Updates of Regulations & Recent Trends in Regenerative Medical Products in Japan

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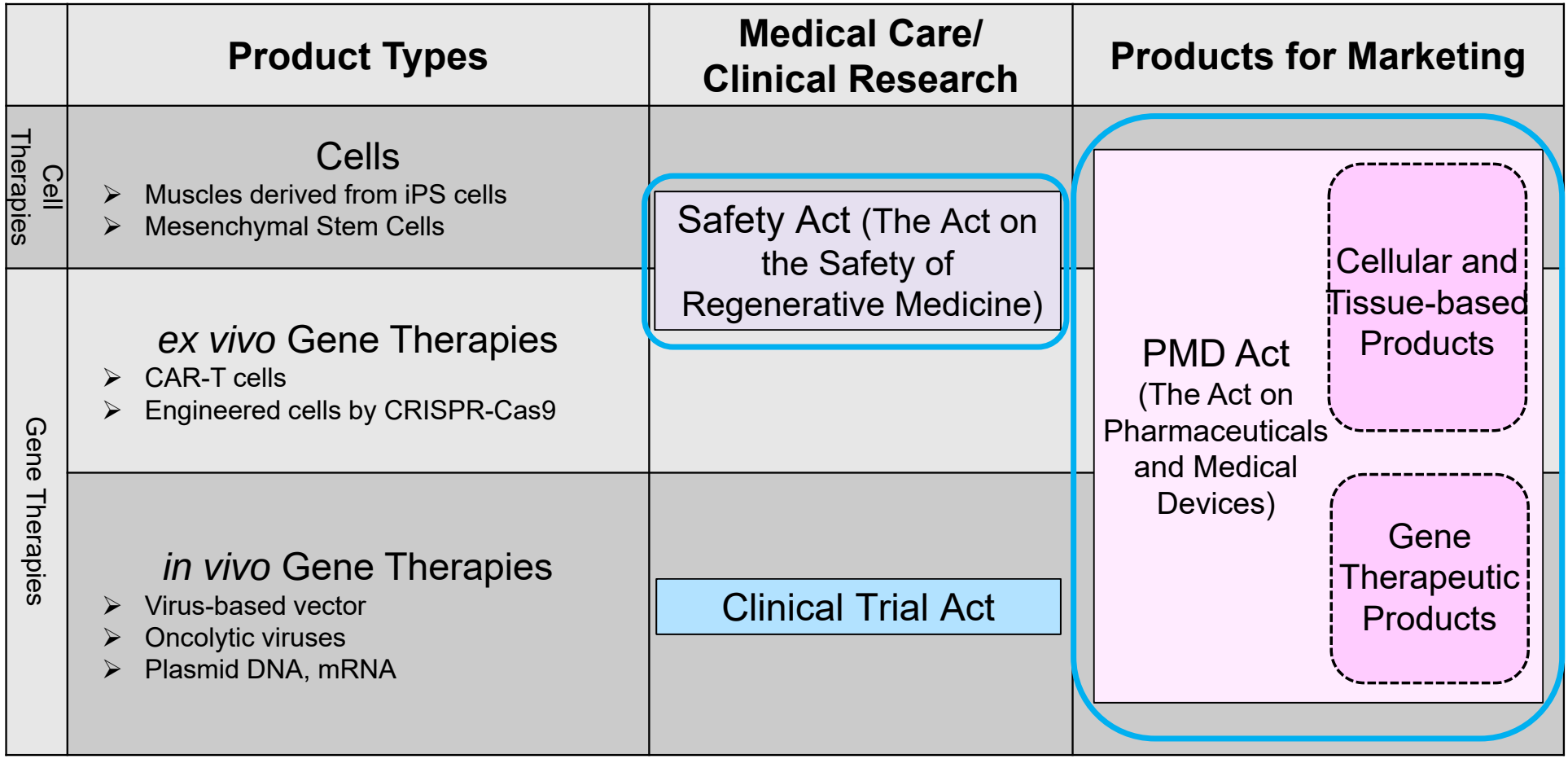
Outline

- Regulations of Regenerative Medicine in Japan
- Regulatory updates and Recent trends of Regenerative Medical Products
  - ✓ Update on Medical Care or Clinical Research under the Act on the Safety of Regenerative Medicine (Safety Act)
  - ✓ Developmental Trends of Regenerative Medical Products under the Pharmaceuticals and Medical Devices Act (PMD Act)
  - ✓ Update on Approved products under the PMD Act

