1-1. Institutional Framework for Promoting the Future Implementation of Regenerative Medicine

Regenerative Medicine Promotion Act [Legislation by Diet members]

Approved on April 26, 2013　Promulgated and came into force on May 10, 2013

Aims at comprehensive promotion of policies on regenerative medicine from R&D to implementation

	Daily practice / Clinical Research	Marketing
	Act on the Safety of Regenerative Medicine **[Approved on Nov 20, 2013, promulgated on Nov 27, 2013]** **[Came into force on Nov 25, 2014]**	**Revised Pharmaceutical Affairs Act** **[Approved on Nov 20, 2013, promulgated on Nov 27, 2013]** **[Came into force on Nov 25, 2014]**
	Standards for institutions providing regenerative medicine and cell culturing and processing facilities are newly formed for the purpose of ensuring, etc., of the safety of regenerative medicine	A revision is made to newly establish an approval and licensing system based on the characteristics of regenerative medical products, which accommodates early implementation of regenerative medicine.
Swiftness	Enables medical institutions to outsource cell culturing and processing to companies	Implements an early approval system for regenerative medical products based on their characteristics
Safety	Stipulates three risk-dependent provision standards and procedures for notification of plans etc. for regenerative medicine as well as standards of cell culturing and processing facilities and licensing procedures, etc.	Adopts post-marketing safety measures such as obtaining informed consent from patients on the use of the product and recording and storing of information on treated people

Swift and smooth implementation of safe regenerative medicine

Provision of various products as early as possible

1-2. Outline of the Act on the Safety of Regenerative Medicine

Aim

Clarify the measures that shall be implemented by organizations who are going to provide regenerative medicine and stipulate the system, etc., for approval of manufacturing, etc., of specified cell products, for the purpose of swift and safe provision, etc., of regenerative medicine

Contents

1. Classification of regenerative medicine

Regenerative medicine is classified into 3 categories, “Class I Regenerative medicine”, “Class II Regenerative medicine”, and “Class III Regenerative medicine” depending on the degree of effects on human life and health, and necessary procedures are stipulated for each category.

2. Procedures pertaining to provision of regenerative medicine

- Class I Regenerative medicine: Submit a provision plan to the Minister of Health, Labour and Welfare (HLW) after hearing opinions of the Certified Special Committee for Regenerative Medicine, and then implement.
  A certain period of restricted implementation period will be imposed, and the Minister of HLW will confirm the safety, etc., by hearing opinions of the Health Science Council within the period. The Minister orders change of the plan if there is nonconformity to the standards of safety, etc.
- Class II Regenerative medicine: Submit a provision plan to the Minister of HLW after hearing opinions of the Certified Special Committee for Regenerative Medicine, and then implement.
- Class III Regenerative medicine: Submit a provision plan to the Minister of HLW after hearing opinions of the Certified Committee for Regenerative Medicine, and then implement.
  * The Certified Special Committee for Regenerative Medicine has a specifically advanced investigation capability and objectivity.
  * Certain requirements on the facility and personnel will be imposed on medical institutions that provide Class I Regenerative medicine or Class II Regenerative medicine.

