Streamline
Your Gene Therapy Product Development with PMDA

Shinichi NODA, Ph.D.

Deputy Review Director, Office of Cellular and Tissue-based Products,

Pharmaceuticals and Medical Devices Agency (PMDA), JAPAN

OUTLINE

1. **Regulations of Regenerative Medicine in JAPAN**
2. **Strategy to facilitate and streamline development of Regenerative Medical Products***
3. **Review Experience of Regenerative Medical Products***

*Regenerative Medical Products = Cell and Gene therapy Products

Approved Regenerative Medical Products in JAPAN

20 products

Regulatory Reform for Regenerative Medicine in JAPAN

These two acts were promulgated in November 2013 by the Japanese Diet (Parliament) in line with the **Regenerative Medicine Promotion Act**, in order to reform the pharmaceutical and medical regulation related to regenerative medicine

Safety Act — **The Act on the Safety of Regenerative Medicine**

PMD Act — **Revision of the Pharmaceutical Affaires Law:**
The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act

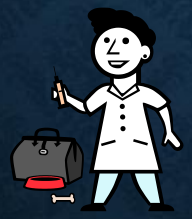
Enacted on 25 November 2014

Two Acts Regulating Regenerative medicine in JAPAN

Regenerative Medicine

Safety Act

- **Medical Care**
- **Academic Research**



All medical **technologies** using processed cells which safety and efficacy have not yet been established

Handled by MHLW

PMD Act

- **Commercial Product**
(Marketing Authorization)

Production and marketing of regenerative and cellular therapeutic **products** by firms

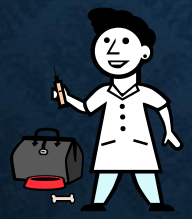
Handled by MHLW & PMDA

Two Acts Regulating Regenerative medicine in JAPAN

Regenerative Medicine

Safety Act

- **Medical Care**
- **Academic Research**



All medical **technologies** using processed cells which safety and efficacy have not yet been established

Handled by MHLW

PMD Act

- **Commercial Product**
(Marketing Authorization)

Production and marketing of regenerative and cellular therapeutic **products** by firms

Handled by MHLW & PMDA

PMD Act

Regenerative Medical Products

Former Law

Drug

Device

Revised Law

Drug

Device

Regenerative Medical Products

- Cellular and Tissue-based Products
- Gene Therapy Products

“Office of Cellular and Tissue-based Products” was established in PMDA

Fast Review By Office Of Cellular And Tissue-based Products

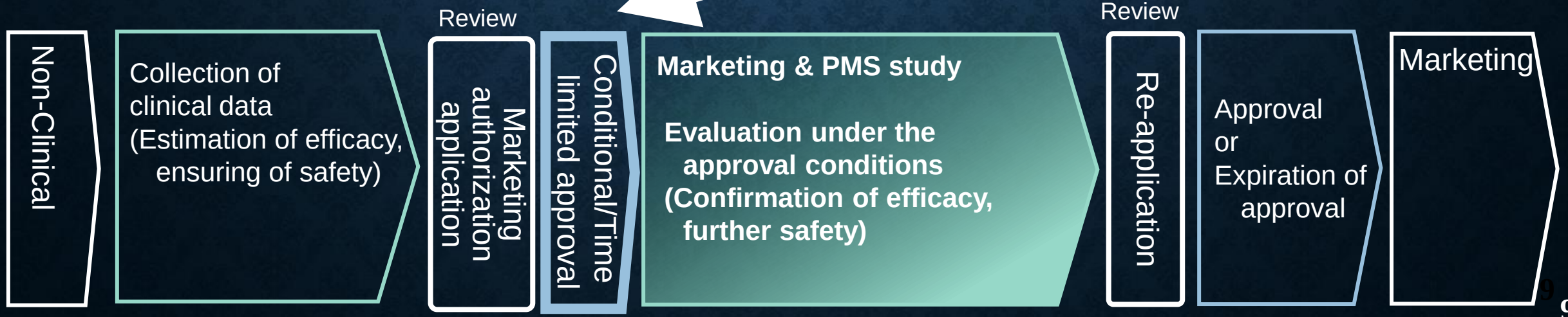
PMD Act

PMD Act

Two market-authorization processes for cell products under PMD Act

[Conventional approval scheme]

[Optional scheme for regenerative medical products]



