Regenerative Medicine in Japan

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CJ PARTNERS

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Japan's Regenerative Medicine Regulatory Environment

Prior Regenerative Medicine Regulatory Landscape

The "Act on the Safety of Regenerative Medicine" and a revision to the "Pharmaceutical Affairs Act" were promulgated by the Japanese government on Nov. 27, 2013 with the aim of providing a route to market that was more in sync with current industry/patient needs. Both laws came into force the following year on Nov. 25, 2014.

Japanese Regenerative Medicine Landscape Prior to Nov. 25, 2014

Medical Treatment at One's Own Expense*1

Main Governing Rules/Regulations

- Medical Care Act
- Medical Practitioners' Act

High-Level Background Information

- As treatment that falls under this category is not covered by the Japanese National Health Insurance (NHI), time to market is drastically reduced
- Treatment is provided by doctors at clinics and private practice in areas such as:
  - Cellular immunotherapy of cancers
  - Augmentation mammoplasty using adipose-derived Stem Cells

# of Studies that were in Progress

- N/A

Clinical Research

Main Governing Rules/Regulations

- Medical Care Act
- Medical Practitioners' Act
- Industry Guidelines

High-Level Background Information

- Large University Hospitals follow guidelines that are put in place by the Japanese Ministry of Health, Labour and Welfare (MHLW) in order to conduct clinical research on stem cell treatments for various diseases/ailments/conditions
- Expenses are covered by the hospitals that provide the therapy treatment

# of Studies that were in Progress

- 84

Clinical Trials + Marketed Drugs/Therapies

Main Governing Rules/Regulations

- Pharmaceuticals Affairs Act

High-Level Background Information

- The traditional route to market involving clinical trials
- 2 therapies had been approved:
  - Autologous Cultured Epidermis
    Japan Tissue Engineering Co., Ltd.
  - Autologous Cultured Cartilage
    Japan Tissue Engineering Co., Ltd
- Further therapies were in the pipeline:
  - Allogeneic MSC GVHD Treatment
    JCR Pharmaceuticals Co., Ltd.
  - Autologous Skeletal Myoblast Sheet
    Terumo Corporation

# of Studies that were in Progress

- 6

Reference: Ministry of Health, Labour and Welfare documentation

*1: On PMDA documentation this is often denoted as "Daily Practice"

High-Level Introduction to Japan's Regulatory Environment

Japan has two laws regulating its regenerative medicine market: the Act on the Safety of Regenerative Medicine (ASRM) and the revised Pharmaceutical Affairs Act (PMD. Act).

ASRM

Category	Comment
Official Name	Act on the Safety of Regenerative Medicine (ASRM)
Effective Date	November 25, 2014*1
Purpose	• Establish steps for the practice of regenerative medicine in order to ensure the safe and ethical administration of regenerative medicine technologies • Ensure the safe yet accelerated adoption of specific processed cellular products by establishing a manufacturing permit system
Key Definitions	• Regenerative Medicine: Medical care that involves the use of regenerative medicine technologies. • Regenerative Medicine Technologies: Medical care that involves the use of processed cellular products to reconstruct/restore/repair the human body (or its functions) or to cure/prevent a disease. Depending on their risk-level, these technologies are sub-divided into 3 classes. • Specific Processed Cellular Products: Processed cellular products produced under the guidance of a medical institution, for the purposes of "clinical research" or "medical treatment at one's own expense", and meant for the treatment of a specific patient.

PMD. Act

Category	Comment
Official Name	Pharmaceuticals and Medical Devices Act (PMD. Act)
Effective Date	August 10, 1960
Purpose	• Revise the previous Act so as to provide a route to market for regenerative medicine that is more in sync with the current industry/patient needs • Establish regulations for regenerative medicine that are independent from regular ethical drugs, medical devices, and non-medical/cosmetic products
Key Definitions	• Regenerative Medicine Products: Medicinal products, produced by corporate entities for an unspecified large number of people, that involve human/animal cell culturing in order to: ➢ Reconstruct/restore/repair the human/animal body ➢ Cure/prevent a human/animal disease ➢ Obtain a gene expression • Conditional Approval: A system of approval put in place for those regenerative medicine products that have all of the following conditions, and allow for the sale of said products for up to 7 years: ➢ They do not have any major safety concerns ➢ They have "probable" efficacy ➢ They are not uniform in nature

Reference: ASRM, PMD. Act, Guidebook to the Revised Pharmaceutical Affairs Act

*1: The "promulgation" of the Act was on Nov. 27, 2013.

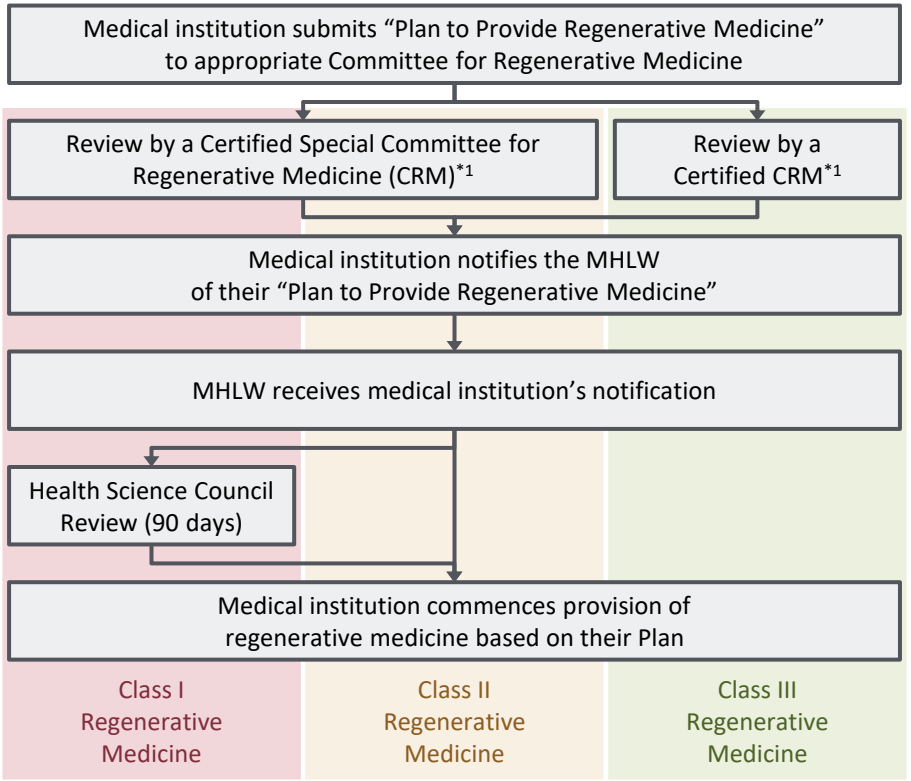
Act on the Safety of Regenerative Medicine (1/2)

The wording of the ASRM necessitates that doctors be the gate keepers of treatment. Pharmaceutical companies that would like to provide their drug/therapy to patients under this law would need to operate in non-traditional sectors of the market, such as operating as a Cell Processing Center (CPC), or receiving royalty payments.

3 Regenerative Medicine Technology Risk Categories

Category	Legal Definition	Comments
Class I Regenerative Medicine (High Risk)	The effects of the regenerative medicine technology on the patient's well-being are either: • not readily apparent; or • the effects of the regenerative medicine technology on a patient's wellbeing are potentially harmful	Regenerative medicine technologies that fall under this category are generally those that utilize iPS or ES cells
Class II Regenerative Medicine (Medium Risk)	The effects of the regenerative medicine technology on the patient's well-being have the potential to have negative repercussions despite providing due care	Regenerative medicine technologies that fall under this category are generally those that utilize somatic (adult) stem cells
Class III Regenerative Medicine (Low Risk)	Regenerative medicine technology that does not fall under the other 2 risk categories	Regenerative medicine technologies that fall under this category are generally those that utilized processed somatic (adult) cells

Route to Market under the ASRM



- As treatments under the ASRM must be provided by a medical institution for the purposes of "medical research" or as a "medical treatment at one's own expense", therapies provided under this framework are not covered by Japan's NHI.