3. Measures for appropriate provision, etc.

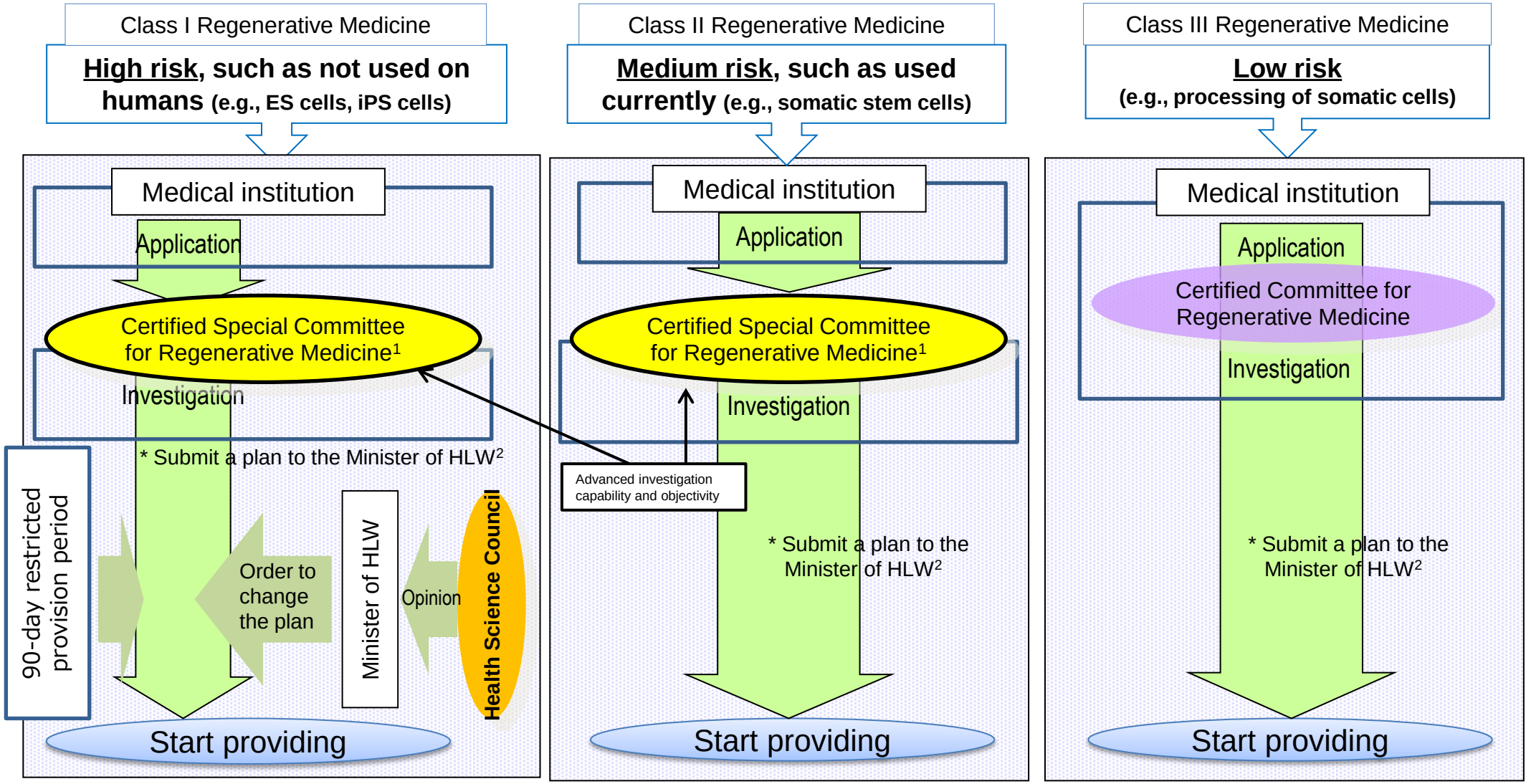
- Measures for informed consent, protection of personal information, etc., are stipulated.
- Any emergence of disease, etc., shall be reported to the Minister of HLW. The Minister will take necessary measures with hearing opinions of the Health Science Council.
- An order for improvement will be issued if necessary for ensuring the safety etc. If violation to the order for improvement is identified, provision of regenerative medicine will be restricted. Emergency measures such as temporary suspension of provision of regenerative medicine will be taken if necessary for prevention of outbreak or expansion of hygiene hazards.
- The Minister of HLW shall periodically gather information on the implementation status of regenerative medicine and publicly announce its outline.

4. Licensing of manufacturing, etc., of specified cell products

- Manufacturing of specific processed cells will be controlled by a licensing system (notification system for medical institutions), and medical institutions must entrust a licensed organization or an organization who submitted a notification when entrusting manufacturing of specified cell products.

Implementation date	November 25, 2014 (Promulgated on November 27, 2013)

1-3. Risk-Dependent Procedure under the Act on the Safety of Regenerative Medicine



Note 1: "Certified Committee for Regenerative Medicine" is a council-type committee consisting of knowledgeable persons including experts on the technologies of regenerative medicine or legal matters, which is approved by the Minister of HLW through certain formalities. "Certified Special Committee for Regenerative Medicine" is the Certified Committee for Regenerative Medicine with specifically advanced investigation capability and objectivity.

Note 2: The procedure of submitting a provision plan will be obligated. Penalties will be imposed if regenerative medicine is provided without submitting a provision plan.

