Cell and Gene Therapy Medicinal Product Management Act (Draft) General Information

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At present there are still many diseases that cannot be cured by current medical technology and existing chemical or biological drugs; therefore, all relevant circles hope that perfect treatment can be provided at an early date through research and development in advanced medical technology and medicinal products. The medical and pharmaceutical circles and biotechnology industry play a leading active role involved in the research and development of advanced medical technology and medicinal products in seeking a breakthrough in the treatment of human diseases, to benefit numerous patients by relieving their pain, and improving their living quality. So, the development of cell therapy medicinal products or gene therapy-related medicinal products plays a key role, and brings a glimmer of hope of being cured to many patients.

Hence, it is necessary to enact regulations for the medical and pharmaceutical administrations to ensure the quality, safety and efficacy of cell and gene therapy medicinal products, in order to promote patients' rights, safeguard public health, and provide a clear and explicit legal environment that can mediate the existing relevant regulations to urge the researchers and developers of cell and gene therapy medicinal products to abide by them.

Thus, the U.S. Food and Drug Administration (hereinafter referred to as the "FDA"), based on the legislative authorization by the Public Health Service Act (hereinafter referred to as the "PHS Act") made by Congress, enacted the Regulation for the 21 Code of Federal Registration (hereinafter referred to as the "CFR") Part 1271, not only giving a common name as "human cells, tissues, and cellular or tissue-based products" (hereinafter referred to as the "HCT/Ps") to the cell therapy and gene therapy medicinal products and the definition thereof, but also formulating different laws and regulations according to the risk levels of HCT/Ps, as well as explicit stipulations regarding the procedures and

conditions for selling on the market. Besides, the European Union issued Directive 2003/63/EC in June 2003 to amend Directive 2001/83/EC, officially prescribing the gene therapy medicinal product (GTMP) and somatic cell therapy medicinal product (CTMP) as advanced therapy medicinal product (ATMP), and the information required to be submitted when applying for selling on the market. In 2007, it also promulgated the Regulation 1394/2007 with direct binding force on member countries, and then formally included the tissue engineered medicinal product (TEMP) in the scope of ATMP, with clearly stipulated documents and procedures necessary for review concerning ATMP products to be sold on the market. Japan, on the other hand, revised the former Pharmaceutical Affairs Law, and formulated the law related to ensure the quality, efficacy and safety of pharmaceuticals, medical devices and others (Pharmaceutical and Medical Device Act, PMD Act). In addition to the original regulations concerning pharmaceuticals and medical devices, definitions and a special chapter were added for tissue engineered products, cellular therapy products and gene therapy products (collectively called "regenerative medicine and other products"), with explicit stipulations regarding the "licensing" procedures for manufacturing and selling, manufacturing, and selling industries in relation to manufacturing and selling "regenerative medicine and other products" and the "ratification" procedures before review for "regenerative medicine and other products" to be sold on the market, with requirements on quality, effectiveness and safety; even the so-called "ratification system subject to certain conditions or time" was formulated concerning the review for "regenerative medicine and other products" to be sold on the market

In summary, the Cell and Gene Therapy Medicinal Product Management Act was drawn up with reference to relevant legislation at home and abroad, including the United States, Europe, Japan, etc. Besides, taking into consideration the characteristics of cell and gene therapy medicinal products and the situation of their actual medical use, cell and gene therapy medicinal products with human cell processing should comply with the provisions of the Act. However, for cell therapy without processing or in vitro cell culture procedure in the cell

manufacturing or operational process, and if the operational process does not change the original biological characteristics of the cells, it shall not be governed by the Management Act. Any other matters not covered in the Act, such as manufacturer and seller management, issuance or extension of the permit license, disclosure information and patent protection, product labelling, package leaflet, packaging and marking management, safety monitoring, reporting of adverse reactions, audit and banning, etc., shall be handled according to the Medical Care Act, Pharmaceutical Affairs Act and other relevant laws and regulations. The main points of the Act are as follows:

Article	Description
Article 1 (Legislative purpose) The Act is enacted to ensure the quality, safety and efficacy of cell and gene therapy medicinal products, and to prevent the introduction, transmission and spread of infectious diseases caused by the use of the products. Any other matters not prescribed in the Act shall be governed by relevant laws and regulations.	To ensure the quality, safety and efficacy of cell and gene therapy medicinal products, and to prevent the introduction, transmission and spread of infectious diseases caused by the use of the products, the legislative purposes for the cell and gene therapy medicinal products as set forth in the U.S.'s 21 CFR 1271, Japan's Pharmaceuticals and Medical Device Act and EU's Regulation 1394/2007 are referred to; ensuring the quality, safety and efficacy of the cell and gene therapy medicinal products, as well as preventing the introduction, transmission and spread of infectious diseases caused by the use of the products are listed under the legislative purpose of the Act.
Article 2 (Competent authority) "Competent authorities of health" in this Act mean the Ministry of Health and Welfare at the central level; the municipality governments at the municipality level; and the county (city)	Competent authorities at the central and local levels in this Act are explicitly prescribed.