Regulations of Regenerative Medicine in Japan

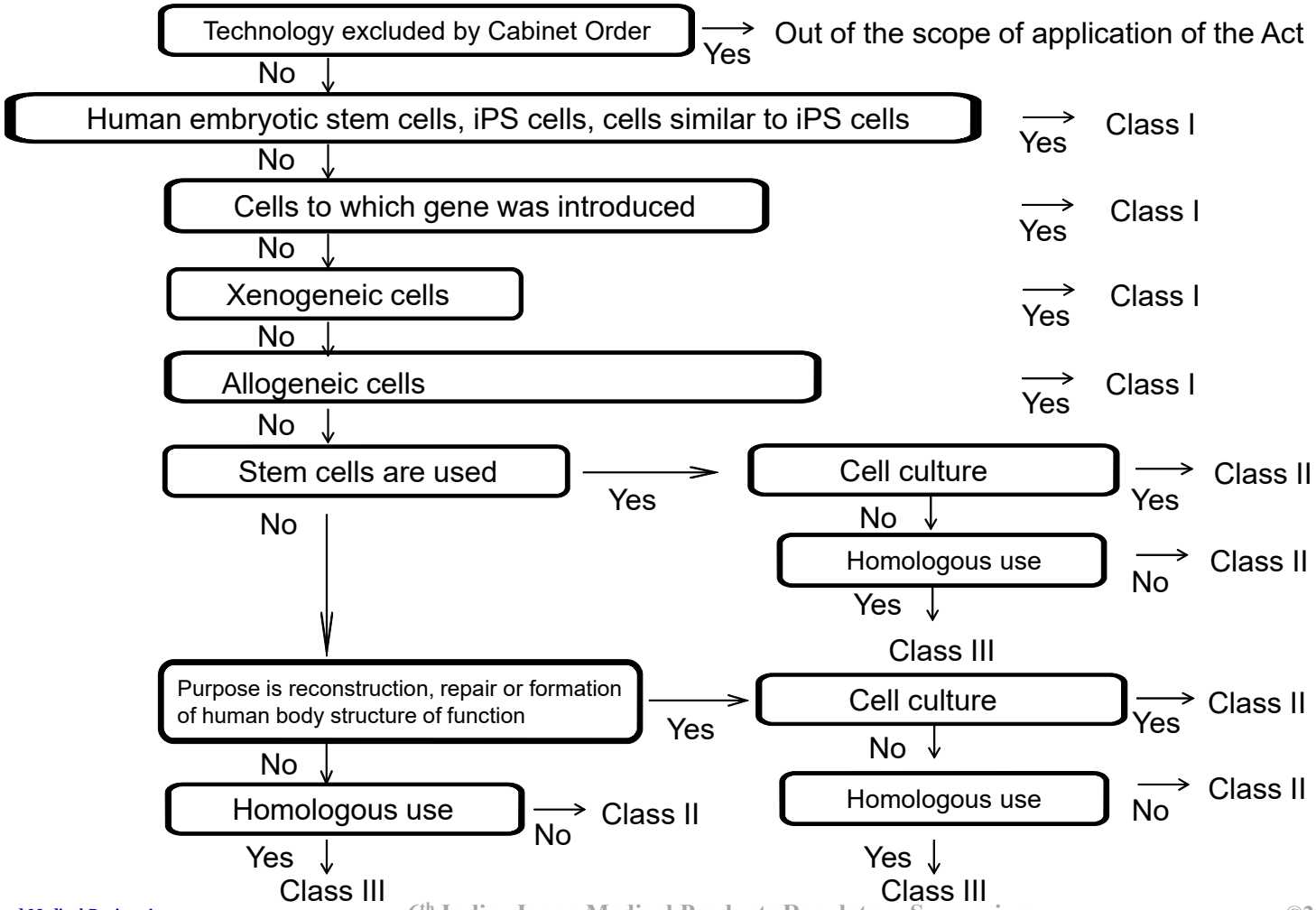


Enacted in 2014

Update on Medical Care or Clinical Research

Under The Safety Act

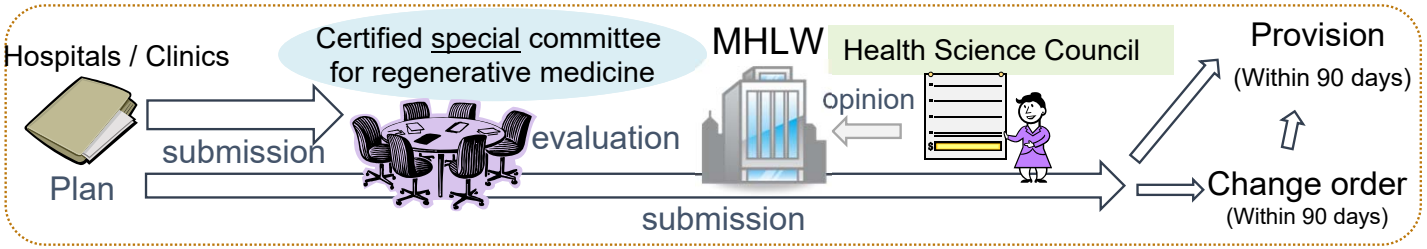
Risk Classification of Regenerative Medical Technology



Rules for Hospitals and Clinics in Safety Act

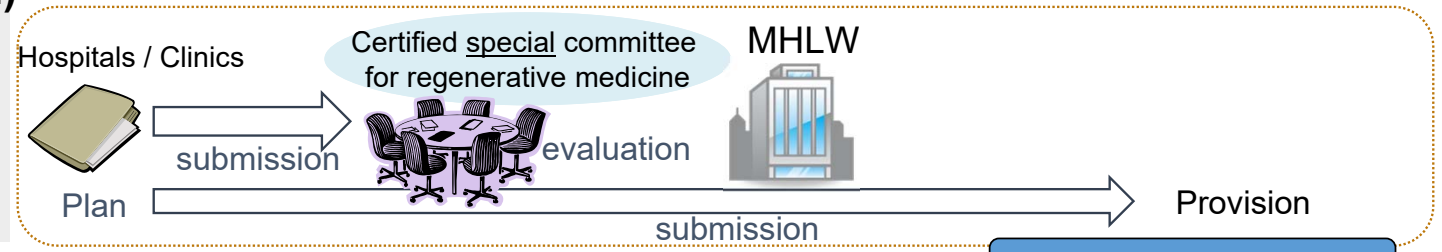
High Risk (class I)

iPS cells, ex vivo therapy,
Allogenic cells, etc.