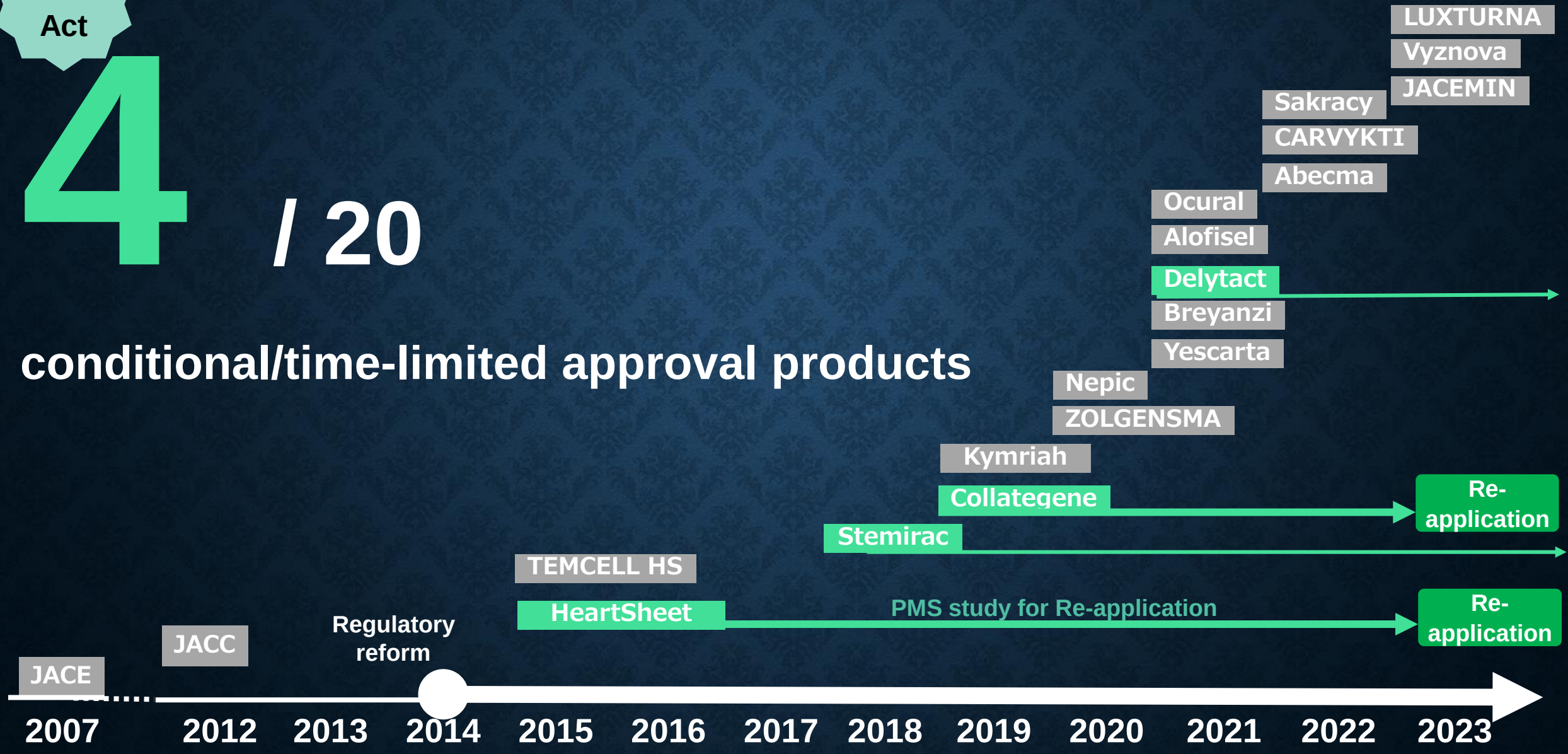
9

Conditional/Time-limited Market-authorization

PMD Act

4 / 20

conditional/time-limited approval products



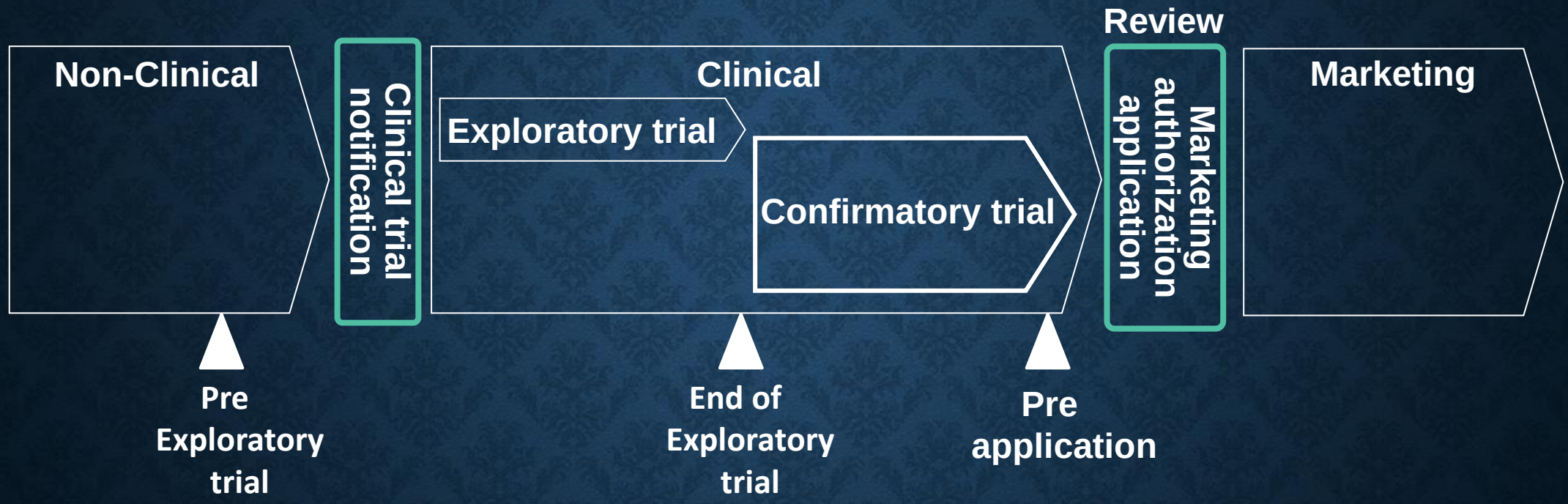
OUTLINE

1. **Regulations of Regenerative Medicine in JAPAN**
2. **Strategy to facilitate and streamline development of Regenerative Medical Products***
3. **Review Experience of Regenerative Medical Products***

*Regenerative Medical Products = Cell and Gene therapy Products

PMD Act

Strategy to Facilitate and Streamline Development of Regenerative Medical Products

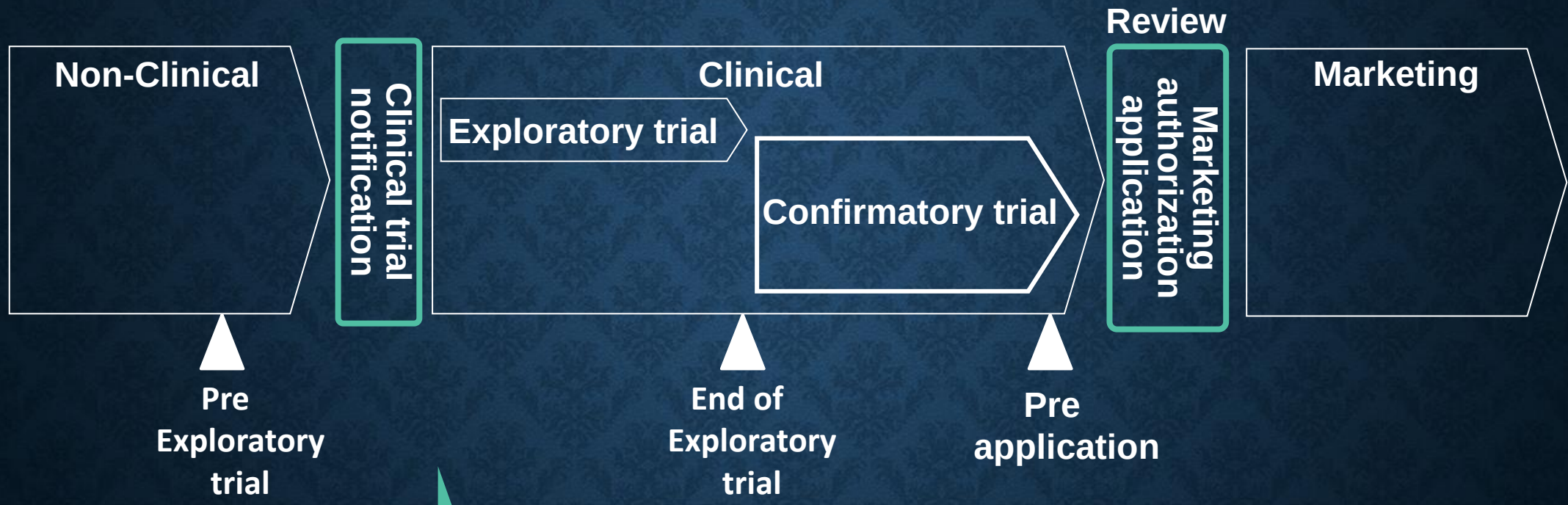


PMDA Consultation

Designation system

PMD Act

PMDA Consultation



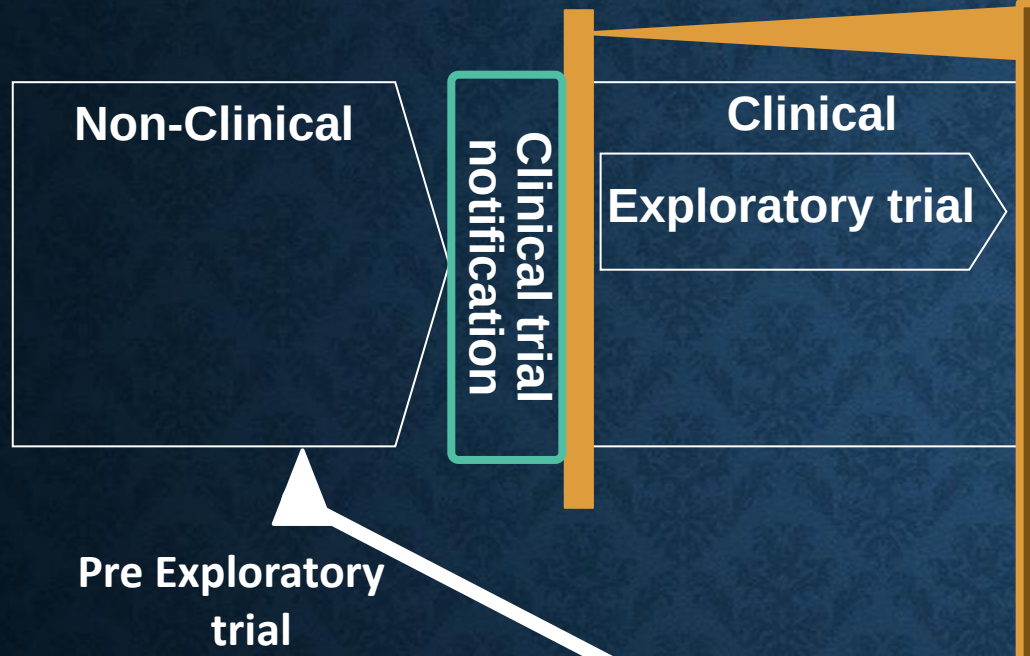
Regulatory Science Strategy Consultation (R&D)

Prior-Assessment Consultation

Merits for applicants

Seek confirmation / advice from PMDA on key development questions

PMDA Consultations (Initial Stage Of Development)



30 days review

* To prevent the occurrence or spread of hazard to the public.

The quality and safety have to be evaluated before starting clinical trials.

