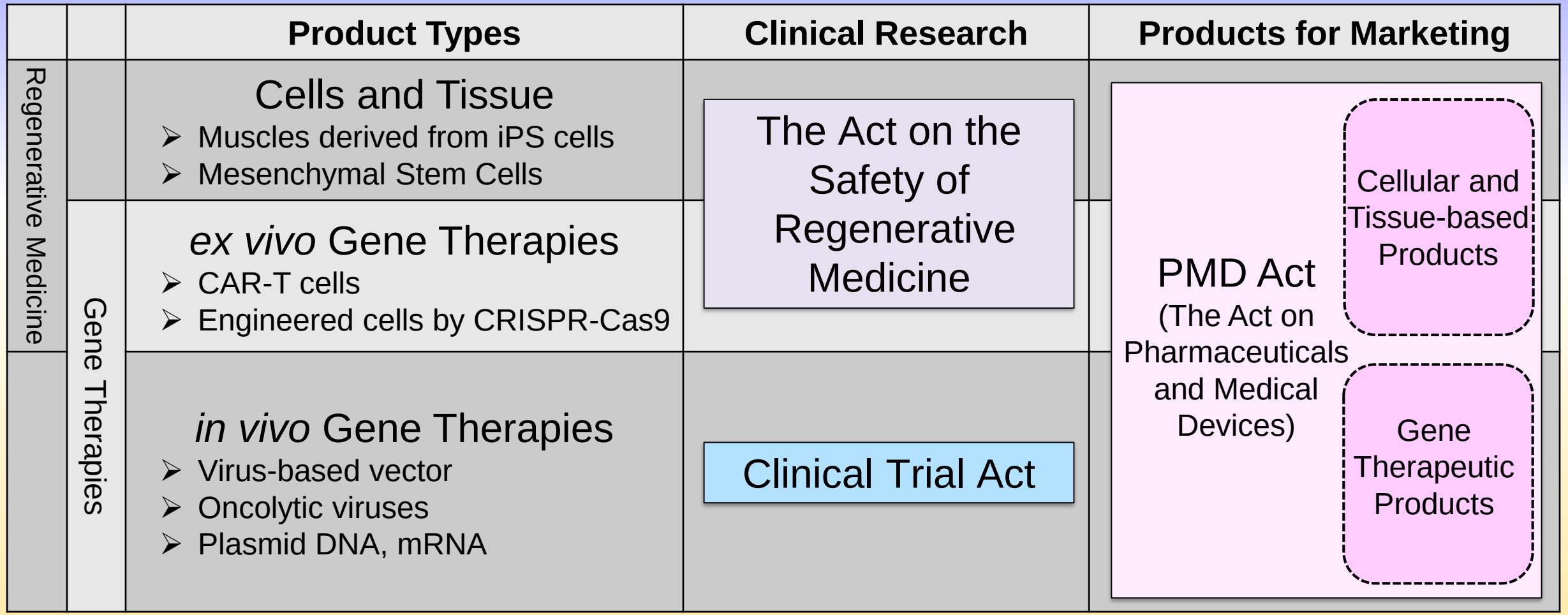
Regenerative Medicine and Gene Therapy in Japan

Akira Sakurai, PhD

Deputy Reviewer Director, Office of Cellular and Tissue-based Products,
Pharmaceuticals and Medical Devices Agency (PMDA)/
Q5A(R2) EWG Deputy Topic Leader (MHLW/PMDA)