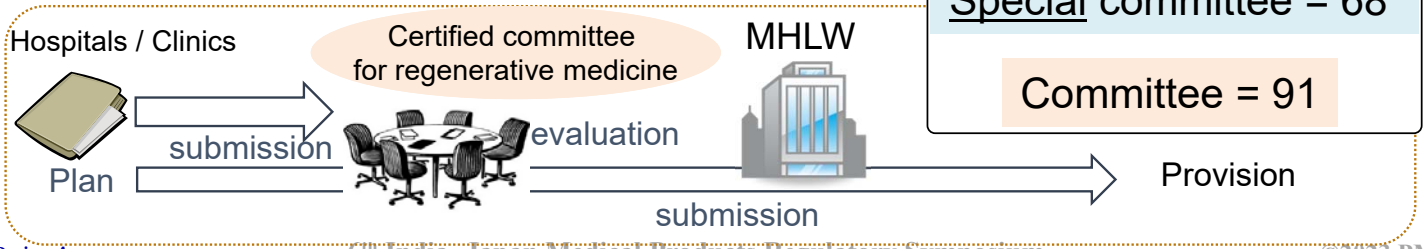
Middle Risk (class II)

(Non class I therapy)
Cell culture,
Non homologous use, etc.



Low Risk (class III)

(Non class I & II therapy)
Non cell culture,
Homologous use.



(As of 30 Nov 2022)

Current status

Plans (4,948)

	Medical care	Clinical research
High Risk (class I)	7	17
Middle Risk (class II)	1,224	43
Low Risk (class III)	3,717	44

Current status

Special committee = 68

Committee = 91

Developmental Trends of Regenerative Medical Products

Under The PMD Act

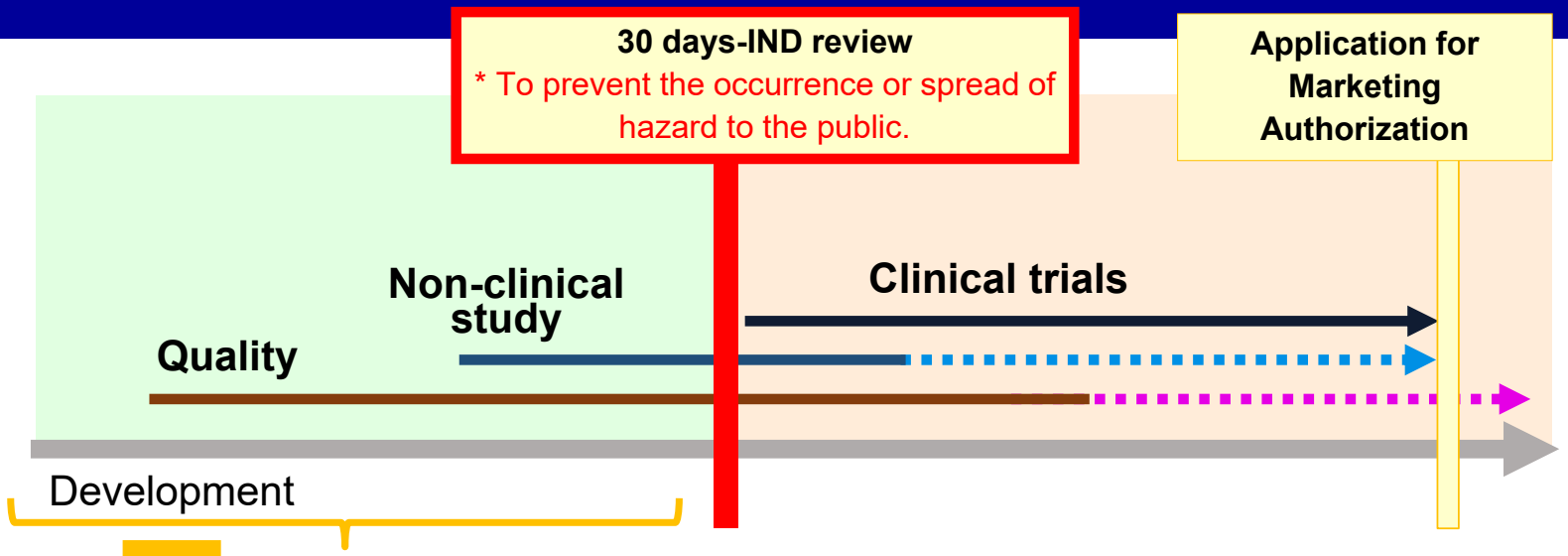
Regulatory Science Strategy Consultations (R&D)

PMDA has been offering Regulatory Science Strategy Consultations (R&D) mainly to universities, research institutions, and venture companies that have promising seed-stage resources to provide guidance and advice concerning studies and clinical trials that are necessary at the initial stage of clinical development.