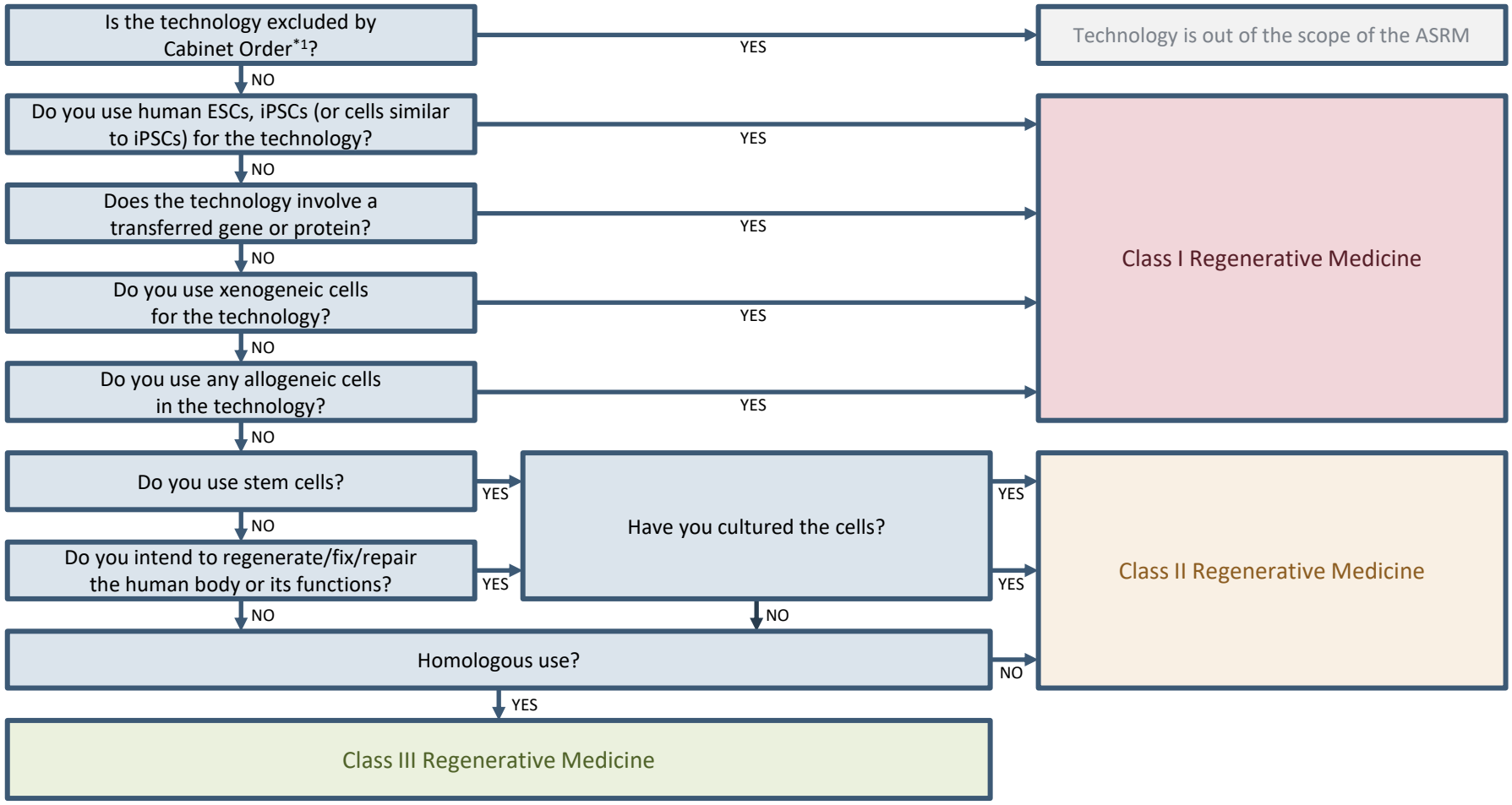
Reference: ASRM, Guidebook to the Revised Pharmaceutical Affairs Act

*1: List of current CRMs under section 1-15-1 <http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryou/saisei_iryou/>

Act on the Safety of Regenerative Medicine (2/2)

The risk categorizations under the ASRM are determined as follows. Almost all pertinent uses will fall either under the Class I or Class II Regenerative Medicine categories.

Determining Risk Categorization of Regenerative Medicine Technologies



Reference: ASRM and related guidelines, Guidebook to the Revised Pharmaceutical Affairs Act, PMDA presentations

*1: Blood transfusions that use processed cells, hematopoietic stem cell transplantations, assisted reproductive technologies, etc.

Pharmaceuticals and Medical Devices Act (1/4)

The Pharmaceuticals and Medical Devices Act (PMD. Act) instituted a conditional approval system for Regenerative Medicine Products in Japan. The minute details of this new path are still being defined, but Terumo Corporation became the first company to receive conditional approval with its HeartSheet product on Sept. 18, 2015.

Regenerative Medicine Product Conditional Approval

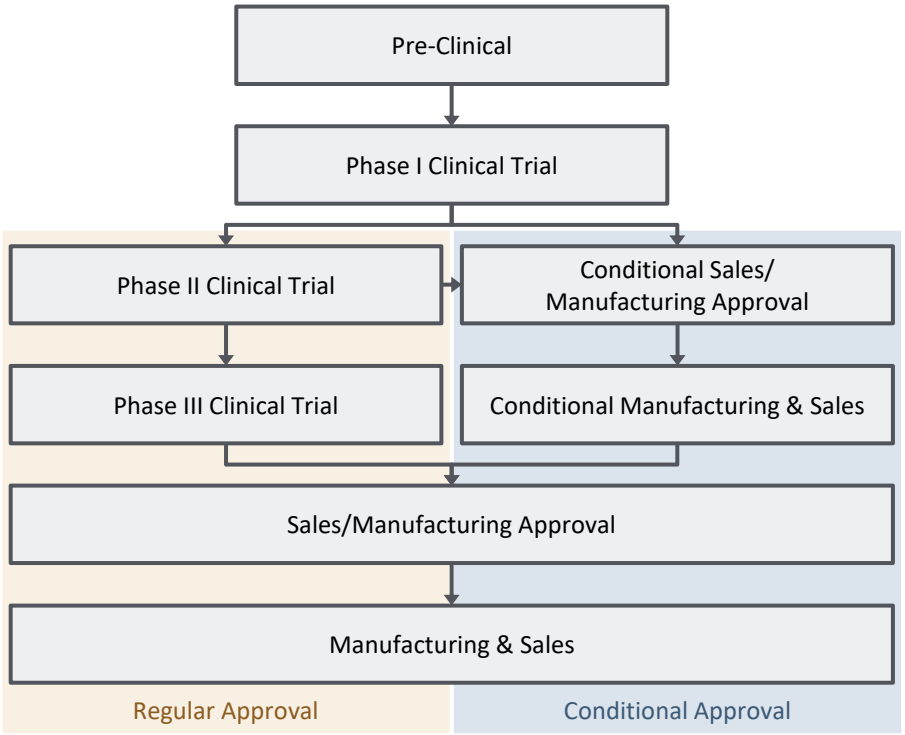
The PMD. Act differs from the law that it revised (i.e. the PAA: Pharmaceutical Affairs Act) by the inclusion of Regenerative Medicine Products as a stand-alone medical category with a novel "conditional approval" system. This system is summarized below:

1. If the Regenerative Medicine Product, that a corporate entity is looking to obtain sales/manufacturing approval for, satisfies all of the following conditions, then said entity can obtain input from a sub-committee of the Pharmaceutical Affairs and Food Sanitation Council and receive conditional approval for said Regenerative Medicine Product's release:
   - It does not have any major safety concerns
   - It has "probable" efficacy
   - It is not uniform in nature
2. Entities that receive conditional approval for a specific Regenerative Medicine Product must re-apply for a full release within the timeframe provided to them under said approval (no longer than 7 years)

Regenerative medicine products are oftentimes produced by processing cells. This "processing" can introduce certain risks including "the manifestation of additional properties that differ from the cells that were originally processed" and "an inconsistency of quality." To help adequately deal with these inherent risks, regenerative medicine products that are provided conditional approval must stay within the following boundaries:

- They must not be carcinogenic
- Conditional approval must not last longer than 7 years, and during this period measures must be taken to ascertain the proper use of the regenerative medicine products
- Upon re-application must demonstrate adequate efficacy & safety

Route to Market under the PMD. Act



- Conditional approval is not guaranteed for Regenerative Medicine Products that meet the requirements delineated at left. Rather the PMDA reserves the right to decide on which Regenerative Medicine Products will be allowed the shortened path to market.

Reference: PMD. Act, Guidebook to the Revised Pharmaceutical Affairs Act

Pharmaceuticals and Medical Devices Act (2/4)

Japan's NHI is only supposed to cover those items that have demonstrated clinical efficacy and allowing conditionally approved therapies to be covered by NHI was counterintuitive. However, by treating them in a similar manner to orphan drugs, the MHLW was able to extend insurance coverage to conditionally approved regenerative medicine products.

Conditional Approval for Regenerative Medicine Products vs. Regular Approval for Pharmaceuticals

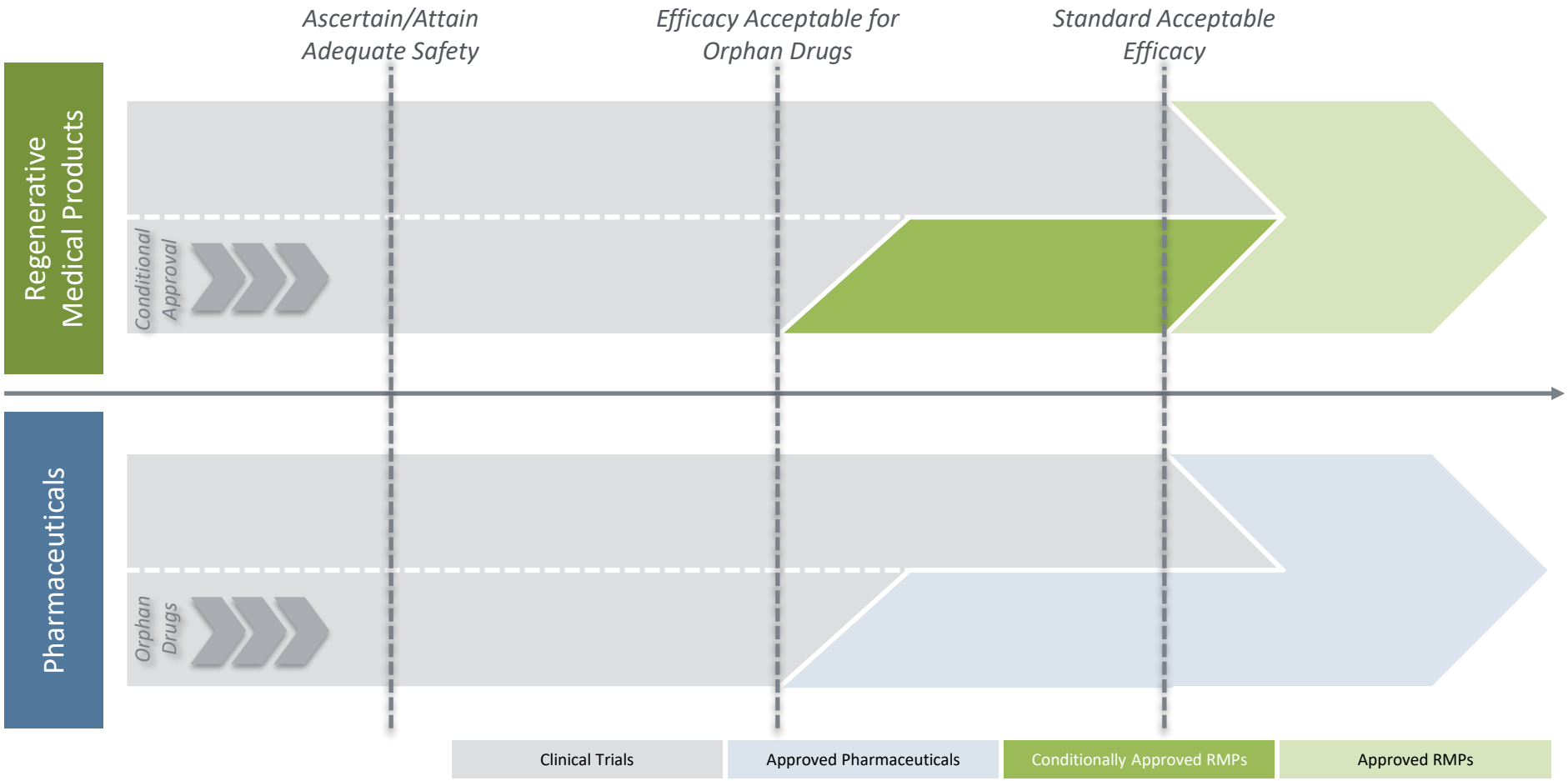
Drug Category	Clinical Trials	Efficacy Evidence	Post Approval
Pharmaceuticals	• Evaluation is conducted on suitably sized clinical trials which are determined based on disease characteristics	• Controlled clinical trial that exhibits a statistically significant difference	• Conduct post-marketing observation studies (PMOS) as necessary
Orphan Drugs	• Evaluation oftentimes needs to be done based on a small number of study participants due to patient scarcity • Controlled clinical trials are oftentimes difficult to perform	• There are cases when it is difficult to conduct rigorous statistical analysis	• Follow-up investigations conducted on all patients (and/or follow-on clinical trials) so as to accumulate adequate data -stipulated condition of approval- • Limit the number of medical institutions that are allowed to administer the drug so as to ensure proper use -stipulated condition of approval-
Regenerative Medical Products (Conditional Approval)	• Evaluation oftentimes needs to be done based on a small number of study participants due to patient scarcity • Controlled clinical trials are oftentimes difficult to perform • Cellular heterogeneity make it difficult to evaluate based on a fixed/limited number study participants	• There are oftentimes cases when it is difficult to conducts rigorous statistical analysis	• Follow-up investigations conducted on all patients (and/or follow-on clinical trials) so as to accumulate adequate data -stipulated condition of approval- • Limit the number of medical institutions that are allowed to administer the drug so as to ensure proper use -stipulated condition of approval- • Limit the number of years of approval to a term of no more than 7 years -stipulated condition of approval-

Reference: Presentation by the MHLW's Medical Device and Regenerative Medicine Product Evaluation Division

Pharmaceuticals and Medical Devices Act (3/4)

Treating conditionally approved regenerative medicine products along the same lines as orphan drugs extends beyond allowing them to be covered by Japan's NHI. The level of efficacy that one needs to obtain for conditional approval is also analogous.