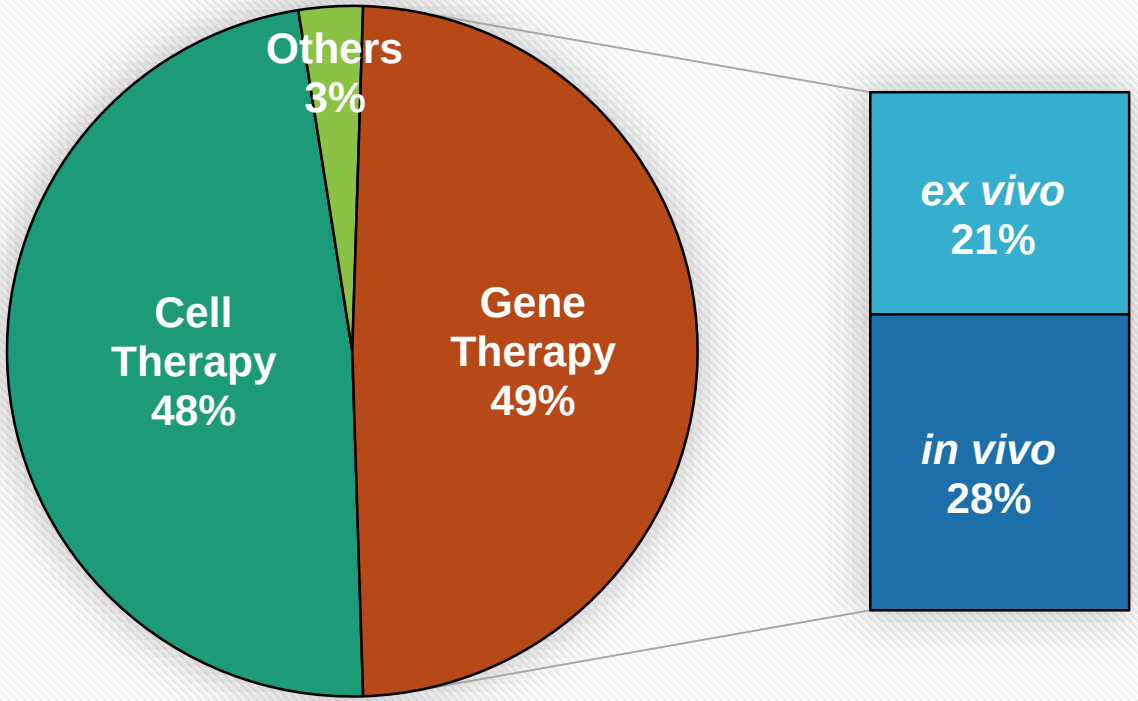
Regulation of Regenerative Medicine and Gene Therapy in Japan