1-4. Outsourcing Cell Culturing and Processing under the Act on the Safety of Regenerative Medicine

(Pharmaceutical and Medical Device Act and the Act on the Safety of Regenerative Medicine)

Clinical study, private practice

Act on the Safety of Regenerative Medicine

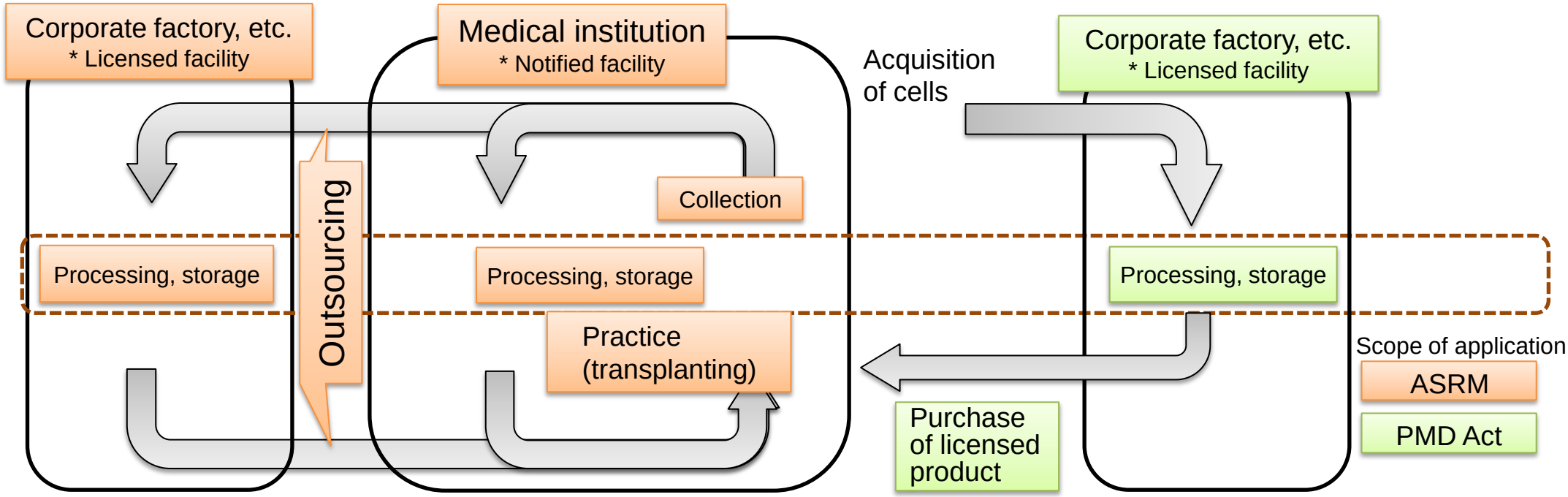
The safety, etc., of regenerative medicine provided as a medical service is ensured by stipulating the practical procedures of, for instance, sampling, standards for medical institutions that provide regenerative medicine and standards for facilities that culture and process cells.