- ✓ Regenerative Medical products is a new technology and well-defined methodology has not yet been established
- ✓ Minimize infection risk because virus inactivation on cell products is impossible
- ✓ Cell products may persist in the body for long periods of time

Regulatory Science Strategy Consultation (R&D)

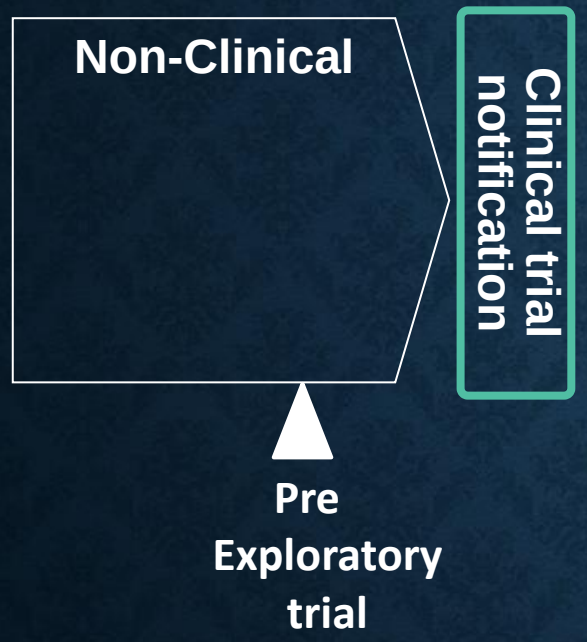
Consultations on

- **Quality and pre-clinical safety**
- **Clinical trials design (up to POC studies)**

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

PMD Act

PMDA Consultation



Regulatory Science Strategy Consultation (R&D)

Providing guidance and advice concerning studies and clinical trials that are necessary at the initial stage of clinical development.

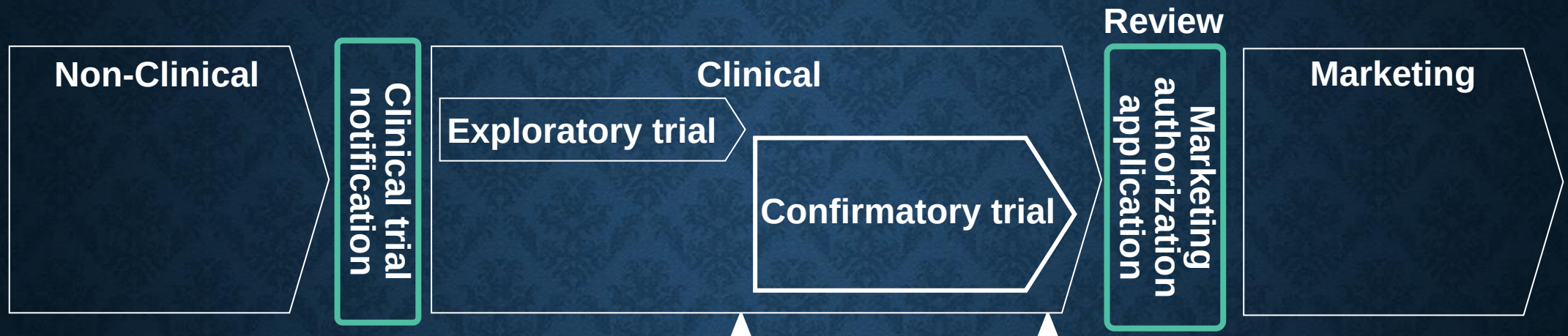
Consultation menu	Quality Study / Non-Clinical Study	Clinical Trial
User fees	1,541,600 yen (10,276 USD)	874,000 yen (5,826 USD)
	▼ 90 % OFF	
・Universities/Research institutions ・Venture companies (meeting requirements specified separately)	154,160 yen (1,027 USD)	87,400 yen (582 USD)

Contact PMDA rs-contact@pmda.go.jp

150 yen = 1 USD

PMD Act

PMDA Consultations (Late Stage Of Development)



Consultations on

Confirmatory trials design

- Selection of subjects
- Selection of Control Group
- Primary efficacy endpoint
- Number of subjects
- Methods to Minimise or Assess Bias, etc.

User fees : 1,687,200 yen
(11,247 USD)

End of Exploratory trial

Pre application

Prior-Assessment Consultation

Consultations on

Sufficiency of evidence in data package for NDA

User fees : 3,684,200 yen
(24,558 USD)

150 yen = 1 USD

PMD Act

PMDA Consultation

Quick Answer

Provision of Official Minutes

Applicant submit consultation questions and materials

Pre-Inquiry

PMDA's Opinion

3 weeks

Applicant's response to PMDA's opinion View

PMDA consultation meeting

5 weeks

The final minutes & the recording is provided to the applicant.

PMD Act

PMDA Consultation

● Pre-consultation meeting (Free) > 365 meetings (2022)

★ PMDA consultation meeting (Charged) : 93 meetings (2022)

Research | Non-Clinical | Clinical trial notification | Clinical (Exploratory trial | Confirmatory trial) | Review (Marketing authorization application) | Marketing

<Model case>

rs-contact@pmda.go.jp

● Providing orientation on overall regulatory system

● → ★ Quality

● Sharing information (Quality)

● Progress report of trial

● Sharing information (Quality)

● Progress report of trial

● Sharing information (Quality)

● → ★ Non-clinical safety

● → ★ Study design (Exploratory trial)

● → ★ Study design (Confirmatory trial)

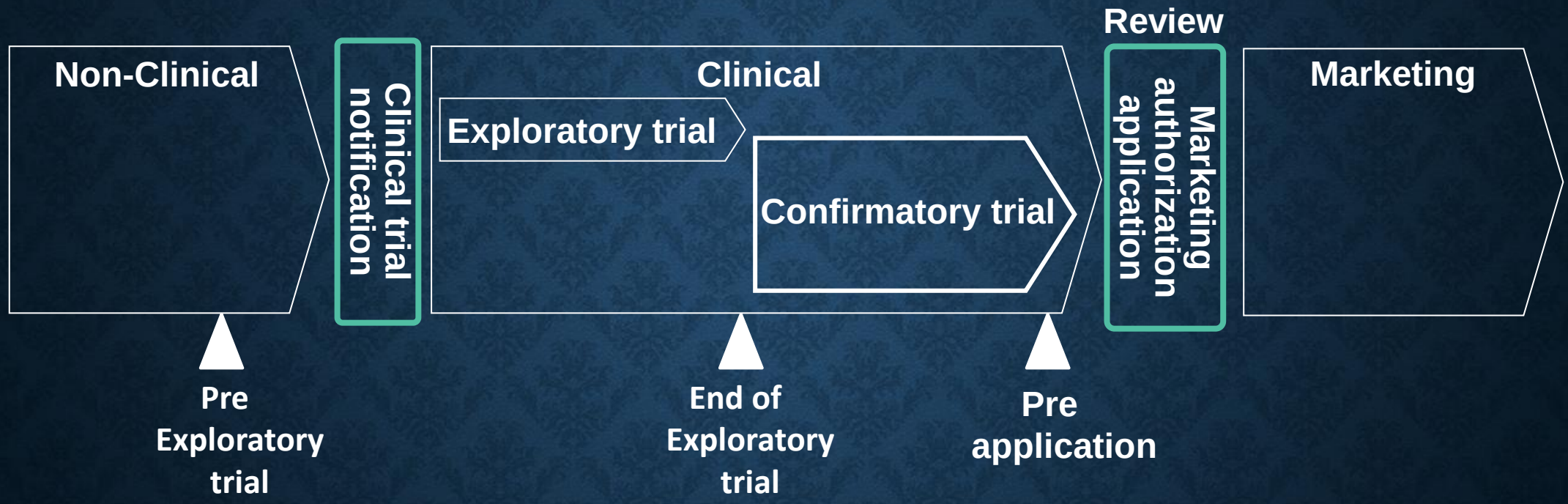
● Follow-up

● → ★ Clinical data package for application

Clarification of discussion points, consultation materials, etc.