Conditionally Approved Regenerative Medicine Products ≈ Orphan Drugs



Reference: Presentation by the Japanese Society for Regenerative Medicine and Presentation by the PMDA

Pharmaceuticals and Medical Devices Act (4/4)

Whether one is able to obtain conditional approval is at the discretion of the regulatory authorities, and guidelines are not yet available. However, the recent approvals of TEMCELL® HS Inj. and HeartSheet provide indications of what the regulators look for when they provide conditional approval (i.e. instances where statistical comparison is difficult).

TEMCELL® HS Inj. [JCR Pharmaceuticals]

- Japan-based clinical trial consisted of a single-cohort of 25 patients
- US-based clinical trial contained 51 placebo patients

→ Statistical comparison possible

- Determined to have adequate efficacy for approval

→ Regular Approval

HeartSheet [Terumo Corporation]

- Japan-based clinical trial consisted of only 7 patients
- Difficult to evaluate due to cellular heterogeneity
- Difficult to evaluate due to patient scarcity

→ Statistical comparison difficult

- 19 patients received treatment though clinical research and this data combined with the trial data was enough to provide “adequate safety” & “probably efficacy” data

→ Conditional Approval

Reference: Presentation by the MHLW’s Medical Device and Regenerative Medicine Product Evaluation Division

Fewer Patients Required to Attain 'Probable Efficacy'

Approval of pharmaceuticals usually requires companies to prove the statistical significance of their product's efficacy. This process usually requires 100s or 1,000+ of patients enrolled in a traditional Phase III clinical trial. Conditional approval's "probable efficacy," allows significantly smaller trials, resulting in materially reduced capital requirements.

Several Japanese Clinical Trials Aiming for Conditional Approval

Trial Sponsor	Product Name	Auto/ Allo	Indication	Cell Source	Phase	Estimated Enrollment	Control	Trial Start	Estimated Trial End	Sakigake
ROHTO	ADR-001	Allo	Hepatitis C NASH-induced Liver Cirrhosis	Adipose	I/II	**15**	N/A	2017, JUL	2018, DEC	N
TWOCELLS	gMSC1	Allo	Osteochondritis Dissecans Cartilage Damage	Synovium	III	**70**	Surgery	2017, JUL	2024, FEB	N
HEALIOS	HLCM051 (MultiStem)	Allo	Ischemic Stroke	Bone Marrow	II/III	**220**	Placebo	2016, OCT	2018, OCT	Y
SanBio	SB623	Allo	Traumatic Brain Injury	Bone Marrow	II	**52**	Sham	2016, JAN	2019, APR	Y
Toshihiko Yamashita*1	STR01 (STEMIRAC)	Auto	Spinal Cord Injury	Bone Marrow	II	**30***	N/A	2014, MAR	2017, NOV	Y

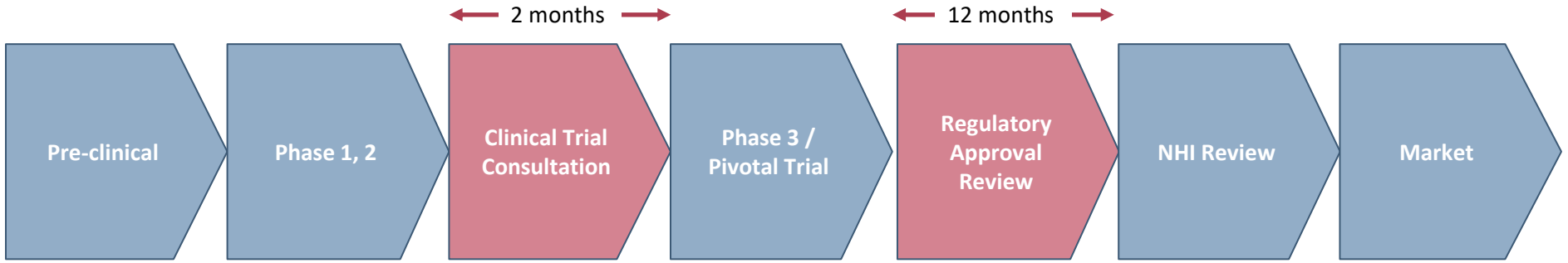
*1: While the trial is an Investigator Initiated Trial at Sapporo Medical University Hospital, NIPRO will commercialize once approved

*2: Actual trial only enrolled 13 patients.

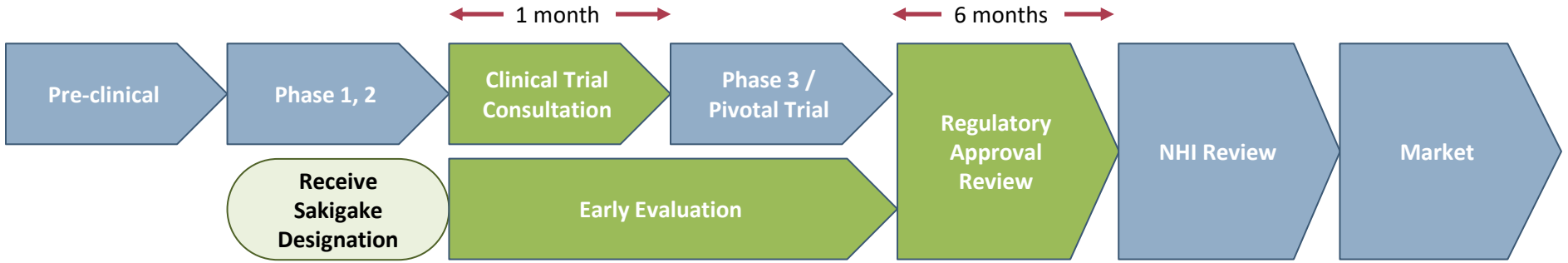
Japan's Sakigake System (1/2)

In addition to "Conditional Approval", the PMDA offers another option for a fast track to market called Sakigake. This service, once granted after meeting certain criteria, provides a number of options that could help accelerate the review process until receiving market approval.

Traditional Development Approach



Development Path Under Sakigake



Reference: PMDA Website

Japan's Sakigake System (2/2)

Sakigake offers a number of exclusive services to help expedite the approval process of those treatments which have received sakigake designation.

Types of services included in Sakigake

1. **Prioritized Consultation**:
   Allows the product to receive reviewal at any time, which on average reduces the consultation period by around 1 month.

2. **Early Evaluation**:
   A new type of consultation that allows the sponsor to consult with the PMDA with preliminary data and draft documentation, which essentially helps the pharmaceutical firm have all necessary documents ready by the time the Regulatory Approval Review commences.

3. **Prioritized Evaluation**:
   The PMDA allocates more resources and strictly manages the time spent on evaluation tasks, which reduces the generally 12 month evaluation time to approx. 6 months.

4. **Evaluation Partner**:
   The PMDA assigns a dedicated PMDA staff to handle the product/application, who will act as a personal concierge for the sponsor.

Conditions to Receive Sakigake Designation

To qualify for Sakigake, a company must show that its product satisfies the following 4 criteria:

1. **Product Uniqueness**: MoA is the most important factor in determining whether your product is unique
2. **Indication is Severe**: the indication is either life-threatening or chronic in nature (making every-day life difficult)
3. **Extremely High Efficacy**: the efficacy over existing treatments looks to be drastically improved (without corresponding safety concerns)
4. **Priority Development in Japan**: Either First-in-Human (FIH) trial or Proof-of-Concept (POC) trials conducted in Japan, and Japan-first approval

Other Items of Note

- 11 regenerative medicine products have been selected as Sakigake products since implementation.

Reference: PMDA webiste

Pharmaceutical Affairs Consultation on R&D Strategy

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Pharmaceutical Affairs Consultation on R&D Strategy (1/2)

In July 2011 the PMDA commenced provision of a new consultation service called Pharmaceutical Affairs Consultation on R&D Strategy to help get new drugs through the so called "Valley of Death." The consultation services, which are mainly for universities, research institutions and biotechs, can help regenerative medicine firms prepare for clinical trials in Japan.