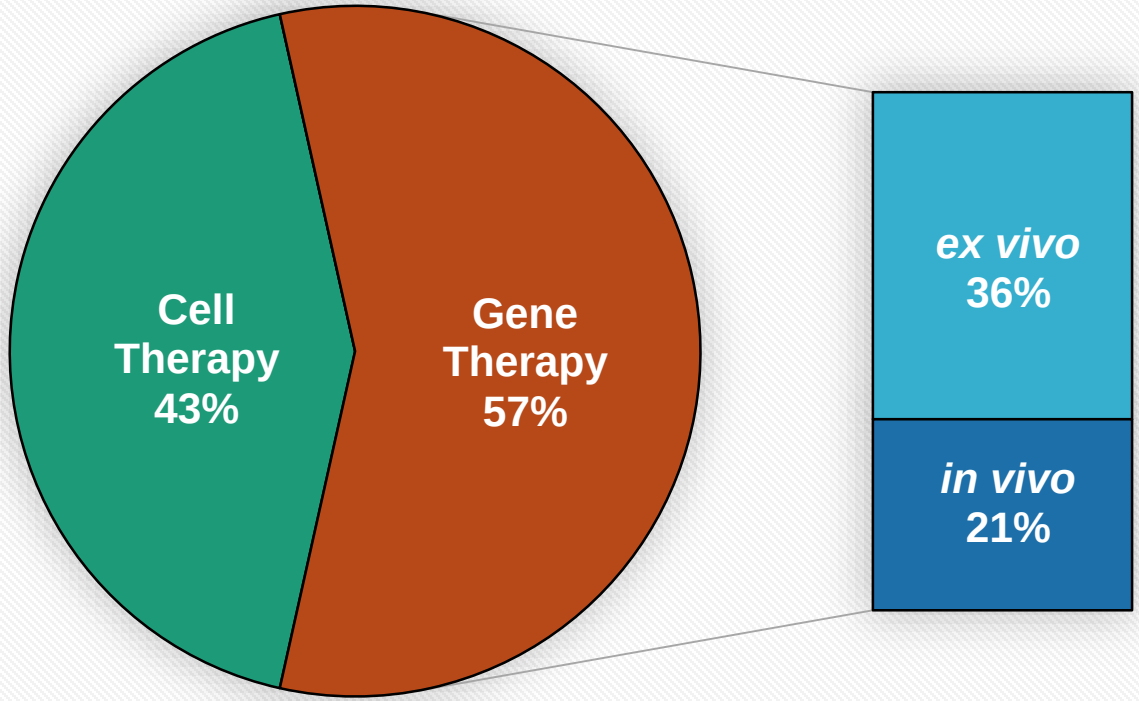


Regulation of Regenerative Medicine and Gene Therapy in Japan

		Product Types	Clinical Research	Products for Marketing
Regenerative Medicine		**Cells and Tissue** ➢ Muscles derived from iPS cells ➢ Mesenchymal Stem Cells	The Act on the Safety of Regenerative Medicine	PMD Act (The Act on Pharmaceuticals and Medical Devices) Cellular and Tissue-based Products
	Gene Therapies	***ex vivo* Gene Therapies** ➢ CAR-T cells ➢ Engineered cells by CRISPR-Cas9		
		***in vivo* Gene Therapies** ➢ Virus-based vector ➢ Oncolytic viruses ➢ Plasmid DNA, mRNA	Clinical Trial Act	Gene Therapeutic Products

The numbers of PMDA consultations and INDs related to gene therapies in Japan





Industry Sponsored Clinical Trials for Gene therapies in Japan

***ex vivo* Gene Therapy (CAR/TCR-T)**		**Condition/Disease**	**Sponsor**
CTL019	CD19-CAR-T cells	FL, NHL, Lymphoblastic Leukemia	Novartis Pharmaceuticals
TBI-1501	CD19-CAR-T cells	Lymphoblastic Leukemia, Acute Adult	Takara Bio Inc.
JCAR017	CD19-CAR-T cells	Lymphoma, Non-Hodgkin	Celgene
KTE-C19	CD19-CAR-T cells	DLBCL, PMBCL, TFL	DAIICHI SANKYO Co.,Ltd.
UCART19	Universal CD19-CAR-T cells	B-ALL	Servier
JNJ-68284528	anti-BCMA CAR-T cells	Multiple Myeloma	Janssen
bb2121	anti-BCMA CAR-T cells	Multiple Myeloma	Celgene
TBI-1301	TCR-T cells	Synovial sarcoma	Takara Bio Inc.

***in vivo* Gene Therapy**		**Condition/Disease**	**Sponsor**
PF-06838435	AAV-vector	Haemophilia B	Pfizer
Ad-SGE-REIC	Oncolytic virus (AdV-vector)	Malignant pleural mesothelioma	Kyorin Pharmaceutical
OBP-301	Oncolytic virus (AdV-vector)	Solid tumor, Esophageal carcinoma, Esophageal cancer	Chugai Pharmaceutical
TBI-1401	Oncolytic virus (attenuated HSV)	Solid tumors with superficial lesions	Takara Bio Inc.

