en/medicines/human/EPAR/hemgenix, updated 13 April 2023, accessed 4 May 2023
12. Pharmaceutical Technology, CSL receives EC CMA approval for haemophilia B gene therapy, CSL receives EC CMA approval for haemophilia B gene therapy (pharmaceutical-technology.com), published 21 February 2023, accessed 20 March 2023
13. CISION PR Newswire, First Gene Therapy for Hemophilia B, CSL's HEMGENIX®, Approved by the European Commission, https://www.prnewswire.com/news-releases/first-gene-therapy-for-hemophilia-b-csls-hemgenix-approved-by-the-european-commission-301751222.html, published 20 February 2023, accessed 20 March 2023
14. HEMGENIX, https://www.fda.gov/vaccines-blood-biologics/vaccines/hemgenix, content current as of 4 January 2023, accessed 22 March 2023
15. TGA, Notice for etranacogene dezaparvovec (CSL Behring Australia Pty Ltd), https://www.tga.gov.au/resources/designations-determinations/notice-etranacogene-dezaparvovec-csl-behring-australia-pty-ltd, date of review outcome 30 August 2022, accessed 22 March 2023
16. PharmaTimes Online, CSL's Hemgenix receives MHRA authorisation, https://www.pharmatimes.com/news/csls_hemgenix_receives_mhra_authorisation_1490181 published 27 March 2023, accessed 29 March 2023
17. ISCT, Australia and New Zealand Legal and Regulatory Affairs - Watchdog Update April 2023, https://www.isctglobal.org/telegrafthub/blogs/lauren-reville/2023/04/12/watchdog-update-australia-and-new-zealand-legal-an, accessed 17 May 2023
18. Dealings not involving intentional release (DNIR), https://www.ogtr.gov.au/sites/default/files/2023-05/may_dnir_list_2023.pdf, updated 22 May 2023, accessed 30 May 2023
19. EMA, First therapy to treat transplant patients with post-transplant lymphoproliferative disease, https://www.ema.europa.eu/en/news/first-therapy-treat-transplant-patients-post-transplant-lymphoproliferative-disease , published 14 October 2022, accessed 29 March 2023
20. EMA, Ebvallo, https://www.ema.europa.eu/en/medicines/human/EPAR/ebvallo, approved 16 December 2022, accessed 29 March 2023.
21. EMA, Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 10-13 October 2022, https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-10-13-october-2022#:~:text=The%20committee%20adopted%20a%20positive,positive%20post%2Dtransplant%20lymphoproliferative%20disease, published 14 October 2022, accessed 1 May 2023.
22. ISCT, North America Legal and Regulatory Affairs – Watchdog Update February 2023, https://www.isctglobal.org/telegrafthub/blogs/lauren-reville/2023/02/07/north-america-legal-and-regulatory-affairs-watchdo, accessed 17 May 2023
23. FDA News Release, FDA Approves First Topical Gene Therapy for Treatment of Wounds in Patients with Dystrophic Epidermolysis Bullosa, https://www.fda.gov/news-events/press-announcements/fda-approves-first-topical-gene-therapy-treatment-wounds-patients-dystrophic-epidermolysis-bullosa, published 19 May 2023, accessed 30 May 2023.
24. FDA News Release, FDA Approves Cell Therapy for Patients with Blood Cancers to Reduce Risk of Infection Following Stem Cell Transplantation, https://www.fda.gov/news-events/press-announcements/fda-approves-cell-therapy-patients-blood-cancers-reduce-risk-infection-following-stem-cell, published 17 April 2023, accessed 30 May 2023.
25. FDA D.I.S.C.O. Burst Edition: FDA approval of CARVYKTI, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-carvykti-ciltacabtagene-autoleucel-treatment-adult-patients, accessed 9 June 2023.
26. EMA, Carvykti, https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti, accessed 9 June 2023.
27. UK MHRA, Orphan Register, https://www.gov.uk/government/publications/orphan-registered-medicinal-products/orphan-register#carvykti, updated 9 June 2023, accessed 9 June 2023.
28. Businesswire, CARVYKTI Receives Approval from MHLW Japan, https://www.businesswire.com/news/home/20220926005847/en/CARVYKTI%E2%84%A2-ciltacabtagene-autoleucel-Receives-Approval-from-Japan%E2%80%99s-Ministry-of-Health-Labour-and-Welfare-MHLW-for-the-Treatment-of-Patients-with-Relapsed-or-Refractory-Multiple-Myeloma, accessed 9 June 2023
29. FDA Supplement Approval – CARVYKTI, https://www.fda.gov/media/165633/download, accessed 9 June 2023.
30. TGA, ARTG ID 410143, Carvykti, https://www.tga.gov.au/resources/artg/410143, accessed 9 June 2023.

