

Order for Enforcement of the Act on the Safety of Regenerative Medicine

(Cabinet Order No. 278 of August 8, 2014)

The Cabinet hereby enacts this Cabinet Order pursuant to the provisions of Article 2, paragraph (2), Article 10, paragraph (1), Article 35, paragraph (4), item (iii) (including as applied mutatis mutandis pursuant to Article 36, paragraph (2) and Article 39, paragraph (2) of the Act on the Safety of Regenerative Medicine (Act No. 85 of 2013)), Article 36, paragraph (1) (including as applied mutatis mutandis pursuant to Article 39, paragraph (2) of the same Act), Article 39, paragraph (2), Article 49, item (iii), Article 50, paragraph (1), item (iv), Article 51, item (iii), and Article 57, paragraphs (1) and (2) of the same Act.

(Scope of Regenerative Medicine Technology)

Article 1 The medical technology specified by Cabinet Order pursuant to Article 2, paragraph (2) of the Act on the Safety of Regenerative Medicine (referred to below as "the Act") refers to medical technology intended to be used for the reconstruction, repair, or formation of the structure or function of the human body, or for the treatment or prevention of human diseases, and is stated in the following items:

- (i) among medical technology stated in Article 2, paragraph (2), item (i) of the Act, medical technology other than the following:
 - (a) blood transfusion using processed cells (excluding those using blood cell components (meaning red blood cells, white blood cells, or platelets; the same applies below in (a)) whose properties have been altered, or blood cell components produced from human or animal cells (excluding medical technology stated in (c)));
 - (b) hematopoietic stem cell transplantation prescribed in Article 2, paragraph (2) of the Act on the Appropriate Provision of Hematopoietic Stem Cells for Transplantation (Act No. 90 of 2012) (excluding transplantation using hematopoietic stem cells that have undergone processing that alters their properties, or transplantation using hematopoietic stem cells produced from human or animal cells (excluding the medical technology stated in (c)));
 - (c) medical technology using human sperm (including sperm cells and spermatocytes whose number of chromosomes is equal to that of sperm; the same applies below in this sub-item (c) and the following item), unfertilized eggs (meaning unfertilized egg cells and oocytes whose number of chromosomes is equal to that of unfertilized egg cells; the same applies

below in this sub-item (c) and the following item), or embryos produced by fertilization between human sperm and unfertilized eggs, which have been cultured or otherwise processed (excluding those using embryonic stem cells derived from human sperm and unfertilized eggs collected from a human, or those cultured or otherwise processed from such embryonic stem cells (excluding those using human sperm or unfertilized eggs derived from such embryonic stem cells, or those cultured or otherwise processed from the sperm, unfertilized eggs, or embryos produced by fertilization between them));

- (d) medical devices prescribed in Article 23-2-5, paragraph (1) of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960), or specially controlled medical devices or controlled medical devices designated pursuant to the provisions of Article 23-2-23, paragraph (1) of the same Act, for which an application for approval under Article 23-2-5 or Article 23-2-17, or for certification under Article 23-2-23 of the same Act (simply referred to below as "approval or certification" in this sub-item (d) and sub-item (a) of the following item), has been filed and approved or certified—limited to applications describing matters concerning the effects of the medical devices or compliance with standards for specially controlled medical devices or controlled medical devices, as specified by Order of the Ministry of Health, Labour and Welfare, in the written application (referred to below as "approved or certified medical devices" in sub-item (a) of the same item)—and only processed cells obtained by culturing or otherwise processing human or animal cells using methods related to the approval or certification (meaning methods of use, effects, and performances; the same applies below in this sub-item (d) and sub-item (a) of the same item);
- (ii) medical technology specified in Article 2, paragraph (2), item (ii) of the Act, which introduces an item listed in the Appended Table into a human cell (excluding sperm, unfertilized eggs, and embryos produced by the fertilization of sperm and unfertilized eggs) in the human body, and which is not any of the following medical technologies:
 - (a) medical technology that uses only nucleic acids and related compounds generated using methods related to the approval or certification obtained for the approved or certified medical devices;
 - (b) medical technology that uses only nucleic acids and related compounds (limited to those specified by the Minister of Health, Labour and Welfare as necessary for the prevention of infectious diseases) that are pharmaceuticals prescribed in Article 2, paragraph (1) of the Act on Securing Quality, Efficacy and Safety of Products Including

Pharmaceuticals and Medical Devices, intended for use in the prevention of human diseases, and are authorized to be sold, provided, or stored or displayed for the purpose of sale or provision in a foreign country as prescribed in Article 14-3, paragraph (1), item (ii) of the same Act.

