DECEMBER 2014

COMMENTARY

Amendment to Drugs and Medical Devices Law in Japan Takes Effect

A material amendment to the law regulating drugs and medical devices in Japan has recently been implemented. The amendment mainly covers (i) establishing a fast-track authorization process for regenerative medicine products (described below), (ii) restructuring medical device regulations, and (iii) establishing reporting obligations for package inserts for drugs and medical devices. In addition, the name of the law regulating drugs and medical devices will be changed from the "Pharmaceutical Affairs Law" (Law No. 145 of August 10, 1960; "PAL") to "The Law on Ensuring Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices, etc." (referred to as the Pharmaceuticals and Medical Devices Law, or "PMDL").

The Law for Partial Amendment to PAL, etc. (Law No. 84 of November 27, 2013) was enacted on November 20, 2013 and promulgated on November 27, 2013. Its relevant Ministerial Ordinances and Notification, which provide detailed regulations concerning GxP quality guidelines for regenerative medicine products, were published during the period of July to November 2014, and the partial amendment was effective November 25, 2014.

Fast-Track Authorization Process for Regenerative Medicine products Established

Background

As shown by the work of Nobel Prize winner Professor Shiya Yamanaka, regenerative medical care using induced pluripotent stem cells is highly anticipated to be one of the methods for innovative medical care, and there is high demand for early access to such regenerative medicine products by patients. There remain, however, concerns regarding safety due to the characteristics of regenerative medicine products. Taking into consideration these issues, the PMDL establishes a new approval process for regenerative medicine products which enables a company to manufacture and market regenerative medicine products at an earlier stage under certain terms and conditions.

Definition of "Regenerative Medicine Products"

Regenerative medicine products are newly defined under the PMDL as follows (Article 2.9 of PMDL):

- A product for medical use in humans and/or animals to reconstruct, restore, or form the structure or function of a human or animal body, which cells of humans and/or animals are cultured or otherwise processed (i.e., regenerative medicine products);
- A product for medical use in humans and/or animals to remedy or prevent the disease, which cells of humans and/or animals are cultured or otherwise processed (i.e., cell therapy products); or
- A product for medical use to remedy the disease of humans and/or animals, which is introduced into the human or animal cells and includes a gene expressed in the body (i.e., gene therapy products).

Authorization Process

The PMDL establishes a new authorization process to manufacture and market the regenerative medicine products. Under the PMDL, there are two routes to obtain authorization. The first route is the same as the standard authorization system for drugs under the PAL (*see* chart (a)) (Article 23-25 of PMDL); thus, the efficacy and safety of the regenerative medicine product must be shown in order to obtain authorization, as is the case in the application for any drug. The concern in following the standard authorization procedure, however, is that it will take a significant amount of time to launch a regenerative medicine product because the quality of regenerative medicine products is heterogeneous by nature. It is therefore difficult to collect the data necessary to evaluate and demonstrate the efficacy of a regenerative medicine product, potentially leading to long delays in the approval process.

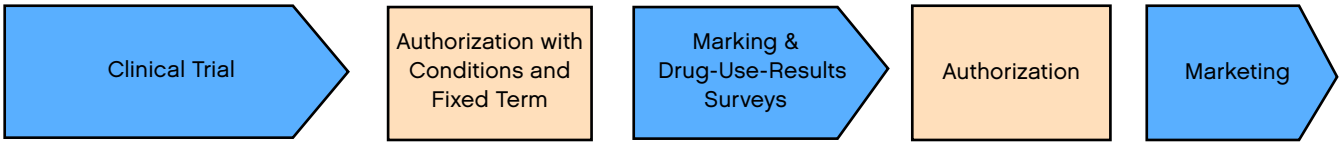
The second route is intended to address this concern. Using this second route, if the regenerative medicine product is heterogeneous, the efficacy of the regenerative medicine product is assumed. Thus, if the safety of the regenerative medicine product is demonstrated through clinical trials, the Minister of the Ministry of the Health, Labor, and Wealth ("MHLW") may authorize the applicant to manufacture and market the regenerative medicine products with certain conditions for a fixed term after receiving an expert opinion from the Pharmaceutical Affairs and Food Sanitation Council (*see* chart (b)).

An example of the "conditions" contemplated by the concept of "with certain conditions for a fixed term" is to restrict marketing places to medical organizations with professional doctors and equipment. A "fixed term" would be a term specified by the Minister of the MHLW upon the authorization, which does not exceed seven years after the authorization date (Article 23-26.1 of PMDL). If the applicant obtains authorization subject to certain conditions with a fixed term, it must conduct drug-use-results surveys in accordance with the regulations of good post-marketing surveillance practice and report the results to the Minister of the MHLW (Article 23-26.3 of PMDL), in parallel with manufacturing and selling the regenerative medicine product. Thereafter, by the end of the fixed term specified by the Minister of the MHLW, the authorization holder must apply for a nonconditional approval to manufacture and market the regenerative medicine product with application materials including drug-use-results surveys that demonstrate the efficacy and safety of the regenerative medicine product (Article 23-26.5 of PMDL).