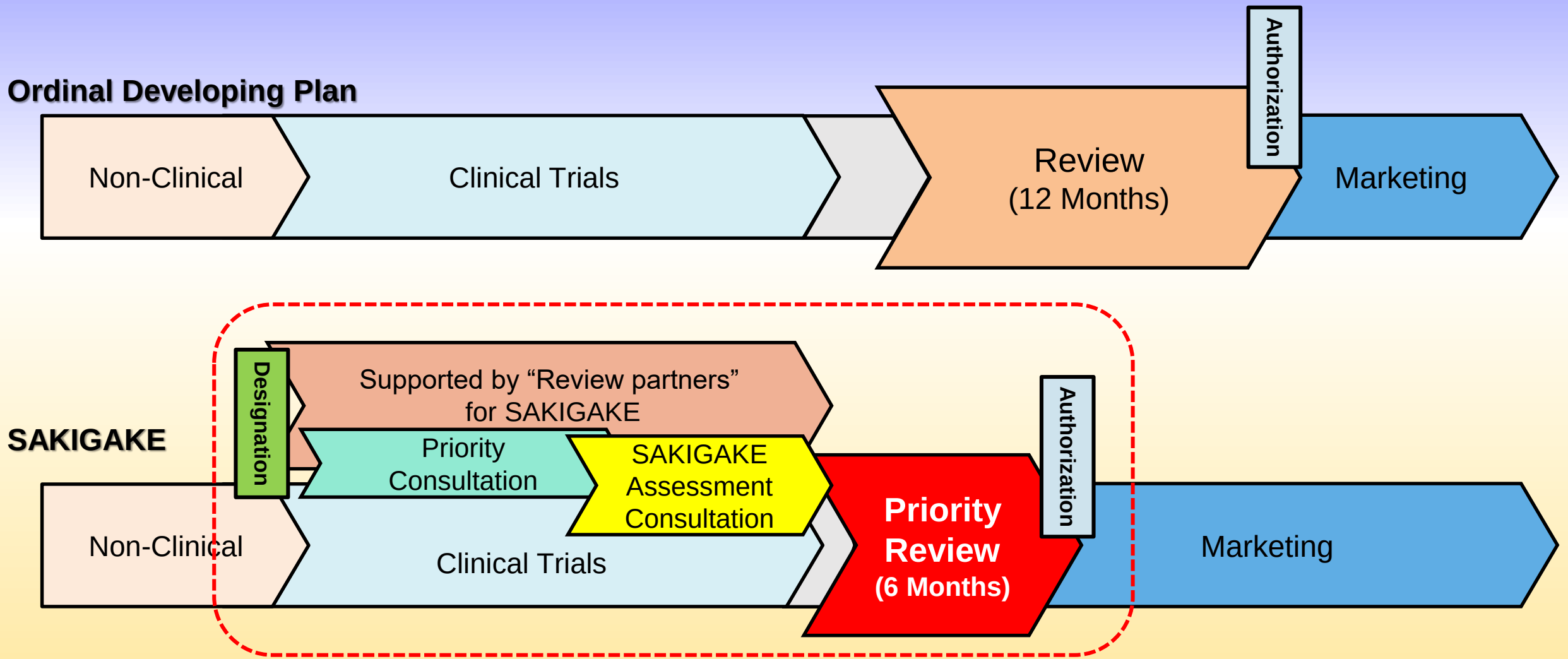
Source; NIPH Clinical Trials Research, ClinicalTrials.gov

Accelerated approval for regenerative medical products and gene therapeutic products in Japan