Basic Research → **Practical Use**

	Quality Study / Non-Clinical Study	Clinical Trial
User fees (per consultation)	1,541,600 yen	874,000 yen
・Universities/Research institutions ・Venture companies (meeting requirements specified separately)	**154,160 yen**	**87,400 yen**

Regulatory Science Strategy Consultations (R&D)

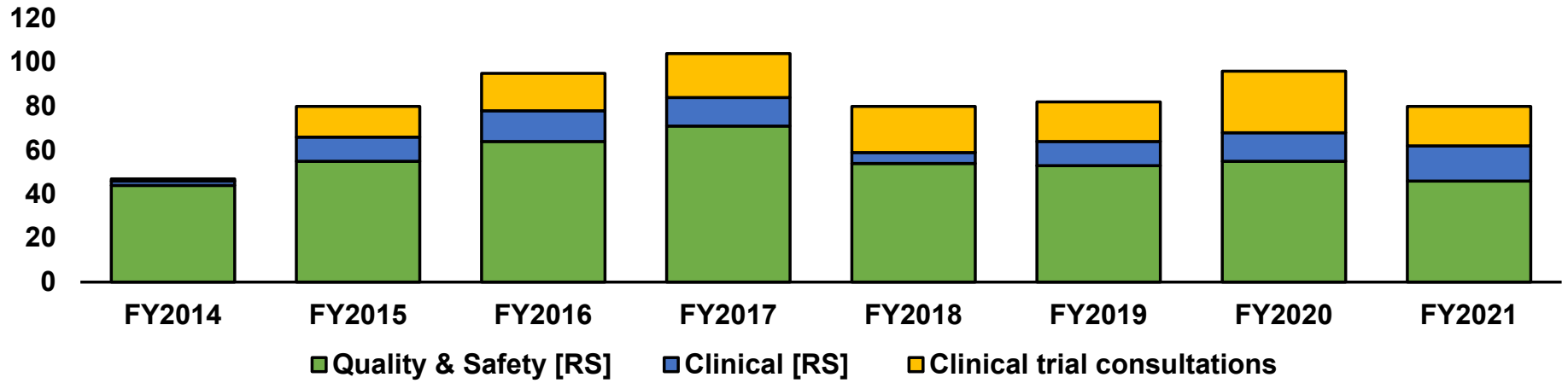


Regulatory Science Strategy Consultations (R&D)

- **Consultations on quality and pre-clinical safety**
- **Consultations on clinical trials (up to POC studies)**

To complete IND review in 30 days, these issues have to be resolved in consultations in advance.

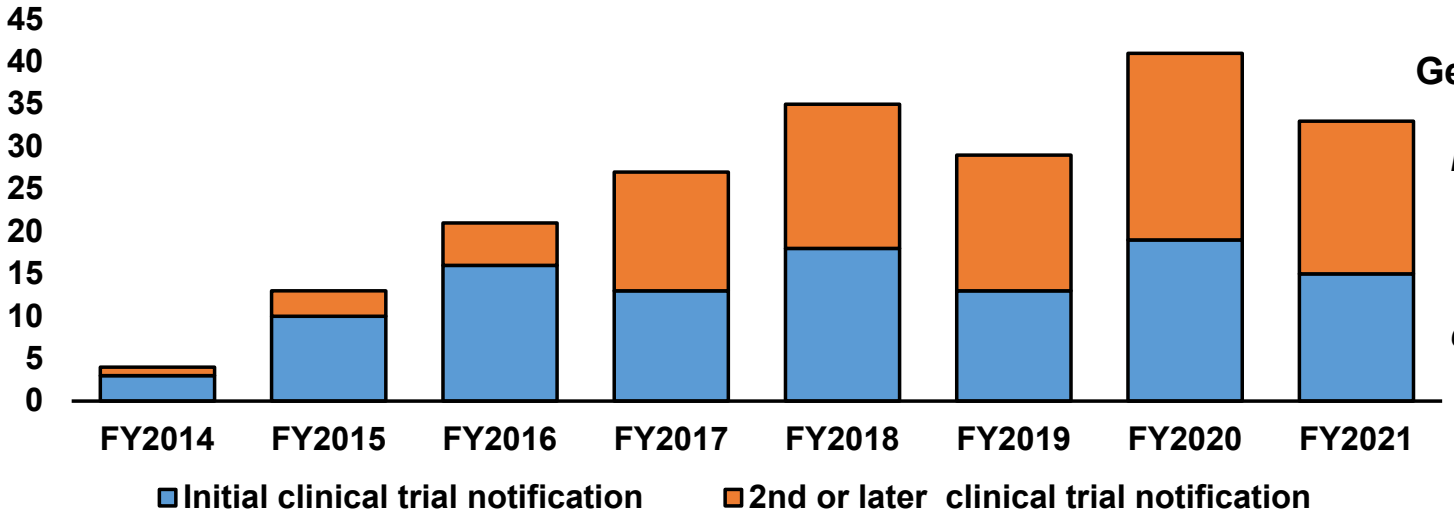
Number of consultations for regenerative medical products