governments at the county (city) level.	
Article 3 (Terms and definitions) Terms and Definitions in this Act are described as follows: 1. The term "cell therapy medicinal product" in this Act means a product obtained through processing on human cells to obtain a diagnostic, therapeutic or preventive effect of human diseases. 2. The term "gene therapy medicinal product" in this Act means a product that makes the human body have a recombinant gene to obtain a diagnostic, therapeutic or preventive effect of human diseases. 3. The term "tissue engineered medicinal product" in this Act means a product with human cells being processed so that it can have tissue structure or function to transplant, repair or reconstruct human tissues or organs. 4. The term "cell and gene therapy medicinal product business" in this Act means manufacturing and selling the cell or gene therapy medicinal product.	1. This Article is about the definitions of the cell and gene therapy medicinal products. Comprehensive references are made to the U.S.'s 21 CFR 1271, Japan's Pharmaceuticals and Medical Device Act and the EU's Directive 2003/63/EC and Regulation 1394/2007. 2. The term "processing" means the handling methods, such as making cell proliferation or differentiation in vitro, transformation of cell activity or biological characteristics, cells mixed with non-cellular components or cells attached to non-cellular components, making cells into slices or stacks, or making cells contain or show foreign genes. 3. According to the management of pharmaceutical firms required by the Pharmaceutical Affairs Act, the firms engaged in the manufacturing and selling of cell and gene therapy medicinal products are collectively called the firms of cell and gene therapy medicinal products.
Article 4 (Ensure the suitability of donors) The suitability of donors should be guaranteed in R&D and manufacturing	1. This Article is formulated to protect the rights and interests of the public and to ensure that human cell products for cell or gene therapy

of cell as well as gene therapy medicinal products to ensure that cell or gene therapy medicinal products have no risk of infectious diseases. The R&D of cell and gene therapy medicinal products can only be conducted after the donors have been clearly informed of, and explained, the relevant rights and obligations with which such R&D are involved, with their full understanding and a written consent signed by them.	meet the safety requirements and have no risk of infectious diseases. 2. The central competent health authority is authorized to prescribe the method to judge the suitability of the donor.
Article 5 (Registration and market approval) For the manufacturing and import of cell and gene therapy medicinal products, the source of active pharmaceutical ingredients, specifications, functions, summary of manufacturing process, and the specification and method of testing, as well as other related information and certificates, accompanied by labels and use instructions in the original and Chinese languages, and samples, together with the fee paid, shall be filed with the central competent health authority for registration and market approval. No manufacturing or importation of such cell and gene therapy medicinal product shall be allowed until a permit license is approved and issued. Only the owners of a cell and gene therapy medicinal product permit license or their authorized persons may apply	1. It is clearly stipulated that no manufacturing or importation of such product shall be allowed until it is filed with the central competent health authority for registration and market approval, and a permit license is approved and issued. Paragraph 1 of this Act is formulated referring to Article 39 of the Pharmaceutical Affairs Act when Item 1 of this article is made. 2. In addition, the central competent health authority is authorized to prescribe the relevant review procedures for registration and market approval.

for import of cell and gene therapy medicinal products pursuant to the provisions of the preceding Paragraph. A cell and gene therapy medicinal product manufacturing or import permit license shall be valid for five (5) years. Where it is necessary to continue the manufacturing or importation of medicament upon permit license expiration, the permit license may be extended with the prior approval of the central competent health authority provided that the term of each extension is limited to no more than five (5) years. The permit license shall be revoked upon expiry of the term thereof if the permit license holder fails to file an application for extension, or if the application for extension is disapproved.	
Article 6 (Temporary license subject to certain conditions or time) When cell and gene therapy medicinal products are presumed to possess the efficacy mentioned in the relevant application and the safety is confirmed, after verification by the central competent health authority, a temporary permit license subject to certain conditions can be issued, but the validity period of the permit license shall not exceed five years. The manufacturers of cell and gene therapy medicinal products who have obtained the above-mentioned temporary permit license shall conduct application effectiveness tests in	1. The efficacy validation has not yet been conducted on part of the cell and gene therapy medicinal products, but there are sufficient data to presume efficacy. To take into consideration the rights of people in the country to use cell and gene therapy medicinal products as soon as possible, given that the safety has been ensured, a temporary license subject to certain conditions or time limit can be granted to differentiate from the permit license as prescribed in Article 6 referring to the provisions of Article 23 to Article 26 of Japan’s Pharmaceuticals and