PMD Act

Strategy to Facilitate and Streamline Development of Regenerative Medical Products



PMDA Consultation

Designation system

PMD Act

Designation System 1 (Orphan Products)

<Objective>

To promote the R&D of the products for rare diseases to provide the patients with safe and effective products as early as possible

<Criteria for designation>

1. Number of patients (< 50,000 patients in JAPAN)
2. Medical needs (Serious diseases with high medical needs)
3. Feasibility of development

<Incentive>

Promoting R&D

- Grant-in-Aid for R&D of orphan designated drugs (NIBIOHN*)
- Tax deduction for R&D expenses
- Priority scientific consultation (PMDA)
- Priority review (9 months) (PMDA)
- Premium drug pricing
- Extension of re-examination period

* National Institutes of Biomedical Innovation, Health and Nutrition

PMD Act

Designation System 2 (SAKIGAKE (Forerunner) Products)

<Objective> **To put innovative products into medical practice in Japan**

<Criteria for designation>

1. **Innovativeness -** new mode of action (in principle)
2. **Severity of the target disease -** life-threatening or no curative therapies
3. **Prominent efficacy -** no existing therapies or probable significant improvement in efficacy or safety compared to existing therapies
4. **Plan/System -** to submit the Marketing authorization application (MAA) in Japan first or at the same timing (within 3 months) as the first MAA submission to other national regulatory authority

<Incentive>

- **Concierge service offered by senior review partner (PMDA)**
- **Priority scientific advice (PMDA)**
- **Pre-review in consultation (PMDA)**
- **Priority review (6 months)(PMDA)**
- **Premium drug pricing**
- **Extension of re-examination period**

Firstest Practical Use in the world

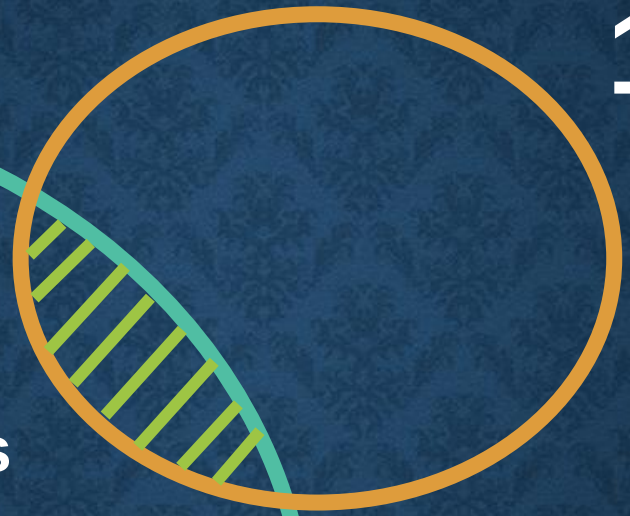
PMD Act

Number of Designated Regenerative Medical Products

12 SAKIGAKE products

5 gene therapy products

7 cell therapy products



30 Orphan products

15 gene therapy products

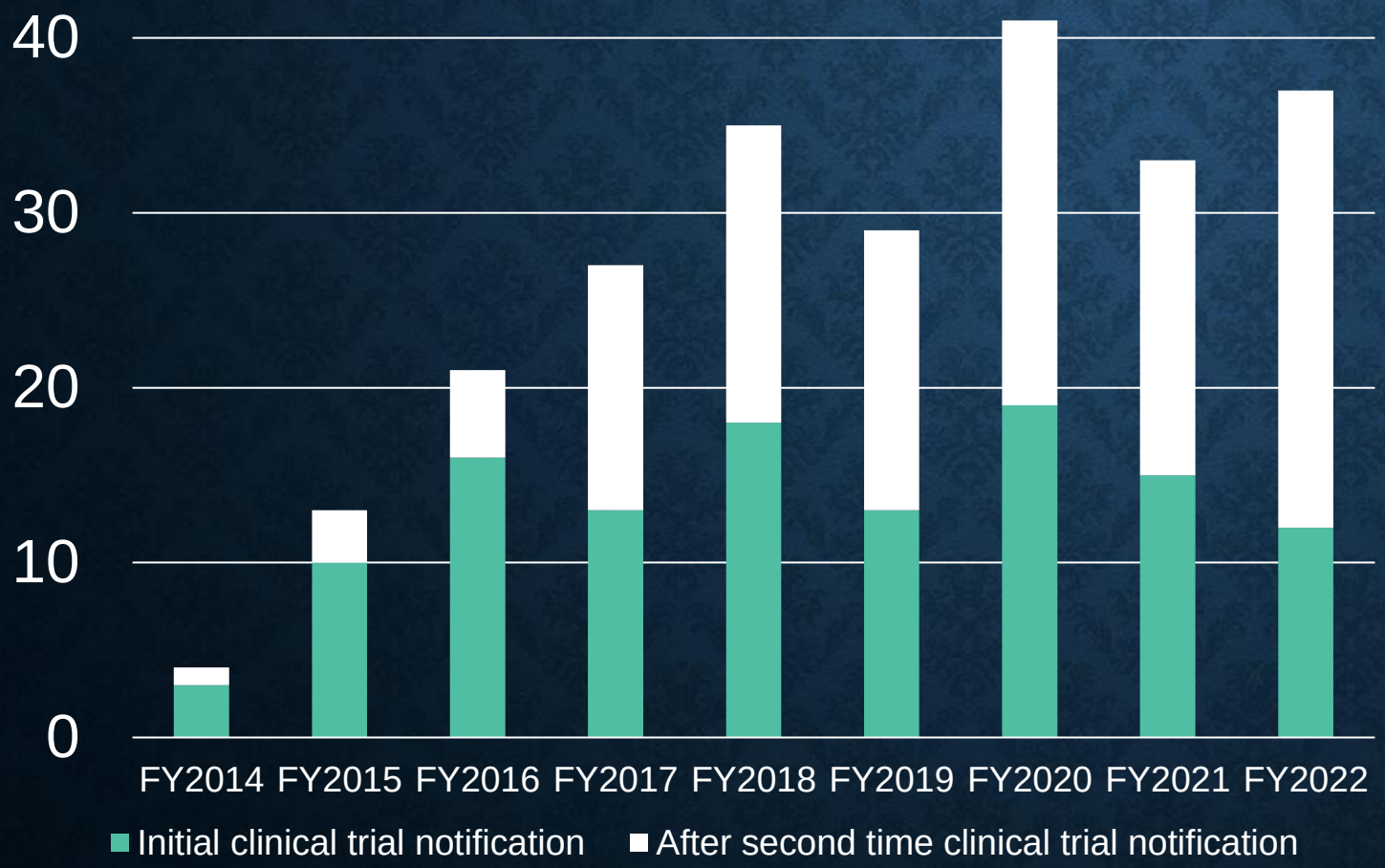
15 cell therapy products

4 Orphan & SAKIGAKE products

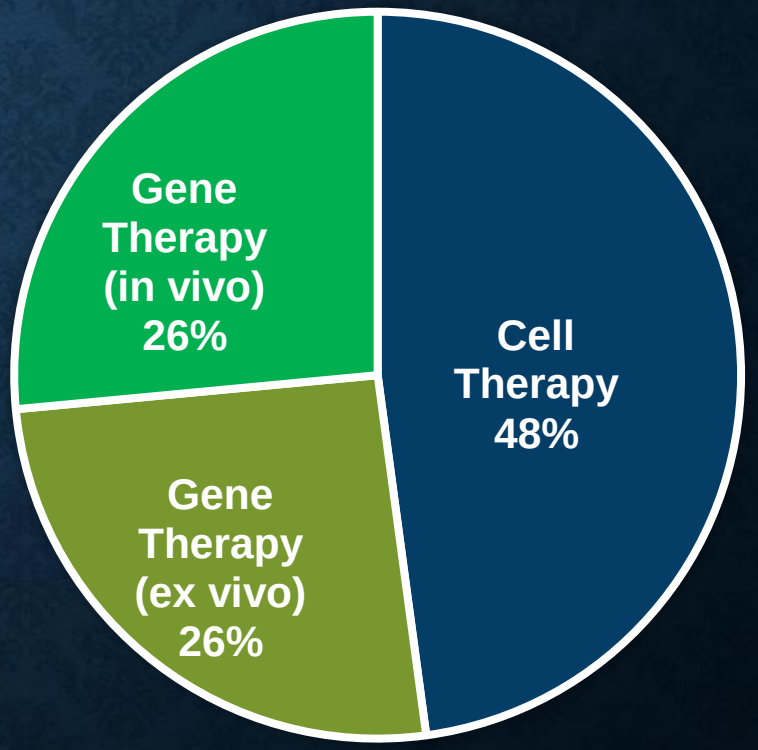
Orphan & SAKIGAKE Product	Indications on the designation	Sponsor	Approval date
TBI-1301 (NY-ESO-1 T cell receptor gene transduced autologous T lymphocytes)	Synovial sarcoma	Takara Bio, Inc.	Under development
SB623 (allogenic bone marrow-derived mesenchymal stem cell that undergo temporary genetic modification)	chronic neurological motor deficits caused by traumatic brain injury	SanBio Co, LTd.	Under Review
onasemnogene abeparvovec (ZOLGENSMA)	Spinal Muscular Atrophy (SMN)	Novartis Pharma K.K.	Mar. 19, 2020
teserpaturev (Delytact)	Malignant glioma	Daiichi Sankyo Co., Ltd.	Jun. 11, 2021