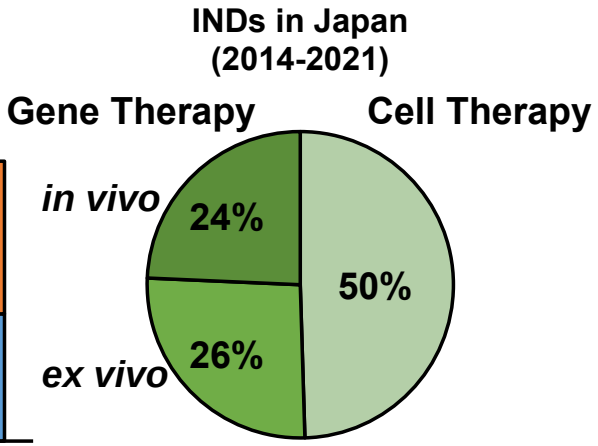


	FY2014	FY2015	FY2016	FY2017	FY2018	FY2019	FY2020	FY2021
RS consultations total	46	66	78	84	59	64	68	62
Quality & Safety	18[44]	29[55]	26[64]	29[71]	25[54]	29[53]	25[55]	25[46]
Clinical	2	11	14	13	5	11	13	16
Clinical trial consultations	1	14	17	20	21	18	28	18

This consultation category includes consultations conducted as Pharmaceutical Affairs Consultation on R&D strategy on and before November 24, 2014.
Some consultations were divided into multiple sessions over several days to confirm the quality and safety of the relevant products before submission of clinical trial notifications. The tables in brackets indicate the total number of these sessions.

Number of clinical trial notifications for regenerative medical products





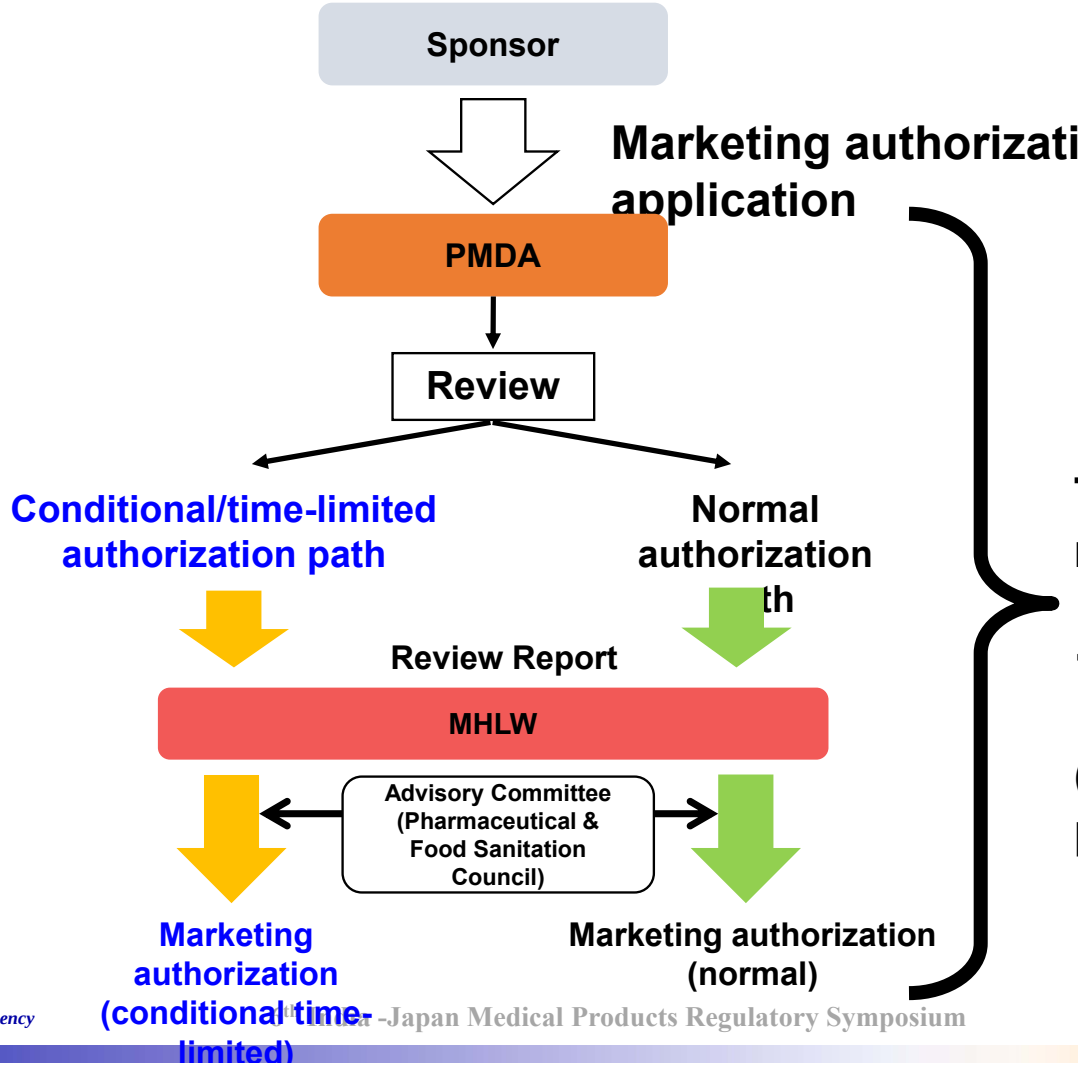
	FY2014	FY2015	FY2016	FY2017	FY2018	FY2019	FY2020	FY2021	**Total**
Initial clinical trial notification	3 [1]	10 [2]	16 [7]	13 [8]	18 [8]	13 [7]	19 [9]	15 [7]	**107 [49]**
2nd or later clinical trial notification	1 [1]	3 [2]	5 [0]	14 [10]	17 [3]	16 [7]	22 [5]	18 [9]	**96 [37]**
Protocol change notification	2	19	52	93	151	206	215	278	**1016**

The table in brackets in parentheses indicate the number of notifications of investigator-initiated clinical trials.
The number within brackets is included in the number outside the bracket.