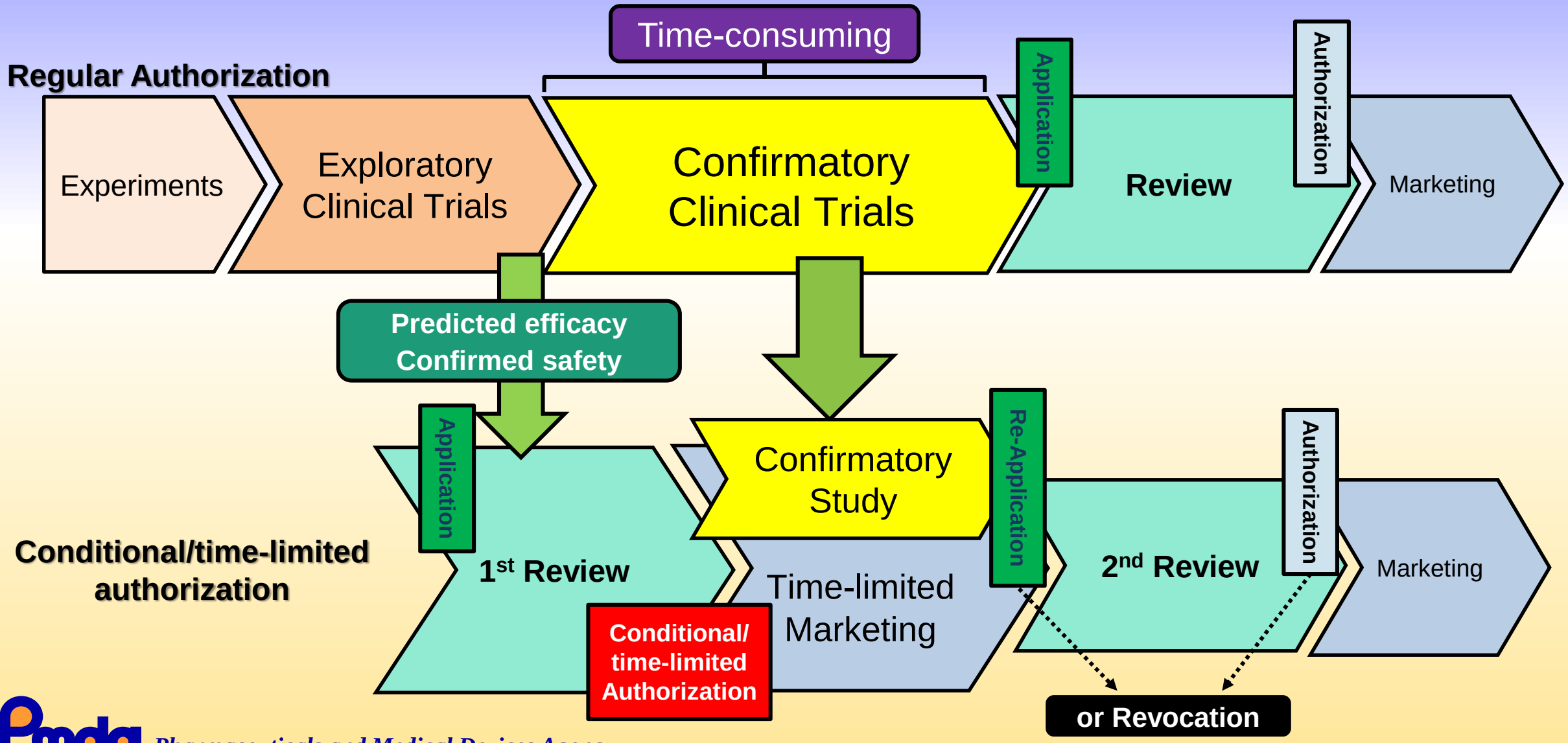
Evolving Early Access Schemes

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	**PRIME (Priority Medicines) Initiative** • Early access 'development support' tool, supporting patient access to innovative medicines by fostering development of therapies with **high public health potential** • Eligibility based on accelerated assessment criteria; unmet medical need based on early clinical data (or potentially compelling non-clinical and tolerability data for academic/ SME applicants)
FDA U.S. FOOD & DRUG ADMINISTRATION	**21st Century Cures Act includes creation of the Regenerative Medicine Advanced Therapy (RMAT) Designation** • Development towards securing an expedited approval (priority review, accelerated approval) • Organisational commitment from the FDA (including senior staff) and frequent meetings • Builds on Breakthrough Designation at FDA
pmda	• SAKIGAKE Designation System • PMD Act – Conditional & Time-Limited Authorization