accordance with the requirements of the central competent health authority, report the results to the central competent health authority, and reapply for the permit license within the approved validity period.	Medical Device Act. 2. When a temporary permit license of cell and gene therapy medicinal products is obtained in accordance with this Article, application effectiveness tests of cell and gene therapy medicinal products should continue to be conducted, and a reapplication for registration and market approval should be made within the validity period; if complying with the provision of Article 6, the temporary permit license can be changed to the product permit license.
Article 7 (Manufacturing standards for cell and gene therapy medicinal products) The manufacture of cell and gene therapy medicinal products shall comply with the good manufacturing practices; the manufacture may only begin after the central competent health authority has completed its inspection and granted approval, and the medicament manufacture license has been obtained. The provisions of the preceding paragraph shall apply mutatis mutandis to overseas manufacturing factories importing cell and gene therapy medicinal products.	To ensure the quality of cell and gene therapy medicinal products and prevent the occurrence, contagion and spread of infectious diseases, the manufacturing factories of cell and gene therapy medicinal products should abide by the standards set by the central competent health authority. The central competent health authority is authorized to prescribe the standards for the factory's related equipment. This Article is formulated referring to Article 57 and Article 57 (1) of the Pharmaceutical Affairs Act.
Article 8 (Information maintenance obligation of the firms of cell and gene therapy medicinal products) The firms of cell and gene therapy medicinal products shall establish the	1. To safeguard the rights and interests of the public, the central competent health authority shall specify a certain period to monitor the safety of cell and gene therapy medicinal

Patient Registration System to track patients who have been given the treatment with cell and gene therapy medicinal products. The registration system as referred to in the preceding paragraph shall continue to be effective within thirty years from the day of the expiration or revocation of the cell and gene therapy medicinal product permit license.	products approved to be manufactured or imported. The Patient Registration System should be established with the firms of cell and gene therapy medicinal products to track patients who have been given the treatment with cell and gene therapy medicinal products. This Article is formulated to effectively monitor the post-marketing safety. 2. The central competent health authority is authorized to prescribe the measures for the post-marketing safety monitoring on the cell and gene therapy medicinal products.
Article 9 (Advertisement management) Persons other than firms of cell and gene therapy medicinal products are not allowed to make advertisements for medicaments. Advertisements of cell and gene therapy medicinal products shall be published in academic medical journals. Interviews, news reports or propaganda containing information implying or suggesting medical efficacy shall be regarded as advertisements of cell or gene therapy medicinal products.	To safeguard the rights and interests of the public and avoid false information in advertisements, the measures are thus formulated to impose restrictions on the advertisements of cell and gene therapy medicinal products.
Article 10 (Measures formulated separately) The suitability of donors as referred to in Article 4, registration and market approval for a permit license of the cell and gene therapy medicinal product as	The central competent health authority shall be authorized to prescribe relevant measures to facilitate the implementation of practices.

referred to in Paragraph 1 of Article 5, or change or transfer of registration of cell and gene therapy medicinal products permit license to be handled in accordance with the regulations, the application criteria, inspection procedure and relevant good manufacturing practices as referred to in Paragraph 1 and 2 of Article 7, the Registration System as referred to in Article 8 and other matters to be complied with shall be prescribed by the central competent health authority.	
Article 11 (Penal provisions) Any person who violates the provisions of Article 5 and Paragraph 1 of Article 7 under this Act shall be subject to punishment with imprisonment for a period of not more than ten (10) years and may in addition thereto, be imposed with a fine of not more than NT$100,000,000. The offender set forth in the preceding Paragraph shall be punished with life imprisonment or imprisonment of not less than ten (10) years and may in addition thereto, be imposed with a fine of not more than NT$200,000,000 in case the said offence results in personal death; or with imprisonment of not less than seven (7) years and may in addition thereto, be imposed with a fine of not more than NT$150,000,000 in case the offence results in serious adverse health consequences. Any person who commits the	Penal provisions of any violation of the provisions under this Act are explicitly formulated.

offence set forth in the first Paragraph hereof by negligence shall be punished with imprisonment of not more than three (3) years, detention, or a fine of not more than NT$10,000,000. An attempt of the offence set forth in the first Paragraph hereof shall be punished.	
Article 12 (Penal provisions) Any person who violates the provisions of Article 8 shall be imposed with a fine of not less than NT$30,000 but not more than NT$2,000,000. A violator of the provision of Article 9 shall be issued a fine of not less than NT$200,000 but not more than NT$5,000,000.	Penal provisions of any violation of the provisions under this Act are explicitly formulated.
Article 13 (Law enforcement agency) The penalties specified in this Act shall be imposed by the municipal or county (city) competent health authority, and by the central competent health authority if necessary. In the event that the fines imposed under this Act are not paid within the time period specified, the case shall be transferred for compulsory execution according to law.	Penal provisions executed by the competent authority(ies) are explicitly formulated.
Article 14 (Enforcement rules) The Enforcement Rules of this Act shall be established by the central competent health authority.	It is made clear that the Enforcement Rules of this Act shall be prescribed by the central competent health authority.
Article 15 (Effective date) The Act shall become effective one year after the date of promulgation. This Act becomes effective after one year from the date of promulgation.	The response time is given to the related bodies including the competent authority for advocacy and preparation for the implementation of the Act.