Update on Approved Regenerative Medical Products

Under The PMD Act

Review Pathway of Regenerative Medical Products



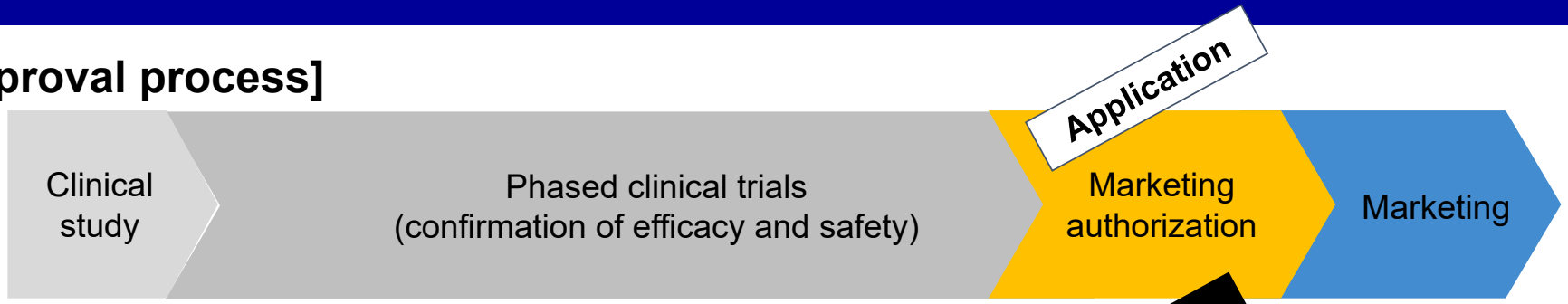
Target Review time for reviewers:

12 months

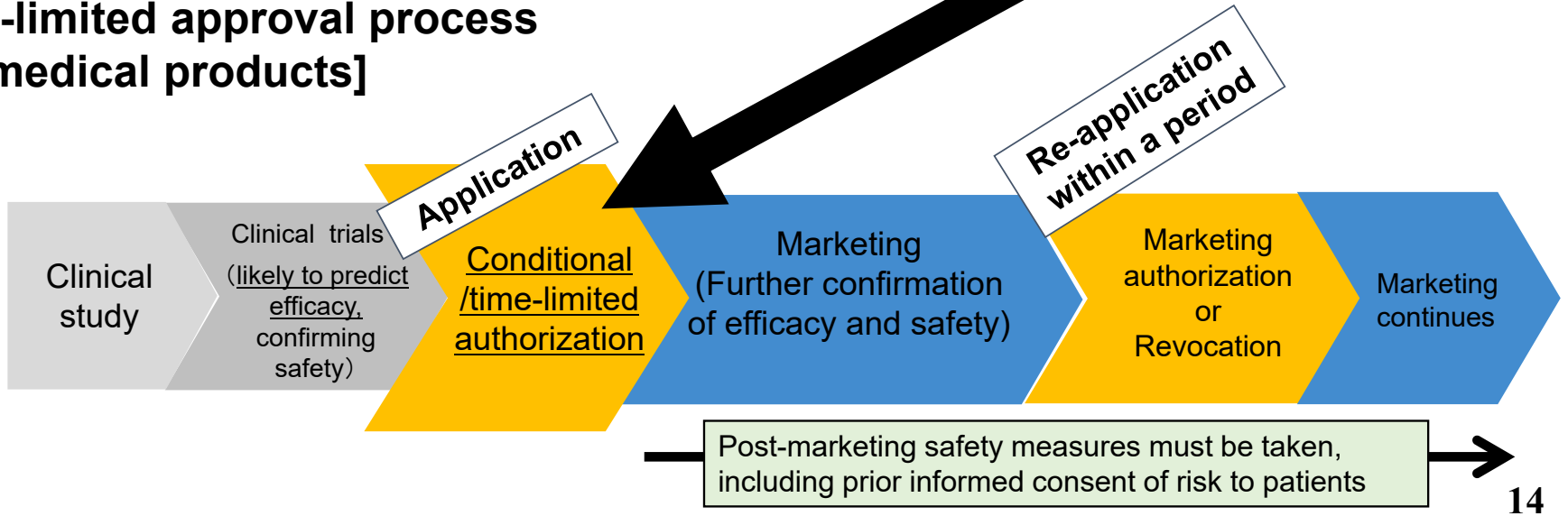
(For Orphan Designation products : 9 months)

Conditional/time-limited approval process

[Conventional approval process]