Regenerative medical products

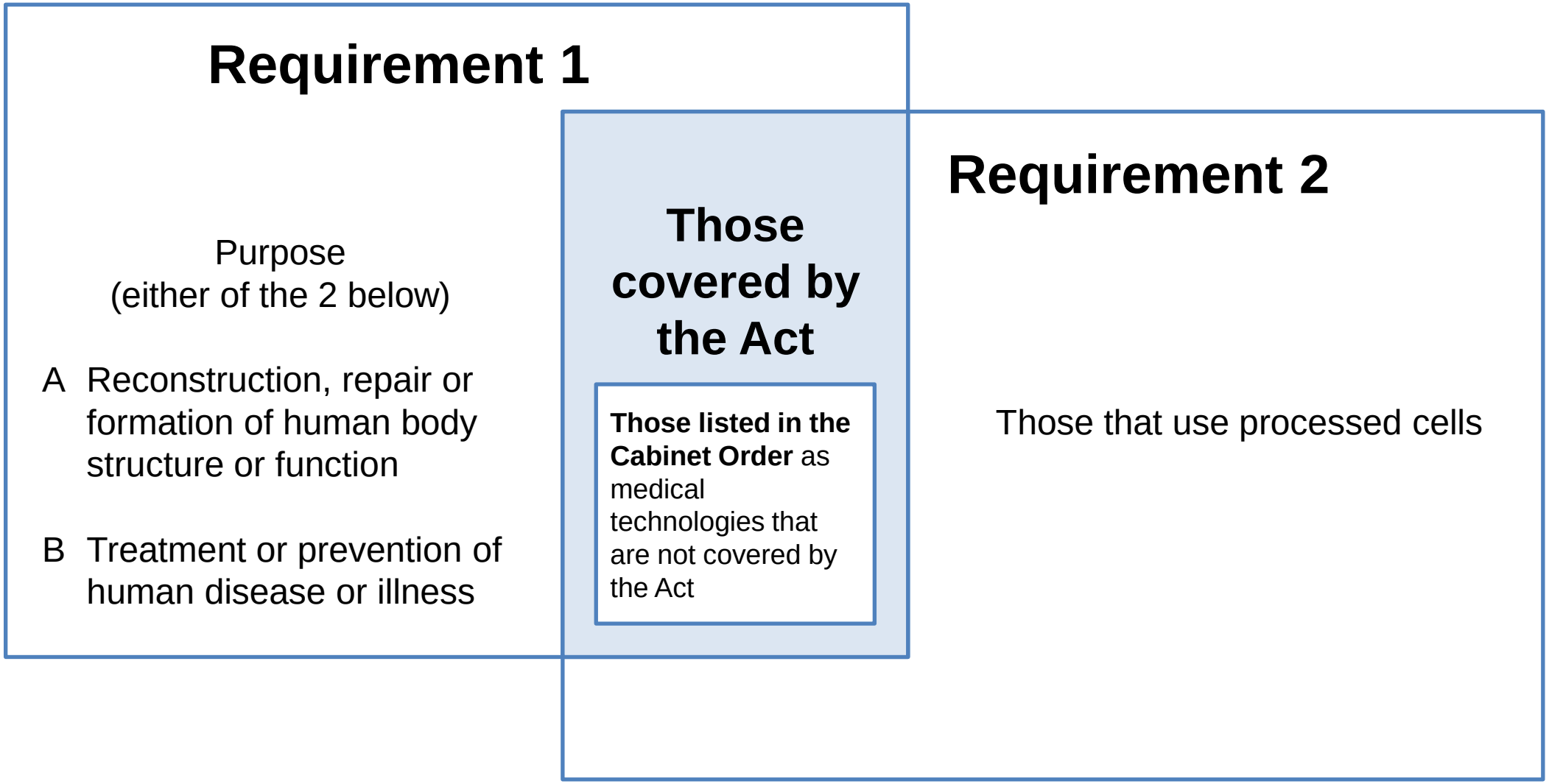
Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics

The efficacy and safety of regenerative medical products are ensured by stipulating standards for manufactory of regenerative medical products.

* Outsourcing of cell culturing and processing carried out under the responsibility of physicians based on the Regenerative Medicine Safety Assurance Act is exempt from the application of the Pharmaceutical and Medical Device Act.



2-1. Scope of Application of the Act <Conceptual Illustration>



2-2. Description of Cabinet Order

Contents of Article 1 (Scope of Regenerative Medical Technology)

