Administrative Notice
December 28, 2012

To: Pharmaceutical Affairs Section, Prefectural Health Department (Bureau)

Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Questions and Answers (Q&A) on Drug Master Files (Part III)

Documents on “Q&A on Drug Master Files” were issued as Administrative Notices dated July 28, 2005 and December 20, 2005. As provided in the attachment, a new document on Q&A has been compiled. Please thoroughly inform the relevant business operators in your jurisdiction of this matter.

(Attachment)

Q&A on the Master File (MF) System (Part III)

(Question 1)	This amendment of the notification additionally qualifies "Materials relating to manufacture of cellular- and tissue-based products" for registration. Please tell reasons for such additional qualifications.

(Answer)

Now, human cellular- and tissue-based drugs and medical devices (hereinafter referred to as "cellular- and tissue-based products") is being actively developed, but from a viewpoint of protecting manufacturers' intellectual properties, information about cells, media, and medium additives used in manufacture of cellular- and tissue-based products is sometimes difficult to disclose among manufacturers, between a manufacturer and a person submitting a clinical trial notification, or among applicants for approval. Such difficulty can compromise safety evaluation of cellular- and tissue-based products, raising concerns. By this amendment that allows registration of these materials in the drug master file (hereinafter referred to as "MF") database, provisions are in place to protect manufacturers' intellectual properties and streamline the clerical review operations.

(Question 2)	From which stages of product development is an application for registration and utilization of the MF allowed?

(Answer)

Applicants are being asked to submit an application for MF registration in a timely manner that enables its utilization at the approval review stage for drugs or medical devices.

However, many manufacturing processes of cellular- and tissue-based products generally have difficulty incorporating steps for removal or inactivation of adventitious agents or adequate purification for removal of process-related impurities. Quality of raw materials and intermediates is highly likely to directly affect the safety of the products. Thus, their details probably need to be checked as a part of safety evaluation, not only at the approval review stage but also at a stage where a clinical trial notification or an application for confirmation of a gene therapy product is submitted in a process aiming at an application for approval or where a face-to-face consultation about such submission (hereinafter referred to as "review, etc.") is held. From a viewpoint of ensuring product safety, therefore, an application for registration of "Materials relating to manufacture of cellular- and tissue-based products" is allowed before the product review, enabling utilization of the MF during the review.

It should be noted that marketing authorization holders must know information directly relating to product safety, including that about manufacture. In addition, it should be understood that (a) the regulatory agency or the Ministry of Health, Labour and Welfare (MHLW) may ask MF registrants to disclose a part of the registered information, even designated as a non-disclosure part, to MF users such as marketing authorization holders based on its necessity during the review, etc.; and (b) for example, in the event where an MF registered for utilization in the manufacture of a product is to be utilized in another product, the information that should be disclosed to the marketing authorization holder during the review, etc. may be different from that disclosed during the previous review because the scope of the information affecting safety can differ depending on the intended use or method of use.

If an MF is utilized for a review, etc., a duplicate copy of the agreement with the MF registrant about utilization of the MF should be submitted. For application for registration of an MF based on another MF, a duplicate copy of the original MF registrant should be submitted when the application is submitted.

(Question 3) What does the term "Materials relating to manufacture of cellular- and tissue-based products" refer to?

(Answer)

It refers to media used in manufacture of cellular- and tissue-based products, biotechnological products/biological products, gene therapy products, medium additives (e.g., serum additives, growth factors, cytokines), and raw materials used for cell treatment. In addition, "Materials relating to manufacture of cellular- and tissue-based products" also include established cell lines. For details, see Question 5. Please refrain from registering cells used for screening for drug discovery and toxicological evaluation that are not applicable to "Materials relating to manufacture of cellular- and tissue-based products."

(Question 4) What types of media and medium additives are eligible for registration?

(Answer)

Eligible media and medium additives used in manufacture of cellular- and tissue-based products as provided in the answer to Question 3 are (a) materials of which ingredients or their quantities are manufacturers' intellectual properties; or (b) biological materials of which detailed information such as the ingredients, their quantities, and origin should be checked for safety evaluation and be disclosed to the regulatory agency during review, etc. but may not have to be disclosed to marketing authorization holders. Therefore, please refrain from registering the media (a) of which information such as the ingredients and the composition are deemed to be publicly known based on prior use (e.g., DMEM, MCDB, HAM, RPMI); (b) which are used in manufacture of drug substances using classical bacterial fermentation technologies for antibiotic production, etc.; and (c) of which detailed information is not required for the "Manufacturing method" field in an approval application form. It should be noted that the regulatory agency or MHLW may ask MF registrants to disclose a part of the registered information, even designated as a non-disclosure part, to MF users based on its necessity during the review, etc.

(Question 5) What types of cells are eligible for registration?

(Answer)

Eligible cells are established cell lines (a) which are expected to have therapeutic effects without undergoing further processing and thus considered as drug substances for pharmaceuticals or (b) which are considered as intermediates in the manufacturing process of a drug substance for pharmaceuticals. If the cells you want to register meet the above, they can be registered as a drug substance or an intermediate (because they are applicable to Section (2) 1) 1. Drug substances for pharmaceuticals, intermediates, and raw materials for formulation [bulk products in special dosage forms] under 2. Scope of MF utilization in the "Guidelines on Utilization of Master File for Drug Substances, etc." [PFSB/ELD Notification No. 0210004, dated February 10, 2005, of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW] [hereinafter referred to as "Amended MF Notification"] partially amended by the "Partial Amendment to the 'Guidelines on Utilization of Master File for Drug Substances, etc.'" [PFSB/ELD Notification No. 1228-27, dated

December 28, 2012, of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW]). This amendment to the notification will expand the existing scope eligible for registration, allowing newly established cell lines to be registered as "Materials relating to manufacture of cellular and tissue-based products" if they are considered as raw materials in the manufacture of a drug substance for cellular- and tissue-based products. The above cells that are allowed to be registered as drug substances, intermediates, or raw materials include human stem cells (e.g., ES cells, iPS cells, somatic stem cells).

(Question 6) What items can be included in an MF of cells to be registered?

(Answer)

Items that can be included in an MF to be registered are conventional "Information included in the registration certificate such as name of manufacturing site, Manufacturing method, Manufacturing process control, Quality control test, Specifications and testing methods, Stability tests, Non-clinical study (mainly for new excipients or additives)" (as provided in (2) 3) under 2. Scope of MF utilization in the Amended MF Notification) as well as, for registration of cells, Cells or tissues used as raw materials, Characteristics of biological raw materials used in manufacture of cellular- and tissue-based products, Information on donors, Characterization of the processed cells, and Non-clinical safety studies.