PMD Act

Number of Clinical Trial Notifications Regenerative Medical Products



2014 - 2022



OUTLINE

1. **Regulations of Regenerative Medicine in JAPAN**
2. **Strategy to facilitate and streamline development of Regenerative Medical Products***
3. **Review Experience of Regenerative Medical Products***

*Regenerative Medical Products = Cell and Gene therapy Products

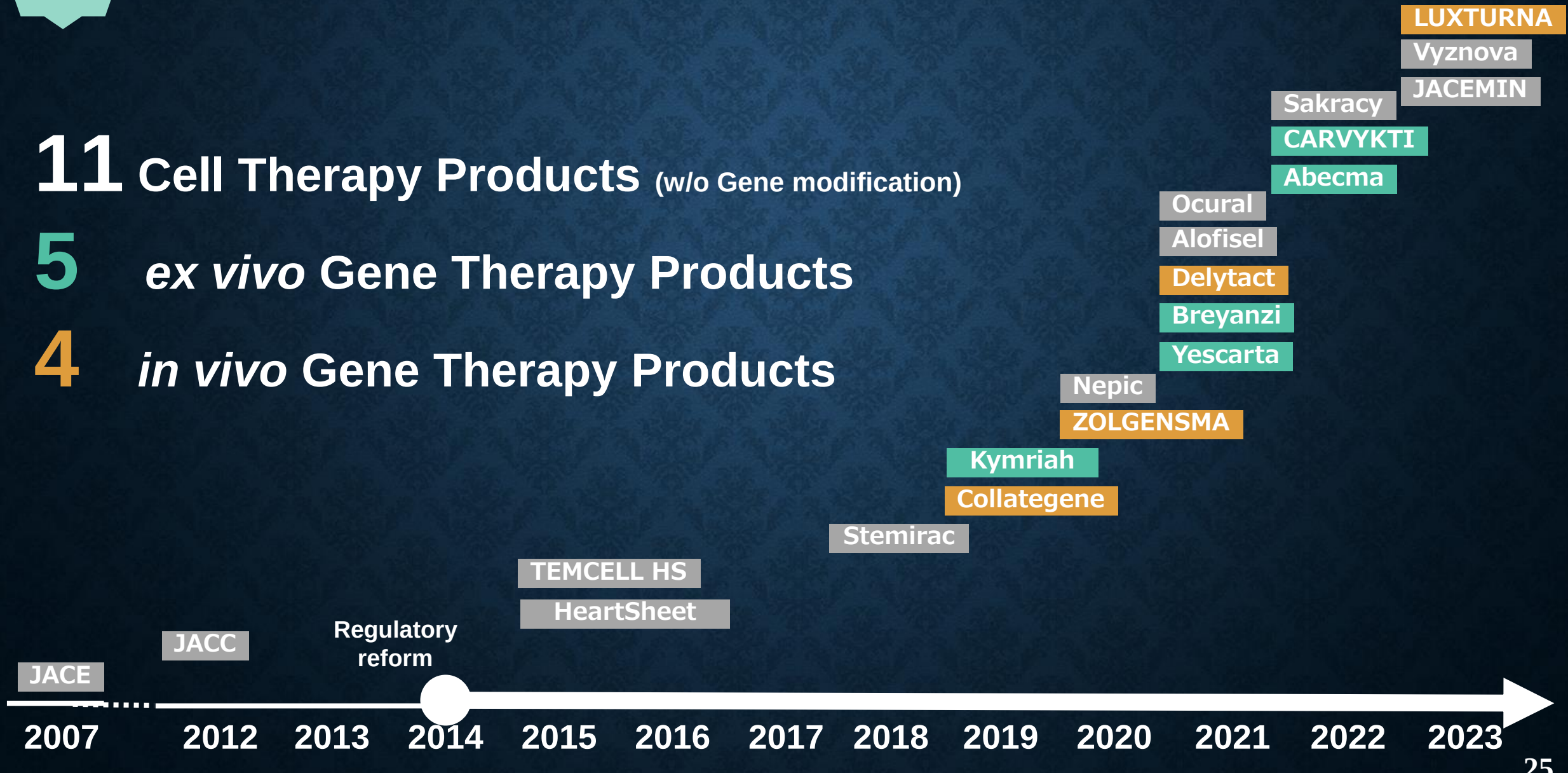
Approved Regenerative Medical Products in JAPAN