Scope of the Consultation Services

Innovative Products within the Following Priority Areas

- Regenerative Medicine (cell- and tissue- based products)
- Cancer
- Incurable disease and orphan disease
- Pediatrics
- Other areas (products using particularly innovative technologies)

Types of Regenerative Medicine Face-to-Face Consultations

- Regenerative Medicine Mfg. Quality / Pre-Clinical Safety Consultation: These consultations are used to ensure that the pre-clinical safety studies and manufacturing quality adhere to applicable Japanese guidelines. The PMDA will usually want these consultations to take place prior to Regenerative Medicine Consultations.
- Regenerative Medicine Consultation: These consultations are very much like those conducted for regular pharmaceutical products in that they look to review study protocol (and other pertinent documentation) prior to the conduct of a clinical trial

Other Items of Note

- Must have a resident Japanese company (or an individual residing in Japan) act as the point of contact with the PMDA
- Face-to-Face Consultation Fees can be reduced if you meet certain criteria
- Documentation must be in Japanese

Type of Consultation Services

Regulatory Science Introductory Consultation

- Used to provide companies with an explanation of the Consultation services and the procedures related to said services
- Free of charge
- 30 minute duration

Pre-Consultation

- Used to assist companies with prep for Face-to-Face Consultations (i.e. highlighting guidelines and providing non-binding answers to high-level questions)
- Free of charge
- 30 minute duration

Face-to-Face Consultation

- Scientific discussions on either Pre-clinical safety, manufacturing quality or proposed trial protocol with binding results
- Fees apply (exact amount depends on the type of Consultation conducted)
- 2 hour duration
- Minutes are provided

Reference: PMD. Act, Guidebook to the Revised Pharmaceutical Affairs Act

Pharmaceutical Affairs Consultation on R&D Strategy (2/2)

Only 53 "Regenerative Medicine Consultations" have taken place since the PMD. Act came into force on Nov. 25, 2014. Most of the consultations for regenerative medicine products have been Pre-Consultations (1,033), Regulatory Science Introductory Consultations or Regenerative Medicine Mfg. Quality / Pre-Clinical Safety Consultations.

PMDA Consultations

Consultation Type	~FY2013 (from Jul. 2011)	FY2014	FY2015	FY2016	FY2017	FY2018	FY2019 (~ December)	Total
Regulatory Science Introductory Consultation	657	271	221	190	231	202	131	1,903
Pre-Consultation (Device, Pharmaceutical, and Regen Med)	753	325	411	388	336	326	259	2,798
Face-to-Face Consultation	194 [215]	85 [111]	114 [140]	100 [138]	127 [169]	105 [134]	75 [86]	798 [991]
Pharmaceutical Consultation	114	48	58	40	61	49	33	403
Medical Device Consultation	49	16	16	20	24	26	15	165
Regenerative Medicine Consultation*1	-	2	11	14	13	5	8	53
Regenerative Medicine Mfg. Quality / Pre-Clinical Safety Consultation*2	31 [52]	18 [44]	29 [55]	26 [64]	29 [71]	25 [54]	19 [30]	177 [370]
Release Roadmap Consultation*1	-	1	0	0	0	0	0	1

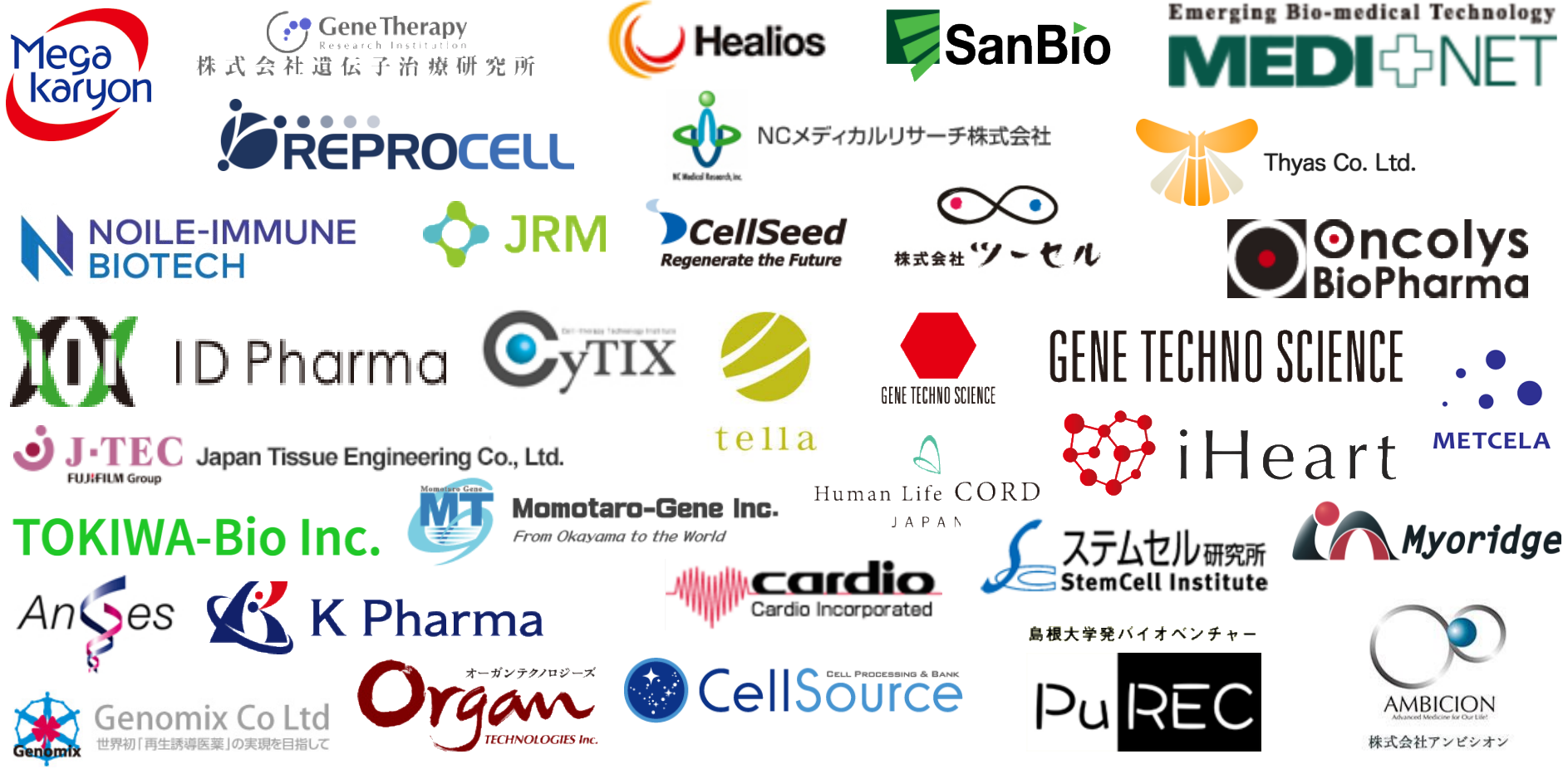
Reference: https://www.pmda.go.jp/files/000233769.pdf

*1: Commenced on November 25, 2014 *2: Numbers outside brackets are unique products while those inside are total mtg #s *3: FY = Apr-March

Japanese Regenerative Medicine Biotechs

Most regenerative medicine databases do not adequately capture the large presence of Japanese biotechs operating in the regenerative medicine field. A quick search provides a selection of over 40 companies[*1] currently involved in this field; a concerted effort to get word out on opportunities that exist in Japan is necessary to help the industry grow even faster.