Methodology: Sources and Scope of Therapies

- Sources for all data come from Citeline (formerly Pharma Intelligence)
  - Pipeline and trial data
    - Data derived from **Pharmaprojects and Trialtrove**
    - Therapeutic classes included in report categorizations:
      - Gene therapies:
      - Genetically modified cell therapies:
      - Cell therapies:
  - Event data
    - Data derived from **Biomedtracker**

Glossary of Key Terms*

Therapy Type Definitions

Gene therapy is the use of genetic material to treat or prevent disease. For the purpose of this report, the following terms shall mean the following:

Gene therapy	Therapies containing an active ingredient synthesized following vector-mediated introduction of a genetic sequence into target cells *in-* or *ex-vivo*. Used to replace defective or missing genes (as in cystic fibrosis) as well as to introduce broadly acting genetic sequences for the treatment of multifactorial diseases (e.g., cancer). Direct administration of oligonucleotides without using vectors is covered separately in the antisense therapy class; RNA interference class; or oligonucleotide, non-antisense, non-RNAi class. Platform technologies for gene delivery are covered separately in the gene delivery vector class.

**The key terms and definitions used in this report are referring to the method the data is pulled, organized, and presented.*

Glossary of Key Terms*

Therapy Type Definitions, cont.

Genetically modified cell therapy includes the following:

Cellular therapy, chimeric antigen receptor	Cellular therapy consisting of T cells that have been modified to express a chimeric antigen receptor (CAR) – this is a cell surface receptor that gives the T cells the ability to target a specific protein and fight the targeted cells
Cellular therapy, other	Cellular therapies that do not fall under "Cellular therapy, stem cell," "Cellular therapy, CAR," "Cellular therapy, TIL," or "Cellular therapy, TCR" categories or the specific cellular therapy is unspecified
Cellular therapy, stem cell	Regenerative therapy which promotes the repair response of injured tissue using stem cells (cells from which all other specialized cells would originate)
Cellular therapy, T cell receptor	Cellular therapies whereby natural T cells collected for the patient are engineered to express artificial receptors (usually through viral transfections) that would target specific intracellular antigens (as peptides bound to proteins encoded by the major histocompatibility complex, MHC)
Cellular therapy, tumour infiltrating lymphocyte	Adoptive cellular transfer of tumour resident T cells from tumor material, their expansion ex vivo and transfer back into the same patient after a lymphodepleting preparative regimen
Lytic virus	Therapies with a replication-competent virus, that lyse pathogenic cells directly. These are normally genetically modified to render them harmless to normal tissues. Examples include oncolytic viruses which specifically attack cancer cells

**The key terms and definitions used in this report is referring to the method the data is pulled, organized, and presented.*

Glossary of Key Terms*

Therapy Type Definitions, cont.

Cell therapy includes the following therapeutic classes:

Cellular therapy, stem cell	Regenerative therapy that promotes the repair response of injured tissue using stem cells (cells from which all other specialized cells would originate).
Cellular therapy, tumor infiltrating lymphocyte	Adoptive cellular transfer of tumor resident T cells from tumor material, their expansion *ex vivo,* and transfer back into the same patient after a lymphodepleting preparative regimen.
Cellular therapy, other	Cellular therapies that do not fall under the categories of cellular therapy, stem cell; cellular therapy, CAR; cellular therapy, TIL; cellular therapy, TCR; or the specific cellular therapy are unspecified.

**The key terms and definitions used in this report is referring to the method the data is pulled, organized, and presented.*

Glossary of Key Terms*

Development status definitions

Pipeline	Drugs that are in active development
Preclinical	Not yet tested in humans
Phase I	Early trials, usually in volunteers, safety, PK, PD
Phase II	First efficacy trials in small numbers of patients
Phase III	Large-scale trials for registrational data
Pre-registration	Filing for approval made to regulatory authorities
Approved	Approval from relevant regulatory authorities for human use

Unspecified indications

Cancer, unspecified	Indications for which the specific tumor type is not specified
Cancer, hematological, unspecified	Indications for which the specific hematological cancer is not specified
Cancer, solid, unspecified	Indications for which the specific solid tumor is not specified

**The key terms and definitions used in this report is referring to the method the data is pulled, organized, and presented.*