PMD Act

11 Cell Therapy Products (w/o Gene modification)

5 *ex vivo* Gene Therapy Products

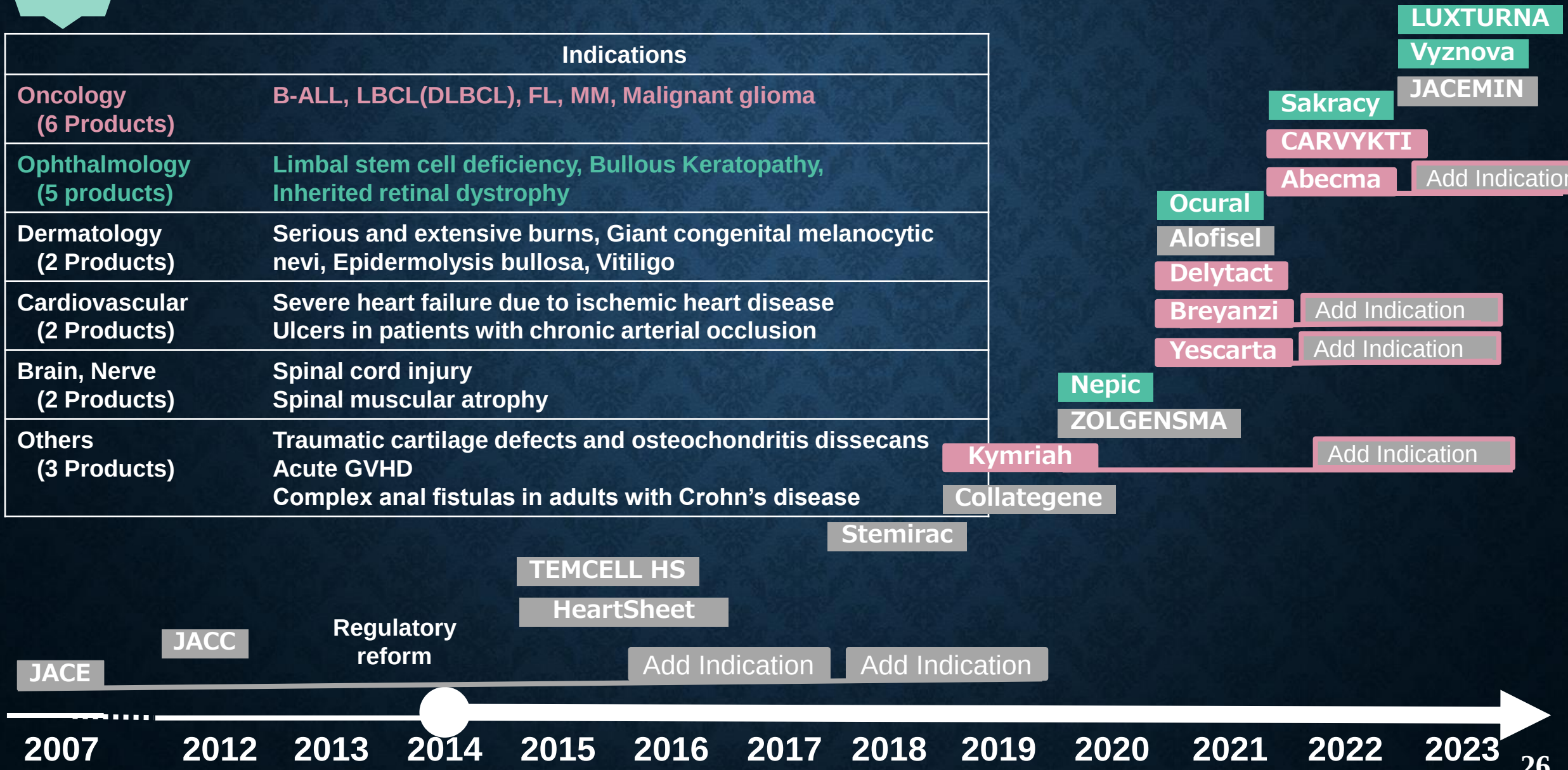
4 *in vivo* Gene Therapy Products



Approved Regenerative Medical Products in JAPAN

PMD Act

	Indications
Oncology (6 Products)	B-ALL, LBCL(DLBCL), FL, MM, Malignant glioma
Ophthalmology (5 products)	Limbal stem cell deficiency, Bullous Keratopathy, Inherited retinal dystrophy
Dermatology (2 Products)	Serious and extensive burns, Giant congenital melanocytic nevi, Epidermolysis bullosa, Vitiligo
Cardiovascular (2 Products)	Severe heart failure due to ischemic heart disease Ulcers in patients with chronic arterial occlusion
Brain, Nerve (2 Products)	Spinal cord injury Spinal muscular atrophy
Others (3 Products)	Traumatic cartilage defects and osteochondritis dissecans Acute GVHD Complex anal fistulas in adults with Crohn's disease

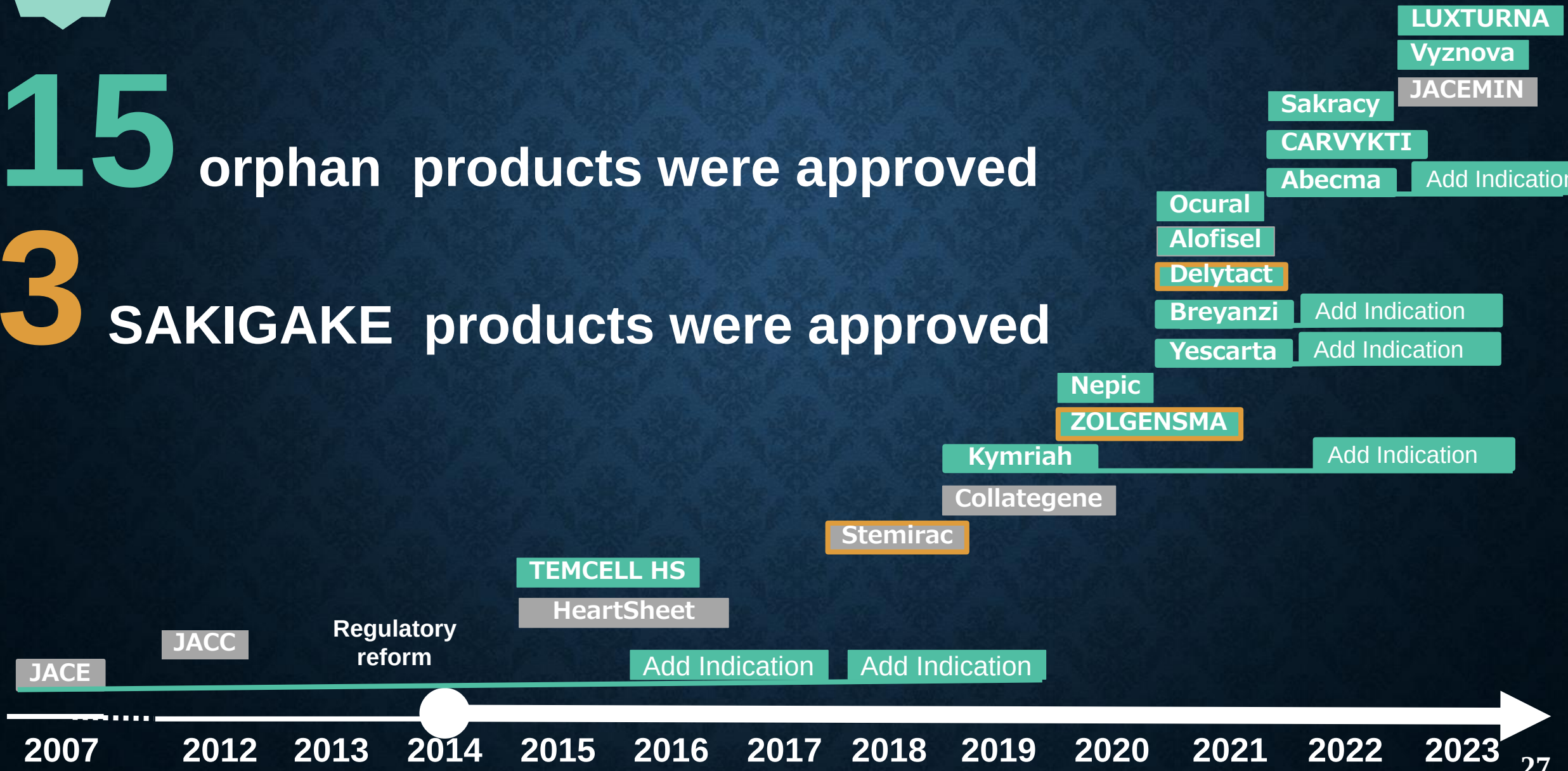


Approved Regenerative Medical Products in JAPAN

PMD Act

15 orphan products were approved

3 SAKIGAKE products were approved



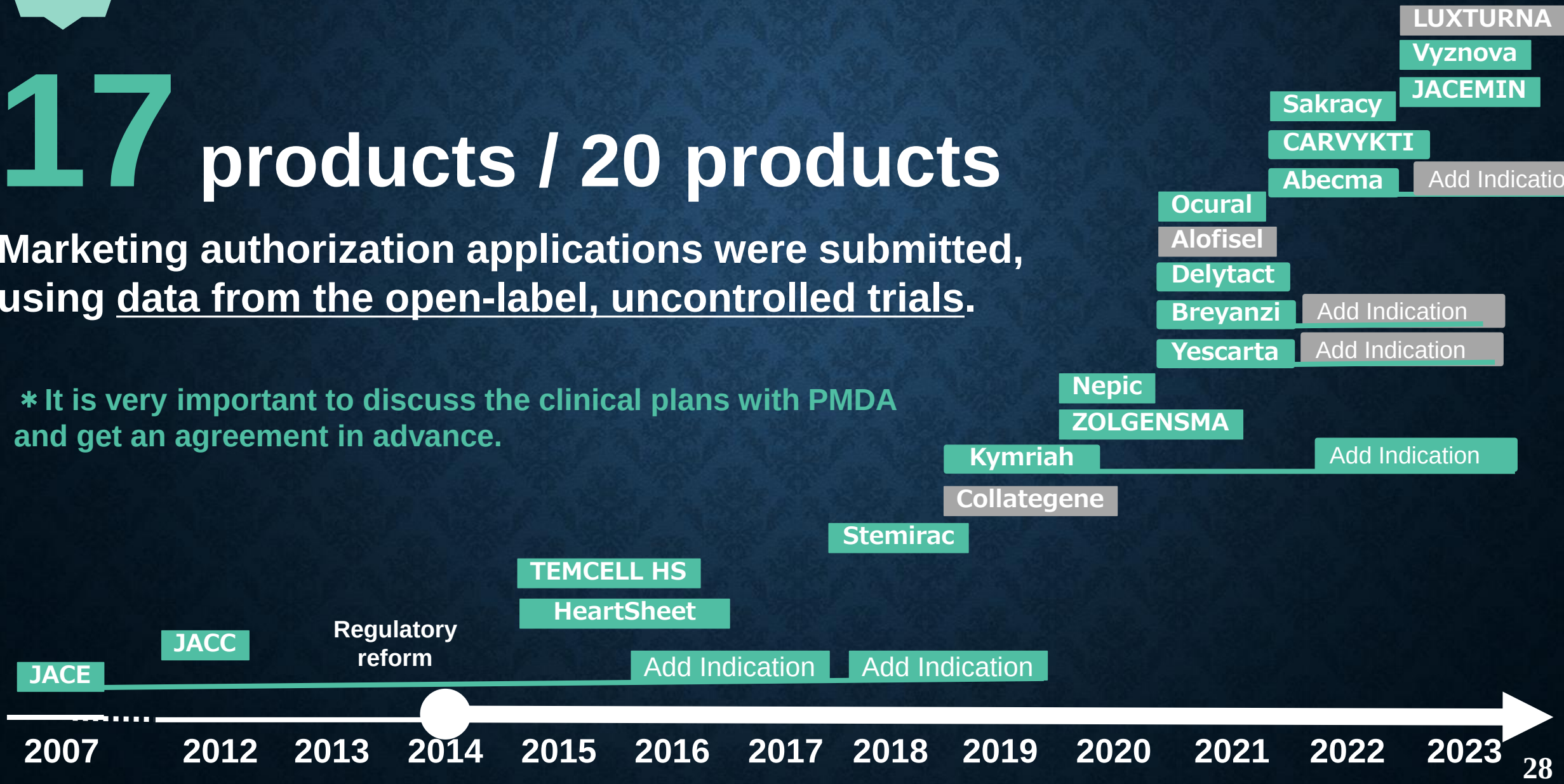
Approved Regenerative Medical Products in JAPAN

PMD Act

17 products / 20 products

Marketing authorization applications were submitted, using data from the open-label, uncontrolled trials.