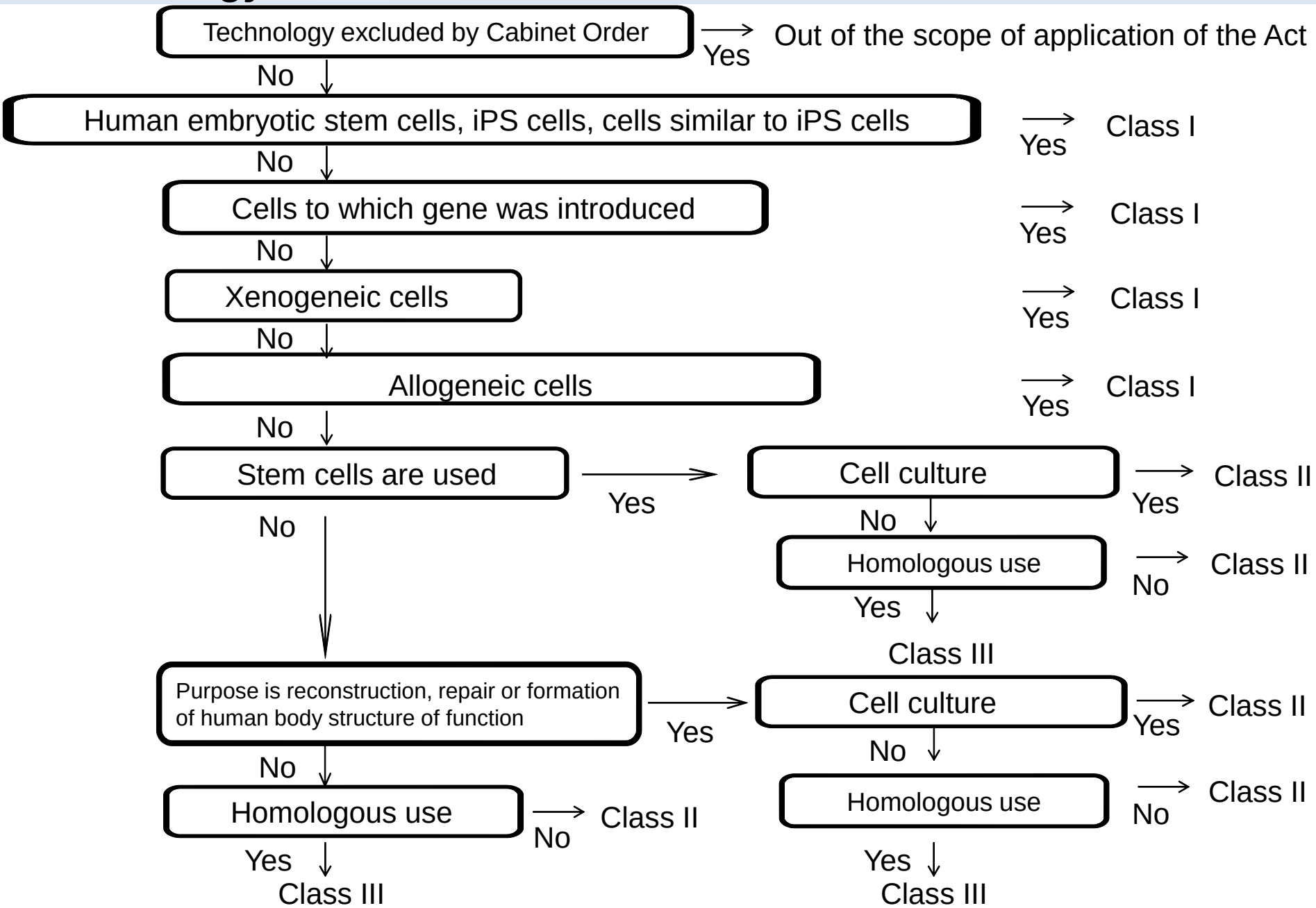
Medical technologies **other than the medical technologies** listed below among those that satisfy the requirement of purpose and that use cell products.

1. Blood transfusion that uses processed cells (excludes those that use gene-transferred blood cell constituents or blood cell constituents manufactured from iPS cells etc.)

2. Hematopoietic stem cell transplantation (excludes those that use gene-transferred hematopoietic stem cells or hematopoietic stem cells manufactured from iPS cells etc.)

3. Assisted reproductive technology: Medical technology that uses processed (e.g., cultured) cells of human sperm or unfertilized eggs (excludes those that use embryotic stem cells established from human sperm or unfertilized eggs collected from humans or processed (e.g., cultured) cells of such embryotic stem cells)

2-3. Risk Classification of Class I, Class II and Class III Regenerative Medical Technology



2-4. Processing

Article 2, Paragraph 4 of the Act

In this Act, “processed cells” refer to human or animal cells that underwent processing (e.g., culturing), “specific processed cells” refer to processed cells used in regenerative medicine other than regenerative medical products, and regarding cell products “manufacturing” refers to processing (e.g., culturing) of human or animal cells and “cell culturing and processing facility” refers to a facility that carries out manufacturing of specific processed cells.

(Definition of processing)

“Processing” stipulated in Article 2, Paragraph 4 of the Act refers to chemical treatment, biological property modification, combination of non-cell constituents, modification by gene engineering means, etc. carried out for the purpose of artificial multiplication/differentiation of cells or tissues, establishment of cells, activation of cells, etc. Separation of tissues, morcellation of tissues, separation of cells, isolation of specific cells (excludes isolation through biological or chemical treatment using chemicals etc.), treatment by antibiotics, cleaning, sterilization by gamma rays etc., refrigeration, thawing, etc. are not regarded as “processing” (this may not apply to procedures that are carried out for the purpose of developing structures or functions that are different from that of original cells).