A Selection of Japanese Regenerative Medicine Biotechs



Reference: Company websites

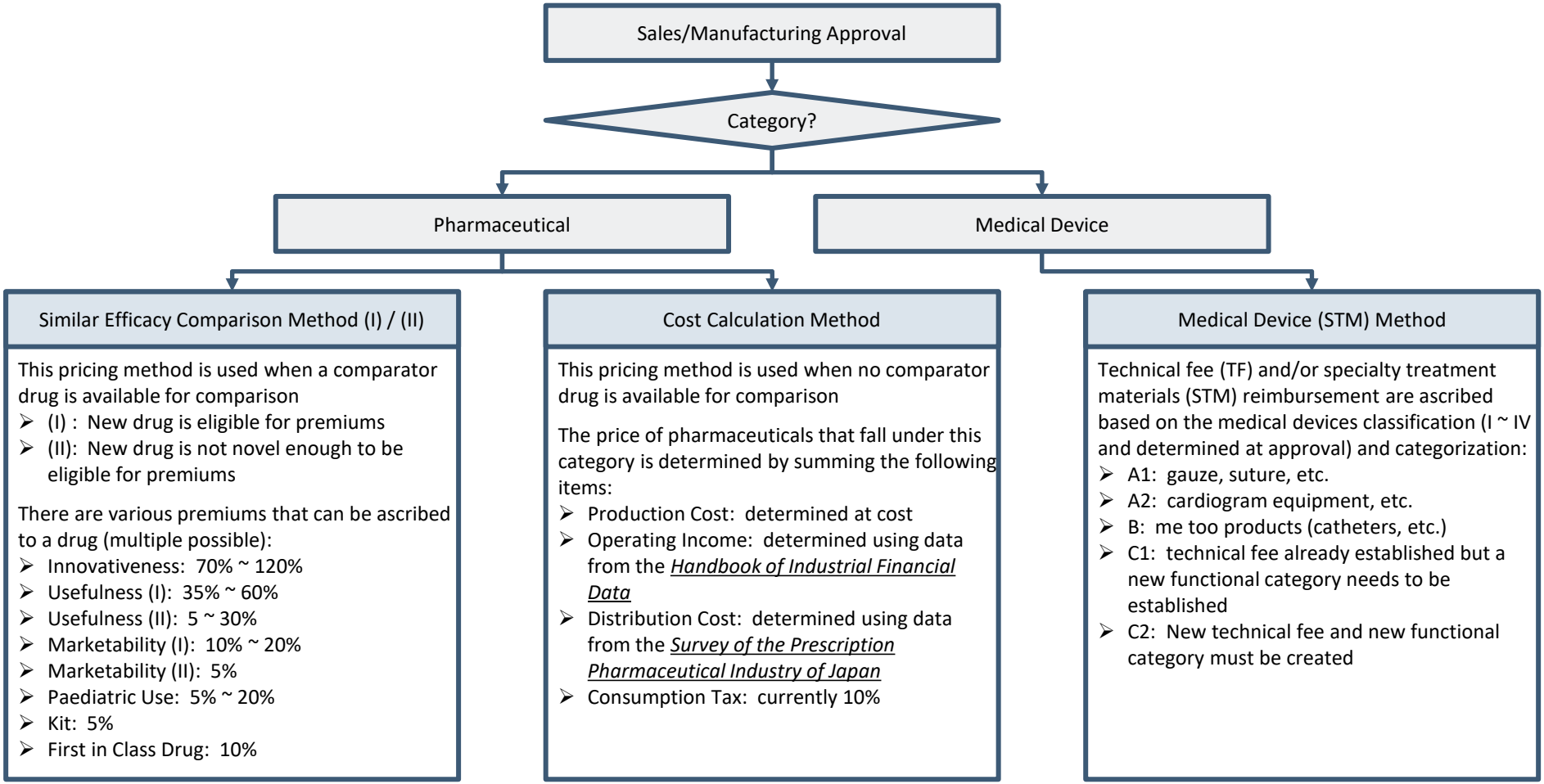
*1: Some of these companies do not currently have company logos (e.g. Cuorips, etc.) and thus do not appear in the above slide

Japan’s NHI Pricing

NHI Pricing Methods

Depending on its categorization, a regenerative medicine product's NHI reimbursement price will be determined by different calculation methods. For those categorized as pharmaceuticals, the "Cost Calculation Method" will most likely be the go-to choice for the foreseeable future.

Different Methods for Calculation of NHI Reimbursement Price



Similar Efficacy Comparison Method (I) / (II)

This pricing method is used when a comparator drug is available for comparison

- (I) : New drug is eligible for premiums
- (II): New drug is not novel enough to be eligible for premiums

There are various premiums that can be ascribed to a drug (multiple possible):

- Innovativeness: 70% ~ 120%
- Usefulness (I): 35% ~ 60%
- Usefulness (II): 5 ~ 30%
- Marketability (I): 10% ~ 20%
- Marketability (II): 5%
- Paediatric Use: 5% ~ 20%
- Kit: 5%
- First in Class Drug: 10%

Cost Calculation Method

This pricing method is used when no comparator drug is available for comparison

The price of pharmaceuticals that fall under this category is determined by summing the following items:

- Production Cost: determined at cost
- Operating Income: determined using data from the *Handbook of Industrial Financial Data*
- Distribution Cost: determined using data from the *Survey of the Prescription Pharmaceutical Industry of Japan*
- Consumption Tax: currently 10%

Medical Device (STM) Method

Technical fee (TF) and/or specialty treatment materials (STM) reimbursement are ascribed based on the medical devices classification (I ~ IV and determined at approval) and categorization:

- A1: gauze, suture, etc.
- A2: cardiogram equipment, etc.
- B: me too products (catheters, etc.)
- C1: technical fee already established but a new functional category needs to be established
- C2: New technical fee and new functional category must be created

Reference: Presentation by the MHLW's Medical Device and Regenerative Medicine Product Evaluation Division

NHI Pricing Examples (Pre-Regulatory Changes)

Both of Japan Tissue Engineering's products, JACE and JACC, were issued approvals prior to the updated regulations on regenerative medicine. As such, both were treated as medical devices, though of different classifications.

JACE	[Japan Tissue Engineering]
Pricing Category	Medical Device (C1 – New Functionality)
Generic Name	Autologous cultured epidermis
Foreign Pricing	None
Total Price	306,000 JPY
Requested Price	467,750 JPY
Primary Objective	This product is an autologous cultured epidermis made from differentiated epidermal cells harvested from the patient. The reconstructed dermis closes wounds through transplantation to the epidermis of the patient and subsequent epithelization.

JACC	[Japan Tissue Engineering]
Pricing Category	Medical Device (C2 - New Functionality, New Technology)
Generic Name	Autologous cultured cartilage
Foreign Pricing	None
Total Price	2,080,000 JPY / patient
Requested Price	2,930,000 JPY / indication / patient
Primary Objective	This product is an autologous cultured cartilage made from differentiated chondrocytes harvested from the patient's own healthy cartilage. The clinical symptoms can be treated through transplantation of these chondrocytes, which are applied through an atelocollagen gel, to the defective area. The relevant indications are traumatic cartilage deficiency of the knee and osteochondritis dissecans.

Reference: Documentation from the results of the 139th and 239th Meetings of the MHLW's Central Social Insurance Medical Council (with JACE listed under 139-総-1-1 and JACC listed under 239-総-1-1)

NHI Pricing Examples (Post-Regulatory Changes) (1/2)

JCR Pharmaceutical's TEMCELL® HS Inj. was categorized as a pharmaceutical with its NHI reimbursement price calculated using the "Cost Calculation Method." On the other hand, Terumo Corporation's HeartSheet was categorized as a medical device.