(Technical Replacement of Terms Relating to the Revision of a Provision Plan for Class I Regenerative Medicine)

Article 2 In cases where the provisions of Articles 8 and 9 of the Act are applied mutatis mutandis pursuant to the provisions of Article 10, paragraph (1) of the Act, the phrase "Article 4, paragraph (1)" in those provisions is deemed to be replaced with "Article 5, paragraph (1)", and the phrase "the provision plan for class I regenerative medicine" is deemed to be replaced with "the provision plan for class I regenerative medicine after revision".

(Laws Specified by Cabinet Order under Article 26, Paragraph (5), Item (ii) of the Act)

Article 3 The laws specified by Cabinet Order under Article 26, paragraph (5), item (ii) of the Act (including as applied mutatis mutandis pursuant to Article 28, paragraph (6) of the Act) are as follows:

- (i) the Child Welfare Act (Act No. 164 of 1947);
- (ii) the Medical Practitioners' Act (Act No. 201 of 1948);
- (iii) the Dental Practitioners Act (Act No. 202 of 1948);
- (iv) the Act on Public Health Nurses, Midwives, and Nurses (Act No. 203 of 1948);
- (v) the Medical Care Act (Act No. 205 of 1948);
- (vi) the Act on Mental Health and Welfare for Persons with Mental Disorders or Disabilities (Act No. 123 of 1950);
- (vii) the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices;
- (viii) the Pharmacists Act (Act No. 146 of 1960);
- (ix) the Long-Term Care Insurance Act (Act No. 123 of 1997);
- (x) the Act on Providing Comprehensive Support for the Daily Life and Life in Society of Persons with Disabilities (Act No. 123 of 2005)
- (xi) the Act on Medical Care for Patients with Intractable Diseases (Act No. 50 of 2014); and
- (xii) the Clinical Trials Act (Act No. 16 of 2017).

(Laws and Regulations Specified by Cabinet Order under Article 35, Paragraph (4), Item (iii) of the Act)

Article 4 The laws and regulations specified by Cabinet Order under Article 35, paragraph (4), item (iii) of the Act (including as applied mutatis mutandis

pursuant to Article 36, paragraph (2) and Article 39, paragraph (2) of the Act) are as follows:

- (i) the Act Regulating the Cultivation of Cannabis Plants (Act No. 124 of 1948);
- (ii) the Poisonous and Deleterious Substances Control Act (Act No. 303 of 1950);
- (iii) the Stimulants Control Act (Act No. 252 of 1951);
- (iv) the Narcotics and Psychotropics Control Act (Act No. 14 of 1953);
- (v) the Opium Control Act (Act No. 71 of 1954);
- (vi) the Act on Securing a Stable Supply of Safe Blood Products (Act No. 160 of 1956);
- (vii) the Pharmacists Act;
- (viii) the Act on the Control of Household Products Containing Harmful Substances (Act No. 112 of 1973);
- (ix) the Act on the Regulation of Manufacture and Evaluation of Chemical Substances (Act No. 117 of 1973);
- (x) the Act Concerning Special Provisions for the Narcotics and Psychotropics Control Act, etc. and Other Matters for the Prevention of Activities Encouraging Illicit Conducts and Other Activities Involving Controlled Substances through International Cooperation (Act No. 94 of 1991);
- (xi) the Act on Pharmaceuticals and Medical Devices Agency, Independent Administrative Agency (Act No. 192 of 2002);
- (xii) the Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003); and
- (xiii) the Clinical Trials Act.

(Valid Period of Permission for Manufacturing Specific Processed Cells, Specific Nucleic Acids, and Related Compounds)

Article 5 The period specified by Cabinet Order referred to in Article 36, paragraph (1) of the Act (including as applied *mutatis mutandis* pursuant to Article 39, paragraph (2) of the Act) is five years.

(Technical Replacement of Terms Relating to Certification for Manufacturing Specific Processed Cells, Specific Nucleic Acids, and Related Compounds Abroad)

Article 6 The technical replacement of terms under the provisions of Article 39, paragraph (2) of the Act is as shown in the following table.

Provisions of the Act that are deemed to be replaced	Terms to be replaced	Terms to be replaced
------------------------------------------------------	----------------------	----------------------

Article 35, paragraph (2)	the preceding paragraph	Article 39, paragraph (1)
Article 35, paragraphs (3) and (4)	paragraph (1)	Article 39, paragraph (1)
Article 35, paragraph (4), item (i)	Article 49	Article 50, paragraph (1)
Article 35, paragraph (5)	Paragraph (1)	Article 39, paragraph (1)
Article 36, paragraph (1)	paragraph (1) of the preceding Article	Article 39, paragraph (1)
Article 37	Article 35, paragraph (1)	Article 39, paragraph (1)
Article 38, paragraph (1)	Article 35, paragraph (5) (omitted)	Article 35, paragraph (5), as applied mutatis mutandis pursuant to paragraph (2) of the following Article
Article 38, paragraphs (2) and (3)	Article 35, paragraph (1)	paragraph (1) of the following Article
	Article 36, paragraph (1)	Article 36, paragraph (1), as applied mutatis mutandis pursuant to Article 36, paragraph (2)

(Laws and Regulations Specified by Cabinet Order under Article 49, Item (iii) of the Act)

Article 7 The laws and regulations specified by Cabinet Order under Article 49, item (iii), Article 50, paragraph (1), item (iv), and Article 51, item (iii) of the Act are those stated in the items of Article 4.