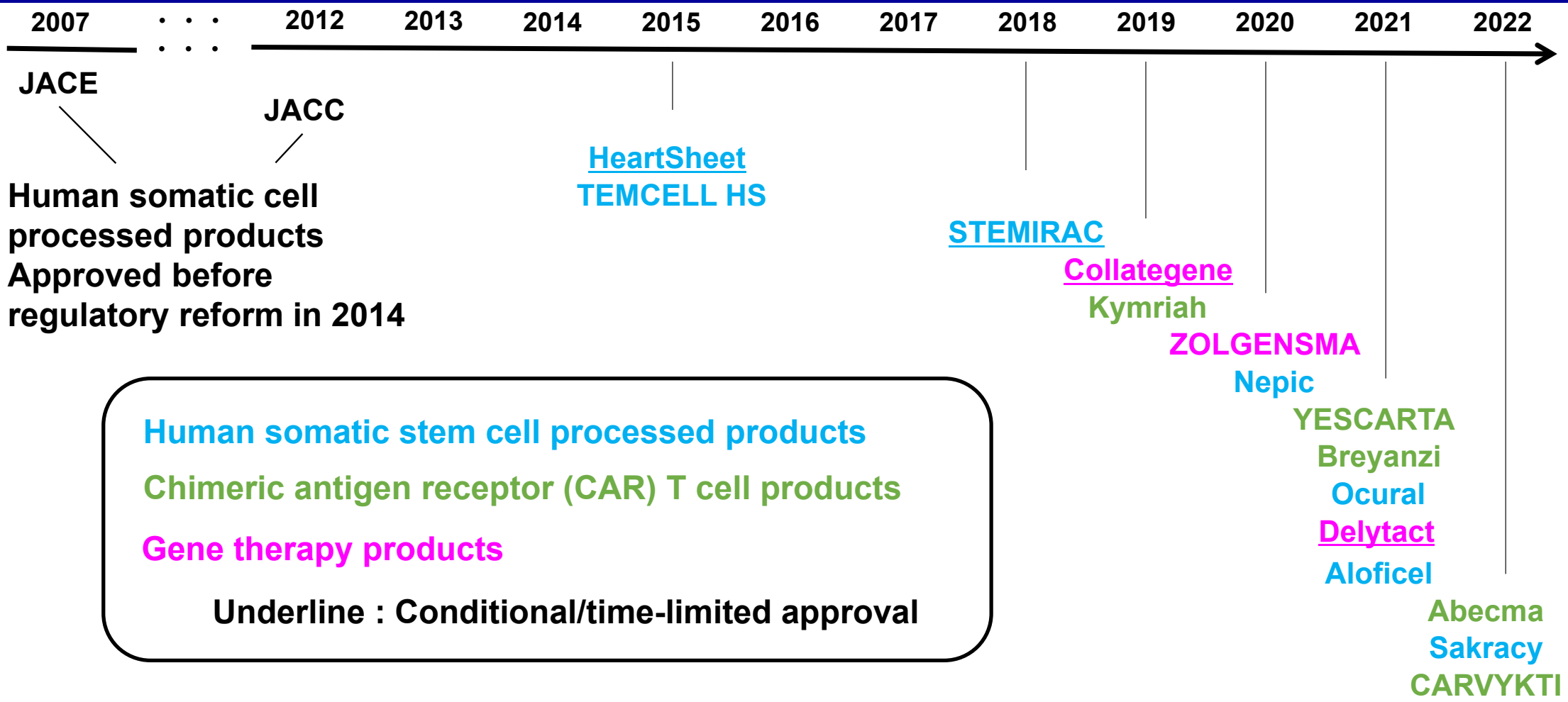
[Conditional/time-limited approval process for regenerative medical products]



Approved Regenerative Medical Products in Japan As of Dec 2022

Brand Name	Non-proprietary Name	Applicant Company	Approval Date	Additional Indications Approval Date
JACE	Human (autologous) epidermal cell sheet	Japan Tissue Engineering Co., Ltd.	Oct. 29, 2007	Sep. 29, 2016、Dec. 28, 2018
JACC	Human autologous tissue for transplantation	Japan Tissue Engineering Co., Ltd.	Jul. 27 , 2012	
HeartSheet	Human (autologous) skeletal myoblast-derived cell sheet	Terumo Corporation	Sep. 18 , 2015	
TEMCELL HS	Human (allogeneic) bone marrow-derived mesenchymal stem cells	JCR Pharmaceuticals Co., Ltd.	Sep. 18 , 2015	
STEMIRAC	Human（autologous) bone marrow-derived mesenchymal stem cell	Nipro Corporation	Dec. 28 , 2018	
Collategene	Beperminogene perplasmid	AnGes, Inc.	Mar. 26 , 2019	
Kymriah	tisagenlecleucel	Novartis Pharma K.K.	Mar. 26, 2019	Aug. 26, 2022
ZOLGENSMA	onasemnogene abeparvovec	Novartis Pharma K.K.	Mar. 19, 2020	
Nepic	human (autologous) corneal limbus-derived corneal epithelial cell sheet	Japan Tissue Engineering Co., Ltd.	Mar. 19, 2020	
YESCARTA	Axicabtagene ciloleucel	Daiichi Sankyo Company, Limited	Jan. 22, 2021	Dec. 20, 2022
Breyanzi	lisocabtagene maraleucel	Celgene Corporation	Mar. 22, 2021	Dec. 20, 2022
Ocural	human（autologous) oral mucosa-derived epithelial cell sheet	Japan Tissue Engineering Co., Ltd.	Jun. 11, 2021	
Delytact	Teserpaturev	Daiichi Sankyo Company, Limited	Jun. 11, 2021	
Alofisel	Darvadstrocel	Takeda Pharmaceutical Company Limited	Sep. 27, 2021	
Abecma	idecabtagene vicleucel	Bristol-Myers Squibb K.K.	Jan. 20, 2022	
Sakracy	human (autologous) oral mucosa-derived epithelial cell sheet using human amniotic membrane substrate	Hirosaki LI, Inc.	Jan. 20, 2022	
CARVYKTI	ciltacabtagene autoleucel	Janssen Pharmaceutical K.K.	Sep. 26, 2022	