TEMCELL® HS Inj. [JCR Pharmaceuticals]

Pricing Category	Pharmaceutical
Type	Human cell/tissue products (Somatic Stem Cells)
Generic Name	Allogeneic bone marrow-derived hMSC
Therapeutic Category	Treatment of acute GVHD after hematopoietic stem cell transplantation
Dosing Regimen	2m hMSCs per kilogram of the patient (with each bag being diluted in 18mL of saline solution) will be slowly (4mL/min) administered via IV drip. Patients are to receive 2 doses per week (with dosing intervals of at least 3 days) for 4 weeks. If symptoms persist, patients may receive a further course of treatment whereby they receive 1 dose per week for 4 weeks.

Price Calculation	Method	Cost Calculation Method (JPY)	
	Costing Breakdown	Production Cost	630,445
		Operating Income	119,193
		Distribution Cost	54,695
		Consumption Tax	64,347
	Overseas Adjustment		0
Total Price (for a 10.8mL bag of TEMCELL® HS Inj.)			868,680

HeartSheet [Terumo Corporation]

Pricing Category	Medical Device (C2 - New Functionality, New Technology)
Generic Name	Autologous Skeletal Myoblast Sheets

HeartSheet A Kit (1 kit used per treatment)

Price Calculation	Method	Cost Calculation Method (JPY)	
	Costing Breakdown	Production Cost	5,389,054
		Operating Income	331,810
		Distribution Cost	167,924
		Consumption Tax	471,103
	Overseas Adjustment		0
Total Price (rounded to the nearest '0,000 JPY)			6,360,000

HeartSheet B Kit (5 kits used per treatment)

Price Calculation	Method	Cost Calculation Method (JPY)	
	Costing Breakdown	Production Cost	1,386,638
		Operating Income	85,377
		Distribution Cost	83,504
		Consumption Tax	124,442
	Overseas Adjustment		0
Total Price (rounded to the nearest '0,000 JPY)			1,680,000

Reference: Documentation from the results of the 313th Meeting of the MHLW's Central Social Insurance Medical Council (with TEMCELL listed under 総-4-1 and HeartSheet listed under 総-4-2.)

NHI Pricing Examples (Post-Regulatory Changes) (2/2)

More recently, STEMIRAC, Collategene and Kymriah – all classified as pharmaceuticals – have received pricing that include adjustments for sakigake designation as well as premiums for usefulness and marketability.

STEMIRAC [Nipro]

Pricing Category	Pharmaceutical		
Type	Human cell/tissue products (Somatic Stem Cells)		
Generic Name	Autologous bone marrow-derived hMSC		
Therapeutic Category	Treatment of neurological symptoms and functional impairment from spinal cord injury limited to traumatic lesions classified as ASIA A-C.		
Dosing Regimen	Harvesting of bone marrow is to be conducted upon considering the state of the patient's entire body and ideally within 31 days to provide treatment as quickly as possible. Patients are to receive a single IV infusion at a rate of 0.7-1.0 mL/min of 0.5 x 10^8 – 2.0 x 10^8 cells (not exceeding 3.34 x 10^6 cells/kg of bodyweight) diluted by a factor of three in a normal saline solution.		
Price Calculation	Method	Cost Calculation Method (JPY)	
	Costing Breakdown	Production Cost	9,991,755
		Operating Income	1,667,236
		Distribution Cost	931,712
		Consumption Tax	1,007,256
	Overseas Adjustment		0
	Sakigake Adjustment		10% (1.0 coefficient)
Total Price (for one infusion)			14,957,755

Collategene [AnGes]

Pricing Category	Pharmaceutical		
Type	Gene therapy product (plasmid vector product)		
Generic Name	Beperminogene perplasmid		
Therapeutic Category	Treatment of ulcers caused by Buerger's Disease and Arteriosclerosis Obliterans (where standard pharmaceutical therapies do not provide sufficient efficacy and revascularization procedures are not possible).		
Dosing Regimen	For adults, 2 rounds of intramuscular injections (4mg each round) spaced 4 weeks apart. Each rount is split into 0.5mg injections into 8 sites at the ischemic location of the limb. Should clinical conditions remain, a 3rd round of injections 4 weeks after the 2nd round is allowed. Each injection is diluted with a saline solution (contained within the Japanese Pharmacopeia) for a total of 3mL unless the target muscle is small, in which case the injection may be diluted to 2mL.		
Price Calculation	Method	Cost Calculation Method (JPY)	
	Costing Breakdown	Production Cost	437,582
		Operating Income	76,615
		Distribution Cost	41,692
		Consumption Tax	44,471
	Overseas Adjustment		0
Total Price (for a 4mg 1.6mL vial)			600,360

Kymriah [Novartis]

Pricing Category	Pharmaceutical		
Type	Human cell/tissue products (Somatic Stem Cells)		
Generic Name	Tisagenlecleucel		
Therapeutic Category	1. Recurrent or refractory CD19+ B-cell acute lymphoblastic leukemia 2. Recurrent or refractory CD19+ diffuse large B-cell lymphoma.		
Dosing Regimen	1. For patients under 25 a single intravenous administration of • 0.2 x 10^6 - 5.0 x 10^6 CAR-T cells/kg for body weight less than 50kg • 0.1 x 10^8 – 2.5 x 10^8 CAR-T cells/kg for body weight more than 50kg 2. For adults, 0.6 x 10^8 – 6.0 x 10^8 CAR-T cells (regardless of bodyweight).		
Price Calculation	Method	Cost Calculation Method (JPY)	
	Costing Breakdown	Production Cost	23,632,062
		Operating Income	4,137,694
		Distribution Cost	682,000
		Consumption Tax	2,276,140
	Overseas Adjustment		0
	Usefulness & Marketability Premium		35% and 10% (0.2 coefficient)
Total Price (per patient)			33,493,407

References: https://www.mhlw.go.jp/content/12404000/000481001.pdf; https://www.mhlw.go.jp/content/12404000/000540832.pdf; https://www.mhlw.go.jp/content/12404000/000508918.pdf

Japanese Regenerative Medicine Market

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A Trident of Support

The Japanese regenerative medicine market receives broad-based support from the Government, Academia, and Industry. The support is comprehensive and forms the foundation of Japan's bid to be the "Regenerative Medicine Capital" of the world.

Broad-based Support of Japan's Budding Regenerative Medicine Market

Reference: PMDA presentation material, FIRM presentation material, METI presentation material, JSRM presentation material

Japanese Regenerative Medicine Market Participants

Japanese Industry is getting behind the government's push to forward regenerative medicine and cellular therapies in Japan. Pharmaceutical companies in particular are increasingly expressing interest in the field. For non-Japanese firms looking for a way into the market, such firms are convenient spring boards with their regulatory knowhow and experience.

Regenerative Medicine & Cellular Therapy Market Players in Japan

CMO/CPC	FSTEC, AGC Biologics, Emerging Bio-medical Technology MEDINET, Showa Denko, PharmaBio, TaKaRa, J-TEC FUJIFILM Group, Nikon, BRI Foundation for Biomedical Research and Innovation KOBE 2001
CRO	CMIC Pharmaceutical Value Creator, I'CROS, EPSGROUP, Clinical Development Partner Linical, A2 Healthcare The Life First Company
SMO	Ohrom, EP-SOGO Co., Ltd., Site Support Institute Co.,Ltd.
Pharmaceutical Company	Takeda, astellas Leading Light for Life, Sumitomo Dainippon Pharma, FUJIFILM Value from Innovation, TERUMO, Healios, Eisai, ···and many many more
Distribution Company (Logistical Support)	MEDIPAL HOLDINGS, SUZUKEN, wanbishi ARCHIVES, Fisher Clinical Services A Thermo Fisher Scientific Brand, alfresa
Other	KAWASAKI, IrvineScientific, MITSUI-SOKO GROUP, Mitsubishi Logistics, OLYMPUS, kaneka KANEKA CORPORATION

Reference: Company websites, various news articles

Multiple Out-Licensing Opportunities

Japan is the only major pharmaceutical market in the world that has not undergone a wholesale pharmaceutical company consolidation phase. This results in there being a large number of companies who are available to discuss licensing opportunities. They are all competing to license the 'best' regenerative medicine opportunities.