(Amount of Fees for Application to Renew Permission for the Manufacturing of Specific Processed Cells, Specific Nucleic Acids, and Related Compounds)

Article 8 (1) The amount of the fee that a person specified in Article 57, paragraph (1), item (i) of the Act must pay to the national government pursuant to the provisions of the same paragraph is 8,200 yen.

(2) The amount of the fee that a person specified in Article 57, paragraph (1), item (ii) of the Act must pay to the national government pursuant to the provisions of the same paragraph is 10,100 yen.

(Amount of Fees for Investigations by the PMDA)

Article 9 (1) The amount of the fee that a person intending to undergo an investigation prescribed in Article 35, paragraph (5) of the Act, regarding the permission prescribed in paragraph (1) of the same Article, provided by the Pharmaceuticals and Medical Device Agency (referred to below as the "PMDA" in this Article), pursuant to the provisions of Article 38, paragraph (1) of the

Act, must pay to the PMDA pursuant to the provisions of Article 57, paragraph (2) of the Act, is specified in each of the following items according to the category of permission stated in those items:

- (i) permission involving an on-site investigation: 144,000 yen; and
- (ii) permission not involving an on-site investigation: 98,200 yen;

(2) The amount of the fee that a person intending to undergo an investigation referred to in Article 35, paragraph (5) of the Act, as applied *mutatis mutandis* pursuant to Article 36, paragraph (2) of the Act, with regard to the renewal of a permission referred to in Article 36, paragraph (1) of the Act, conducted by the PMDA pursuant to the provisions of Article 38, paragraph (1) of the Act, must pay to the PMDA pursuant to the provisions of Article 57, paragraph (2) of the Act, is specified in each of the following items according to the category of permission renewal stated in those items:

- (i) renewal of a permission involving an on-site investigation: 97,100 yen; and
- (ii) renewal of permission not involving an on-site investigation: 48,600 yen.

(3) The amount of the fee that a person intending to undergo an investigation referred to in Article 35, paragraph (5) of the Act, as applied *mutatis mutandis* pursuant to Article 39, paragraph (2) of the Act, with regard to the certification referred to in Article 39, paragraph (1) of the Act, given by the PMDA pursuant to the provisions of Article 38, paragraph (1) of the Act, as applied *mutatis mutandis* pursuant to Article 39, paragraph (2) of the Act, must pay to the PMDA pursuant to the provisions of Article 57, paragraph (2) of the Act, is specified in each of the following items according to the category of certification stated in those items:

- (i) certification involving an on-site investigation: the amount obtained by adding the amount equivalent to the travel expenses to be paid by the PMDA in the case where two employees of the PMDA travel for the investigation (referred to as the "amount equivalent to travel expenses of PMDA employees" in item (i) of the following paragraph) to 120,500 yen;
- (ii) certification not involving an on-site investigation: 54,200 yen.

(4) The amount of the fee that a person intending to undergo the investigation referred to in Article 35, paragraph (5) of the Act, as applied *mutatis mutandis* pursuant to Article 39, paragraph (2) of the Act, with regard to the renewal of the certification referred to in Article 36, paragraph (1) of the Act, as applied *mutatis mutandis* pursuant to Article 39, paragraph (2) of the Act, and conducted by the PMDA pursuant to the provisions of Article 38, paragraph (1) of the Act, as applied *mutatis mutandis* pursuant to Article 39, paragraph (2) of the Act, must pay to the PMDA pursuant to the provisions of Article 57, paragraph (2) of the Act, is specified in each of the following items according to the category of certification renewal stated in those items:

- (i) renewal of certification involving an on-site investigation: the amount

- obtained by adding the amount equivalent to travel expenses of PMDA employees to 56,500 yen;
- (ii) renewal of certification not involving an on-site investigation: 37,100 yen.

Supplementary Provisions [Extract]

Appended Table (Re: Article 1, item (ii))

- (i) nucleic acids (limited to those containing genetic information necessary for gene expression);
- (ii) substances that have the function of processing the substances stated in the preceding item;
- (iii) substances that have the function of processing the substances specified by the Order of the Ministry of Health, Labour and Welfare as closely related to gene expression, other than those listed in item (i) (excluding those located outside the nucleus of cells);
- (iv) substances containing the substances stated in the preceding three items (excluding cell secretions).