With this amendment, it is expected that companies attracted by this fast-track authorization process may initiate research and development of regenerative medicine products and may commence to market such products earlier than previously anticipated, allowing patients to have earlier access to regenerative medicine products.

(a) Standard Authorization Process

(b) Fast-Track Authorization Process



Patent Term Extension on Regenerative Medicine Products

Under the current Patent Law (Law No. 121 of April 30, 1959) in Japan, the patent term is 20 years after the date of the patent application (Article 67.1 of Patent Law), and if the patent cannot be implemented due to safety or other reasons, including those arising under pharmaceutical regulations, the patent term can be extended for a maximum of five years upon the request of the patent holder (Article 67.2 of Patent Law, Article 3.2 of Enforcement Order of Patent Law). The period when the patent cannot be implemented is the term from the date of commencement of clinical trials for the drug or the registered date of the patent, whichever is later, to the date the patent holder receives the notice of drug authorization (Patent Examination Guideline on Patent Term Extension).

Along with the establishment of the fast-track authorization process for regenerative medicine products, the term extension for patents covering regenerative medicine products is also established by the new legislation. Under the amendment of Enforcement Order of the Patent Law,[1] the same patent term extension applies to regenerative medicine products. The period when the patent cannot be implemented in this case is the term from the date of commencement of clinical trials for the drug or the registered date of the patent, whichever is later, to the date the patent holder receives the notice of drug authorization with certain conditions and fixed term (Report by Working Group to Consider Patent Term Extension of the Regenerative Medicine Products of Patent System Subcommittee of Intellectual Property Committee of Industrial Structure Council on February 26, 2014). With this amendment, regenerative medicine products receive the same protection from a patent extension as that of standard pharmaceutical products.

Others

Due to the characteristics of regenerative medicine products, health care professionals are obligated to use significant efforts to explain the use of regenerative medicine products in an appropriate manner and obtain the informed consent of the user of these products (Article 68-4 of PMDL).

As with the regulations of certain medical devices, in order to prevent expansion of health care risks, the holder of a business license for the manufacture and marketing of regenerative medicine products must keep records of, and adequately maintain, the name, address, and other information concerning the distributor, hospital, or medical clinic and other related entities (Article 68-7.1 of PMDL). At the same time, the health care professional must keep records of the name, address, and other information concerning the users of regenerative medicine products (Article 68-7.3 of PMDL).

Restructuring of Medical Device Regulations

Background

As indicated by its name, the Pharmaceutical Affairs Act ("PAL") was focused on the regulation of drugs rather than medical devices. Recently, however, medical devices have been recognized to have the following characteristics that distinguish them from drugs: (i) medical devices are clinically

implemented, (ii) medical devices are continually undergoing improvement and the life cycle of any individual medical device is short, (iii) the efficacy and safety of medical devices depend largely on the doctor's technique, and (iv) a great number of types, but a small amount of each type, of medical devices are clinically used. Further, it takes a significant amount of time for new medical devices to be authorized and launched in Japan, and Japanese regulations need to be harmonized with international regulations for medical devices so that medical devices created in Japan can be commercialized globally. Taking into consideration these issues, the PMDL restructures the regulation of medical devices as follows.

Expansion of the Scope for Certification of the Registered Certification Body

The PAL incorporates the concept of the classification of medical devices in accordance with the classifications agreed upon by the December 2003 Global Harmonization Task Force ("GHTF") and classifies medical devices as follows:

Classification under GHTF	**Classification under PAL**		**Regulatory Requirements**
Class I	General Medical Devices	Extremely low risk to the human body in case of the failure of the medical devices	Notification to the Pharmaceuticals and Medical Devices Agency ("PMDA")
Class II	Controlled Medical Devices	Relatively low risk to the human body in case of the failure of the medical devices	Certification by a registered certification body (some medical products require authorization by the Minister of the MHLW after the PMDA review)
Class III	Specially Controlled Medical Devices	Relatively high risk to the human body in case of the failure of the medical devices	Authorization of the Minister of the MHLW after the PMDA review
Class IV	Specially Controlled Medical Devices	Highly invasive to the patients and life-threatening in case of the failure of the medical devices.	Authorization of the Minister of the MHLW after the PMDA review

Under the PMDL, the regulatory requirement of some medical devices (e.g., dental implants, contact lenses) that are classified as Class III changes from authorization by the Minister of the MHLW after the PMDA review to certification by a registered certification body. With this change, the PMDA is able to concentrate its resources on the review of high-risk medical devices and to speed up its review procedures (Article 23-2-23.1 of PMDL).