＊It is very important to discuss the clinical plans with PMDA and get an agreement in advance.

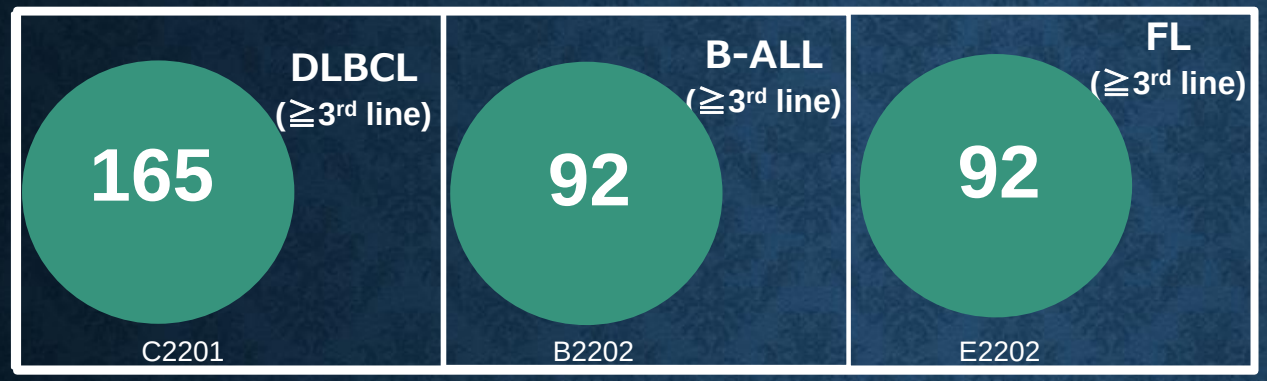


PMD Act

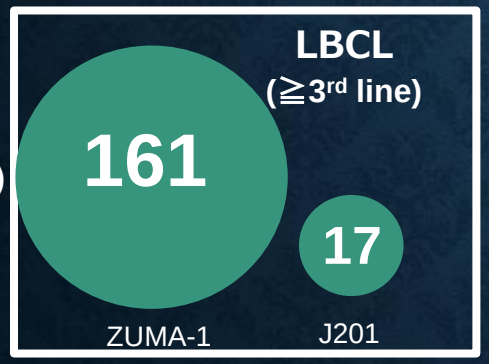
Clinical-data packages of approval Gene therapy products* in JAPAN

(* CAR-T products and AAV products)

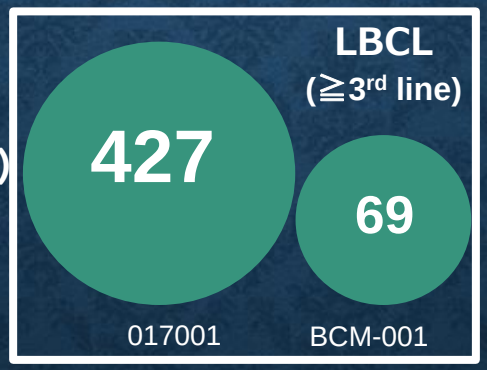
Kymriah (CD19CAR-T)



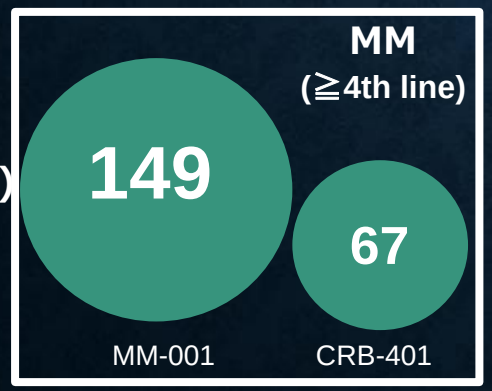
Yescarta (CD19CAR-T)



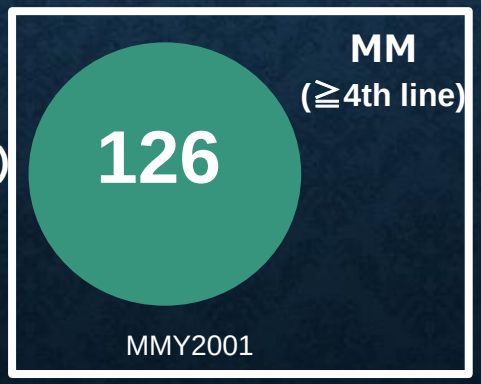
Breyanzi (CD19CAR-T)



Abecma (BCMA CAR-T)

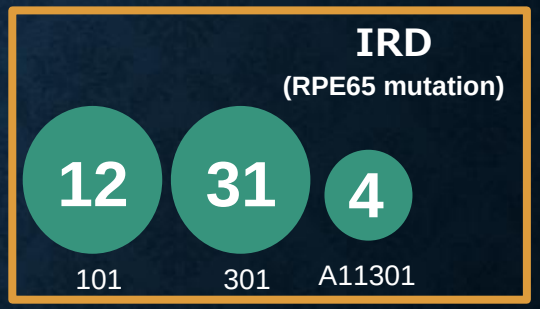


Carvykti (BCMA CAR-T)



Zolgensma (AAV-9)

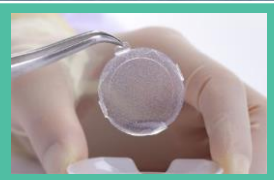
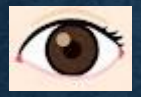
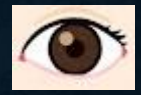
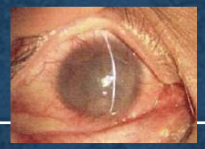
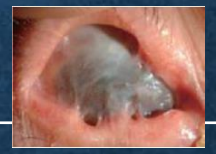
Luxturna (AAV-2)



Marketing authorization applications were submitted, using data from the open-label, uncontrolled trials.

PMD Act

Clinical design considering disease condition, conventional treatments, etc.