2-5. Homologous Application

Manager Notification Ministerial Ordinance, Article 3, Item 3 related

(Definition of homologous use)

"Homologous use" refers to an administration method where the collected cells have the same function as that of cells at the relevant location of the recipient of regenerative medicine. For instance, while collection of fat cells from the abdominal region, separation of adipose-derived stem cells from the relevant cells and administration of the stem cells to the affected part of breast cancer therapy for the purpose of reconstruction of the breast falls under the category of homologous use, transvenous administration of the adipose-derived stem cells for the purpose of diabetes treatment does not fall under the category of homologous use because the purpose is not reconstruction. Additionally, regarding medical technologies where centrifuged peripheral blood is used without culturing, for instance, administration to the skin or inside the mouth falls under the category of homologous use, while administration to tissues with poor blood flow (e.g. articular cavity) does not fall under the category of homologous use.

3-2. Matters to Be Observed by Cell Processing Facilities

Article 2, Paragraph 8 of the Act

“Specific processed cells manufacturer” refers to an entity who received license/approval of manufacturing specific processed cells or an entity who submitted a notification on manufacture of specified processed cells.

- When manufacturing in places other than medical institutions etc. in Japan: License
- When manufacturing outside Japan: Approval
- When manufacturing in medical institutions etc. in Japan: Notification

  * License, approval and notification are required for each cell processing facility.

● Standards of structure and equipment (Article 42 of the Act)

Structure and equipment of cell processing facilities must conform to the standards of structure and equipment

● Standards of manufacture management, quality control, etc. (Article 44 of the Act)

Specified cell product manufacturers must observe the standards of manufacture management, quality control, etc.
(Contents of the Standards) Method of manufacturing and quality control of cell products, implementation method of testing and inspection, method of storage, etc.

3-3. Comparison with Revised Pharmaceutical Affairs Act

	Act on the Safety of Regenerative Medicine	Revised Pharmaceutical Affairs Act (regenerative medical products)
Structure and equipment	Standard based on Article 42 of the Act (Ministerial Ordinance) Outside hospital: License (PMDA investigation) Overseas: Approval (PMDA investigation) Inside hospital etc.: Notification	Pharmacy etc. structure and equipment standard (PMDA investigation)
Manufacture management, quality control, etc.	Standard based on Article 44 of the Act (Ministerial Ordinance) * Site inspection or inquiry by the Minister of HLW or PMDA depending on the circumstances	GCTP Ministerial Ordinance (PMDA investigation)

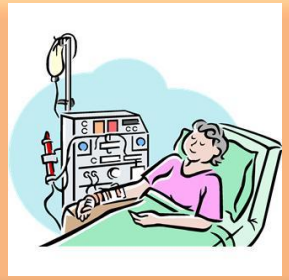
- For both Article 42 and Article 44 of the Act, **the same standards apply** regardless of the risk classification of regenerative medical technologies or manufacturing location of specified cell products (inside hospital or outside hospital).
- Conformity to Article 42 of the Act is required for licensing, approval or notification of cell culturing and processing facilities.

3-4. Structure and Equipment Standard Based on Article 42 of the Act

Structure and equipment standards for cell processing facilities (extract)

Structure of cell culturing and processing facilities	Placement of necessary equipment and apparatus, cleaning and maintenance, sanitary equipment, sectioning of areas (e.g., storage)
Laboratory	Lighting and ventilation, sectioning from unhygienic places, area, structure and equipment for protection from dust, insects and mice, equipment or apparatus necessary for processing waste water and waste, processing facility if toxic gas is used
Workroom	Necessary structure and equipment, structure of drainage facility, structure of the ceiling, structure of pipes, ducts, etc.
Workroom or work control area	Structure and facility that enable maintenance and control of the temperature and, if needed, humidity
Cleanliness control area	Cleanliness of the ceiling, wall and floor, sterilization or disinfection of equipment and apparatus, structure of drainage facility, non-installation of drainage outlets
Sterilization area	Cleanliness of the ceiling, wall and floor, sterilization or disinfection of equipment and apparatus, structure of drainage facility, non-installation of drainage outlets, non-installation of sinks
Storage facility	Installation of thermostat, thermometer and other necessary instruments
Testing and inspection	Installation of equipment and apparatus for testing and inspection

6-2. Conceptual Illustration of Procedures under the Regenerative Medicine Safety Assurance Act



Provision of regenerative medicine

Obligation to submit regenerative medicine provision plans

Medical institution

Enabled outsourcing of cell culturing/processing

Certified Committee for Regenerative Medicine

Certification

Cell culturing and processing

Cell culturing and processing facility

Obligation to notify or obtain license of cell processing facility

Notification (e.g., inside medical institution) or application for a license (e.g., corporate)

Minister of Health, Labour and Welfare

* The Act applies to regenerative medicine (clinical research, daily practice) that is carried out at medical institutions.