New Regulations on Medical Device Software

Medical device software (e.g., a program for processing, storage, and display of graphic data photographed by MRI (magnetic resonance imaging), etc.) by itself was previously not subject to the PAL, and it was reviewed along with the medical device hardware into which the medical software was incorporated. Due to the development of new systems using IT technology and harmonization with U.S. and EU regulations, however, the PMDL now covers medical device software as an independent medical device. Accordingly, software may be authorized as a medical device independent of the medical device hardware into which it is incorporated.

System Change for Medical Devices Manufacturing

Under the PAL, a company that wishes to manufacture a medical device must obtain authorization to do so. The PMDL changes this system so that a company may manufacture a medical device when the company registers such medical device (Article 23-2-3.1 of PMDL). With this change, the burden on the company manufacturing the medical device is mitigated to some extent (e.g., the company is not subject to an inspection of the manufacturing site's buildings and facilities).

Streamlined Quality Management Service ("QMS") Inspection

Under the PAL, a QMS inspection was performed for each medical device for its authorization and its renewal. Under the PMDL, this regulation is streamlined, which means that the QMS inspection is performed for each category of medical products. Thus, the company that applies for the authorization of a new medical device or has obtained approval is exempted from a QMS inspection if the following conditions are met:

- The company has already obtained a QMS regulation conforming certificate on its existing medical device and the existing medical device falls into the same category as the new medical device separately stipulated by a Municipal Order; and
- The new medical device will be manufactured at the manufacturing site in such regulation conforming certificate (Article 23-2-5.7 of PMDL).

For example, if a company has obtained a QMS regulation conforming certificate on an artificial blood vessel using collagen (Category: Artificial Blood Vessel) at site A and the company applies for authorization for an artificial blood vessel using gelatin (Category: Artificial Blood Vessel) at site A, the company will be exempted from the QMS inspection on an artificial blood vessel using gelatin. With this change, the QMS inspection burden on a company that applies for authorization of a medical device or requests renewal of an authorization will be mitigated.

Establishment of Notification Obligation for Package Inserts

Background

Under the PAL, the package insert for drug and medical devices must include certain information on the proper use of such drug or medical devices (Article 52 and 63-2 of the PAL), but the holder of a business license for the manufacture and marketing of drugs and medical devices is not obligated to obtain authorization for the package insert from, nor even notify, the Japanese government. In this respect, the "Panel to consider drug administration to prevent drug-induced hepatitis" pointed out that it is necessary to reconsider the legal status of package inserts and to clarify the responsibility of the government in its first proposal on April 30, 2009. Further, the "Committee to consider the revision of drugs, etc. regulations" of the Health Science Council issued its report on the revision of drugs, etc. regulations on January 24, 2011. According to the report, the committee discussed how to clarify the Japanese government's authority

regarding package inserts under the PAL. Eventually, the majority concluded that a company manufacturing and marketing a drug or medical device must notify the Japanese government regarding the contents of the package insert in advance of commencing manufacturing and marketing the drug or medical device and, if necessary, revise the package insert. Another proposal to require the government's authorization of the package insert was not adopted mainly due to the possible chilling effect such obligation would have on the provision of medical care. It was also pointed out that it is important to reflect the latest findings concerning drugs and medical devices, which is not clear under the PAL.

New Rule

Under the PMDL, when the holder of a business license for the manufacture and marketing of regenerative medicine products, drugs,[2] or medical devices manufactures and markets these products, the license holder must notify the Minister of the MHLW of the contents of the package insert, including any cautionary statements necessary to use and deal with these products and the other items, before it manufactures and markets them. The same rule applies when the license holder changes the package insert (Article 52-2.1, 63-3.1 and 65-4.1 of PMDL). Immediately after the license holder provides such notification, the license holder must publish the contents of the package insert on the website of the PMDA (Article 52-2.2, 63-3.1 and 65-4.2 of PMDL).

Lawyer Contacts

For further information, please contact your principal Firm representative or one of the lawyers listed below. General email messages may be sent using our "Contact Us" form, which can be found at www.jonesday.com

Scott T. Jones
Tokyo
+81.3.6800.1813
sjones@jonesday.com

Colleen M. Heisey
Washington
+1.202.879.3449
cmheisey@jonesday.com

Mark Mansour
Washington
+1.202.879.3883
mmansour@jonesday.com

Mitsutaka Okano
Tokyo
+81.3.6744.1606
mokano@jonesday.com

Laurie A. Clarke
Washington
+1.202.879.3498
lclarke@jonesday.com

Masatoshi Adachi
Tokyo
+81.3.6800.1837
madachi@jonesday.com

Endnotes

1 This amendment was promulgated on October 22, 2014 and came into effect on November 25, 2014.

2 Certain category of drugs including, but not limited to, in vitro diagnosis and drugs manufactured by drugstores are exempted from this rule.