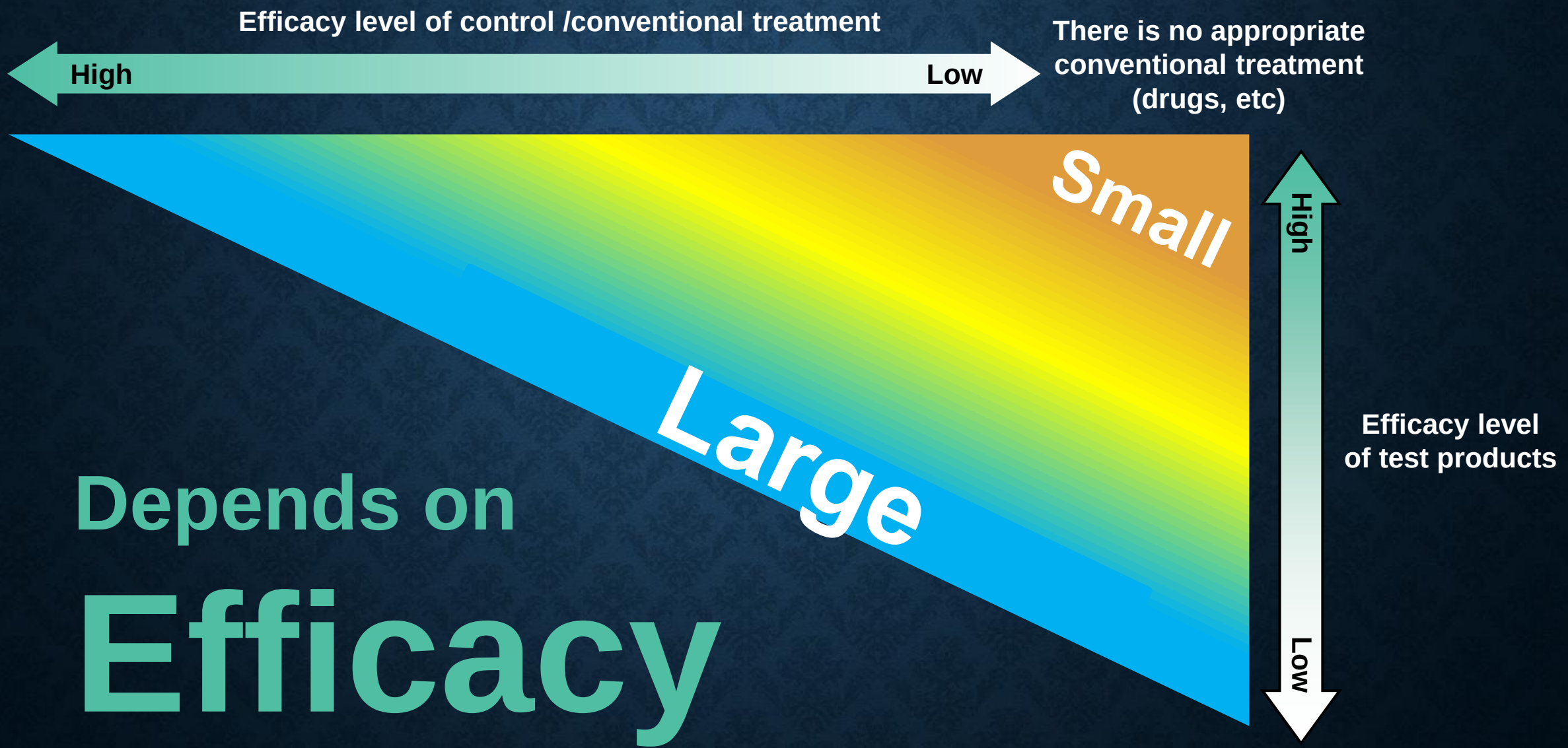
	Nepic	Ocural	Sakracy	Vysnova
	 https://www.jpte.co.jp/business/regenerative/	 https://www.jpte.co.jp/business/regenerative/	 http://hirosaki-li.co.jp/products_sakracy.html	
Source	Autologous Corneal limbus 	Autologous Oral mucosa 	Autologous Oral mucosa 	Allogenic Corneal endothelium 
Target disease	**Limbal stem cell deficiency (LSCD)** [No spontaneous cure]  https://www.pmda.go.jp/regenerative_medicines/2020/R20200413001/index.html  https://www.pmda.go.jp/regenerative_medicines/2022/R20220107001/index.html			**Bullous Keratopathy** [No spontaneous cure]
Conventional Treatment	**Corneal transplantation** ・Donor limitation (allograft), etc.			 N Engl J Med 2018; 378: 995-1003

Pivotal study for marketing application

Design	**Open-label, uncontrolled**			
Endpoint	Reconstitution	Reconstitution	Alleviation of adhesions	Reconstitution
# Patients in the study	**8**	**6**	**7**	**12**
Study type	Sponsor-initiated	Investigator-initiated		

30

Number Of Patients Required For Efficacy Analysis In Trials



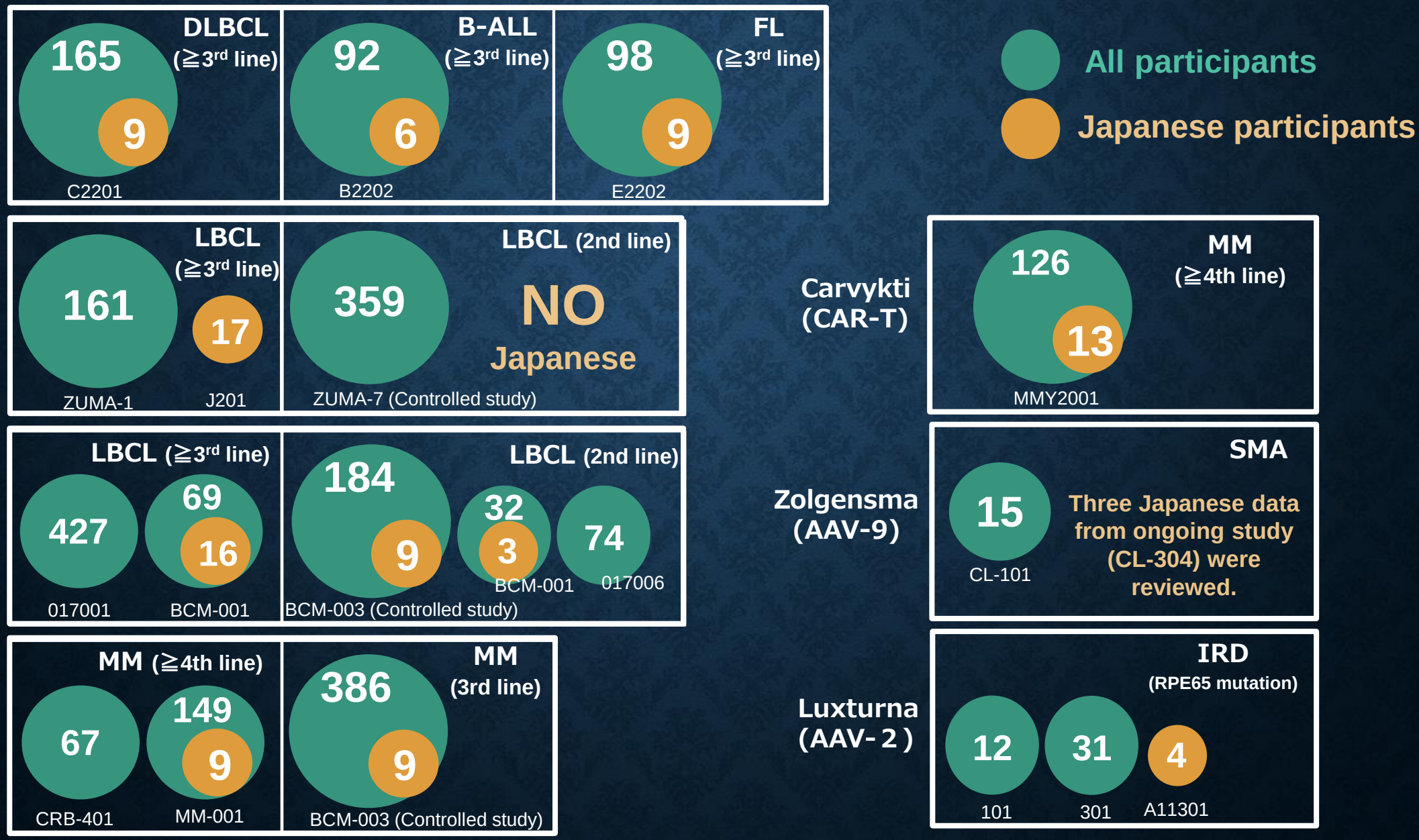
Depends on

Efficacy

PMD Act

Clinical-data packages of approval Gene therapy products* in JAPAN

(* Early clinical development proceeded outside JAPAN)



Summary

1. Regulations of Regenerative Medicine in JAPAN

- Safety Act (Medical Care or Clinical Research)
- PMD. Act (Commercial Product)

2. Strategy to facilitate the efficient development of Regenerative Medical Products

- PMDA Consultations and Designation systems (Orphan / SAKIGAKE(forerunner) product)
- Importance of close communication between developer and PMDA.
- Contact **rs-contact@pmda.go.jp**

3. Approved Regenerative Medical Products in JAPAN

- 20 products has been approved in JAPAN
- PMDA is ready to discuss about clinical trial design flexibly based on disease condition, conventional treatments, endpoint, etc.
- Although Japanese clinical data was needed for MAA in JAPAN, PMDA reviewed flexibly.

Thank you

Contact PMDA **rs-contact@pmda.go.jp**