SAKIGAKE Designation System



Conditional and Time-Limited Authorization



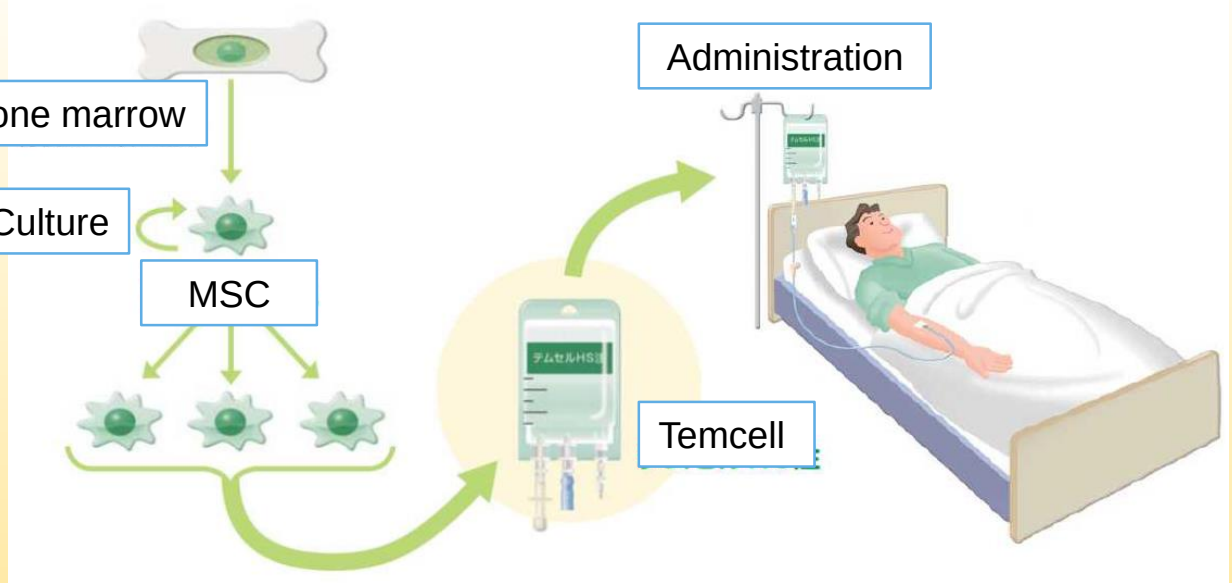
Approved regenerative medical products and gene therapeutic products in Japan

Approved Cellular and tissue-based products (Autologous cell sheet and tissue)

Brand Name	Product Type	Approval Date	Summary of indication
JACE	Human (autologous) epidermis-derived cell sheet	Oct. 29, 2007	(2007) Severe burns (2016) Giant congenital melanocytic nevi (2018) Epidermolysis bullosa
JACC	Human (autologous) cultured cartilage	Jul. 27, 2012	Traumatic cartilage defect or osteochondritis dissecans of the knee
Nepic	Human (autologous) corneal limbus-derived corneal epithelial cell sheet	Mar. 19, 2020	Limbal stem cell deficiency
オキュラル (English Brand Name has not been available yet.)	Human (autologous) oral mucosa-derived corneal epithelial cell sheet	Jun. 11, 2021	Limbal stem cell deficiency
HeartSheet	Human (autologous) skeletal myoblast-derived cell sheet	Sep. 18, 2015 **Conditional/Time-limited**	Severe Heart Failure

Approved Cellular and tissue-based products (Mesenchymal Stem Cells: MSCs)

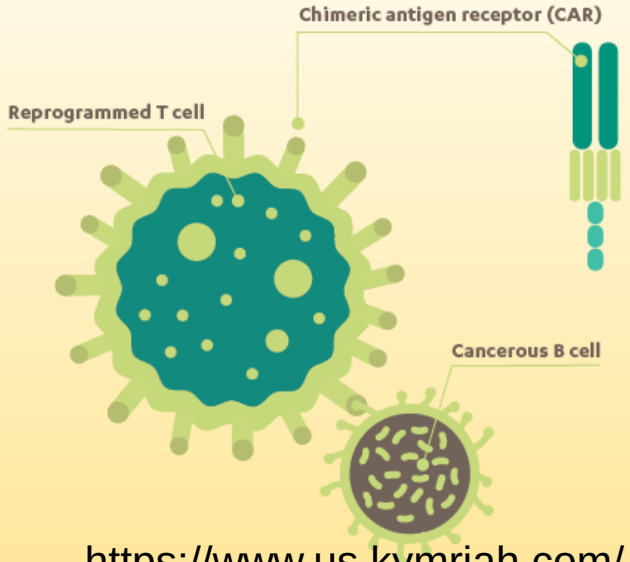
Brand Name	Product Type	Approval Date	Summary of indication
Temcell	Human (autologous) bone marrow-derived MSC	Sep. 18, 2015	Acute graft versus host disease
Stemirac	Human (autologous) bone marrow-derived MSC	Dec. 28, 2018 **Conditional/Time-limited**	Neurological symptoms and functional disorders associated with spinal cord injury