Approved Regenerative Medical Products in Japan As of Dec 2022



Human somatic stem cell processed products

Chimeric antigen receptor (CAR) T cell products

Gene therapy products

Underline : Conditional/time-limited approval

Update on Approved Products

idecabtagene vicleucel：**ABECMA**
（Bristol-Myers Squibb K.K.）

ciltacabtagene autoleucel：**CARVYKTI**
（Janssen Pharmaceutical K.K.）

BCMA-directed genetically modified autologous T-cell immunotherapy（CAR-T cell therapy）

Indication: Relapsed or refractory multiple myeloma

- **The marketing applications were submitted using data from multi-regional clinical trial including Japanese patients**

- **Optical Clinical Use Guidelines**

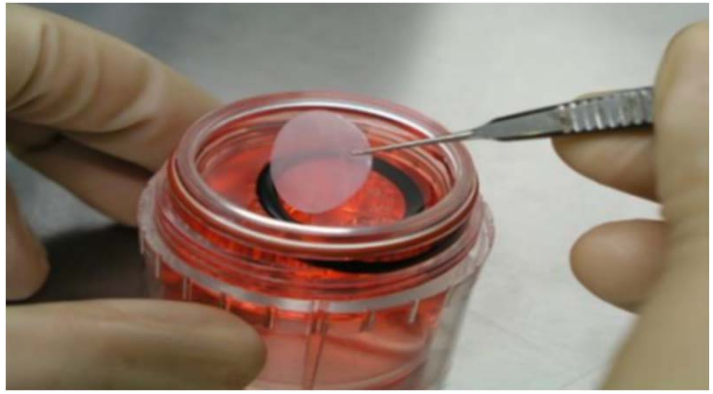
Typically includes:
(1) Introduction
(2) Characteristics and action mechanisms of the drugs
(3) Clinical data
(4) Requirements for medical institutions
(5) Eligibility criteria of patients
(6) Points to consider for administration

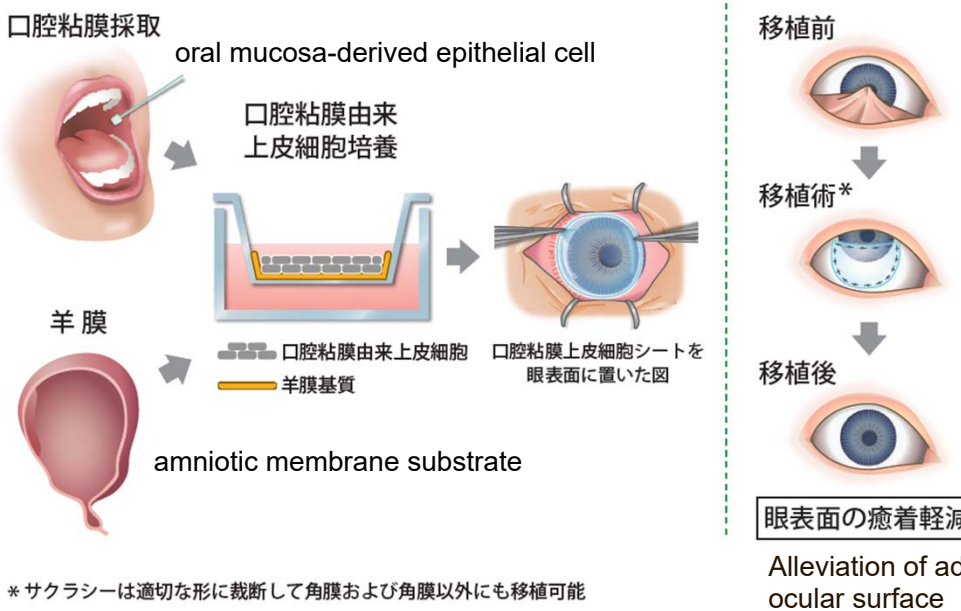
Update on Approved Products

human (autologous) oral mucosa-derived epithelial cell sheet using human amniotic membrane substrate：**Sakracy（Hirosaki LI, Inc.）**

Indication: Alleviation of adhesions on the ocular surface in Limbal Stem Cell Deficiency

The marketing applications were submitted using data from the investigator-initiated study.





Alleviation of adhesions on the ocular surface

Modified from http://www.hirosaki-li.co.jp/products_sakracy.html

Summary

- **Research and development of Regenerative Medical Products for practical use is very active.**

  global : CAR-T, gene therapy, etc.

  in Japan : tissue engineering products (eye, skin, cartilage), etc.

- **17 regenerative medical products has been approved in Japan, 3 of which has been approved in 2022.**
- **We continue to provide the effective advices and strategies to enhance the development of Regenerative Medical Products.**