A Sampling of Japanese Companies Participating in Regenerative Medicine

Japanese Regenerative Medicine Deals

Numerous licensing deals, CMO tie-ups and M&A deals involving Japanese pharmaceutical companies have taken place over the last several years with over 25 such deals taking place since 2016.

Regenerative Medicine Licensing Deals

Regenerative Medicine CMO Deals

Regenerative Medicine M&A & Option Deals

Major Japanese Regenerative Medicine Deals

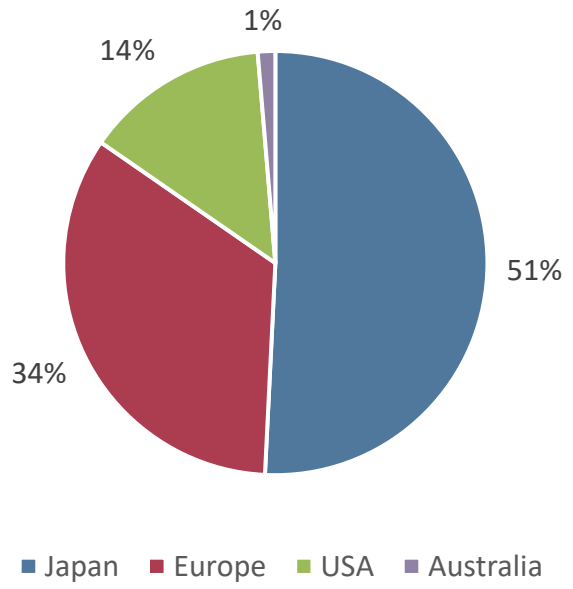
Date	Licensor (Acquired)	Licensee (Acquirer)	Therapy (Technology)	Phase	Territory	Upfront (USD)	Potential Total (USD)
13 MAY 2013	RepliCel	Shiseido	RCH-01	Phase Ⅰ	Asia (incl. Japan)	4,200,000	35,700,000
26 SEPT 2014	SanBio	Sumitomo Dainippon	SB623	Phase Ⅱ	North America	6,000,000	199,000,000
07 MAR 2015	Athersys	Chugai	MultiStem	Phase Ⅱ	Japan	10,000,000	205,000,000
08 JAN 2016	Athersys	Healios	MultiStem	Phase Ⅱ	Japan	15,000,000	230,000,000
25 APR 2016	TWOCELLS	Chugai	gMSC1	Pre-Clin	Japan	???	???
10 MAY 2016	Celixir	Daiichi Sankyo	Heartcel	Phase Ⅱ	Japan	18,000,000	???
05 JUL 2016	TiGenix	Takeda	Cx601	Phase Ⅱ	Ex-US Global	29,000,000	413,000,000
11 JUL 2016	Celyad	Ono	NKR-2	Phase Ⅱ	Japan, Korea, Taiwan	12,500,000	311,500,000
01 NOV 2016	Kolon Life Science (TissueGene)	Mitsubishi Tanabe	Invossa	Phase II	Japan	24,000,000	410,000,000
11 NOV 2016	Steminent Biotherapeutics	ReproCELL	Stemchymal	Phase II	Japan	1,000,000	4,000,000
20 DEC 2016	Pluristem	Sosei	PLX-PAD	Phase II	Japan	N/A	N/A
09 JAN 2017	Kite Pharma	Daiichi Sankyo	KTE-C19	Phase II	Japan	50,000,000	250,000,000
19 JAN 2017	Cynata Therapeutics	FUJIFILM	CYP-001	Phase I	Global*1	3,000,000	45,000,000
22 SEP 2017	Bone Therapeutics	Asahi Kasei	PREOB	Phase III	Japan	2,000,000	11,000,000
20 OCT 2017	Universal Cells	Astellas	UDC	Pre-Clin	Global	9,000,000	115,000,000
21 DEC 2017	Histogenics	MEDINET	NeoCart	Phase III	Japan	10,000,000	87,000,000
13 SEP 2018	Rohto	Shionogi	ADR-001	Phase I/II	Japan	???	???
8 APR 2019	Oncolys BioPharma	Chugai	OBP-301	Phase II	Japan, Taiwan	???	???
11 JUN 2019	Mesoblast	JCR Pharmaceuticals	TEMCELL (expansion)	Marketed	Japan	5,500,000	550,000,000
17 SEP 2019	Cynata Therapeutics	FUJIFILM	CYP-001	Phase I/II	Global	3,000,000	43,000,000
09 DEC 2019	EVASTEM	MEDIPOST	CARTISTEM	Phase II	Japan	???	4,500,000
07 MAY 2015	Lonza	Nikon	Quality & Op System	N/A	Japan	???	???
14 MAR 2016	PCT	Hitachi Chemical	CT Tech & Knowhow	N/A	Asia (incl. Japan)	5,600,000	25,000,000
29 DEC 2016	Regeneus	Asahi Glass	Progenza & Knowhow	Phase I	Japan	5,500,000	16,500,000
25 SEP 2019	Innovacell	ID Pharma	ICEF-15	Phase II	Japan	???	???
30 MAR 2015	Cellular Dynamics International	FUJIFILM	N/A	N/A	N/A	307,000,000	
10 FEB 2016	Ocata Therapeutics	Astellas	N/A	N/A	N/A	384,000,000	
19 JAN 2017	Cynata Therapeutics	FUJIFILM	CYP-001 (option)	N/A	N/A	3,000,000	
07 APR 2017	Regenerative Patch Tech.	Santen	N/A	N/A	N/A	???	
05 JAN 2018	TiGenix	Takeda	N/A	N/A	N/A	630,000,000	
14 FEB 2018	Universal Cells	Astellas	N/A	N/A	N/A	102,500,000	
29 MAR 2018	Irvine Scientific	FUJIFILM	N/A	N/A	N/A	800,000,000	
26 JUN 2019	Oxford Biomedica	Santen	LentiVector (option)	N/A	Global	???	
2 DEC 2019	Audentes Therapeutics	Astellas	N/A	N/A	N/A	3,000,000,000	

Reference: Company websites, various news articles

Investments by Japanese Entities

Since 2015, Japanese entities (primarily venture funds) have invested more than 27 billion JPY into biotechs in the regenerative medicine space. While half of investments are towards domestic/Japanese biotechs, the average investment amount is also much less than that for non-Japanese biotechs.

Regional Dist. by Total Investment Amount Since 2015



- Japanese biotechs are the recipients of roughly 51% of the investments over this time period
- The remainder has gone primarily to biotechs in Europe and the US
- Almost all the investments are into biotechs that have not listed on any stock exchange

Average Amount Per Investment by Region (MM JPY)

Region	Number of Investments	Average Investment
Europe	18	519
USA	11	352
Australia	2	184
Japan	111	126*

- The average investment into Japanese biotechs is smaller since many are very early stage investments (Seed, Angel, Series A)
- The investments into European and US biotechs are larger because they are often later stage investments (Series B, Series C, Pre-IPO)

* Due to the lack of publicly available information on investment sizes, this average is less than the true amount; though we expect it to remain far below that of the USA and Europe, and closer to that of Australia.

ご清聴ありがとうございました

Thanks for Listening

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