http://www.mhlw.go.jp/stf/shingi2/0000104129.html

Approved Cellular and tissue-based products (*ex vivo* gene therapy, CAR-T Cells)

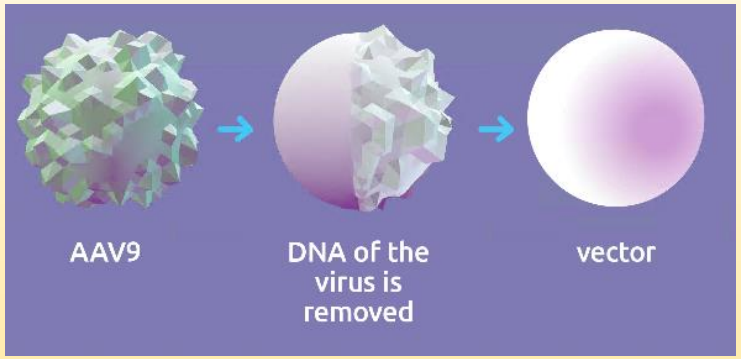
Brand Name	Product Type	Approval Date	Summary of indication
Kymriah	CD19-CAR-T cell	Mar. 26, 2019	B-cell acute lymphoblastic leukemia Diffuse large B-cell lymphoma
Yescarta	CD19-CAR-T cell	Jan. 22, 2021	Diffuse large B-cell lymphoma
Breyanzi	CD19-CAR-T cell	Mar. 22, 2021	Diffuse large B-cell lymphoma Follicular lymphoma

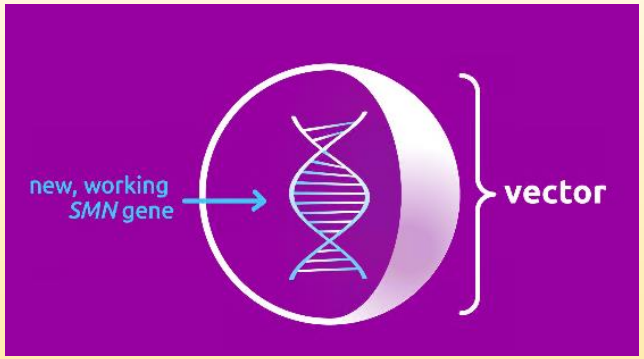


https://www.us.kymriah.com/

Approved gene therapeutic products (*in vivo* gene therapy)

Brand Name	Product Type	Approval Date	Summary of indication
Collategene	Plasmid	Mar. 26, 2019 **Conditional/Time-limited**	Chronic arterial occlusive disease
ZOLGENSMA	AAV9-based vector	Mar. 19, 2020	Spinal Muscular Atrophy
Delytact	HSV-1-based oncolytic virus	Jun. 11, 2021 **Conditional/Time-limited**	Malignant Glioma





Ref Zolgensma.com.

Cartagena act

As environmental risk assessment

Significance of Cartagena Act's Scheme

Type	How to use	Points for review	Examples
Type-1 (Approval)	Deliberate release The Use of LMO without preventive measures against their dispersal into environment	Environmental Risk Assessment + Risk Assessment for third party	Gene-expression Virus Vector for human use.
Type-2 (Confirmation)	Containment Use The manufacturing, shipping, and transport of LMO while taking preventive measures into environment	Reasonable system according to risks for using of LMO	Use Genetically modified Virus Vector for manufacturing process of gene modified cells.

On April 2019, new consultation menu starts on the appropriateness of application dossier for Regulations on Type I or Type II use.

Activity of CARTAGENA ACT for Medical products