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April 28, 2016

To: Directors of Prefectural/Cities with Established Health Centers/District Health Department (Bureau)

Counsellor of Minister's Secretariat, Ministry of Health, Labour and Welfare
(Evaluation and Licensing of Medical Device/Cellular and Tissue-based Products)
(Official seal omitted)

Director of Compliance and Narcotics Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Legislation Notice to Applicants for Marketing Authorization of DNA Sequencers and Related Products Utilized for Genetic Testing Systems

The base sequence of nucleic acid extracted from biological specimens or specific DNA region amplified or concentrated from the extracted nucleic acid can be determined by DNA sequencers. Products detecting and utilizing such sequence information for disease diagnosis, etc., including companion diagnostic systems that determine whether or not pharmaceuticals can be administered, are expected to be used in medical practice. Based on the Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145, dated 1960. Hereinafter referred to as "Pharmaceuticals and Medical Devices Law"), the legislation notice of DNA sequencers and related products utilized for genetic testing systems is defined as follows. This notification is issued to ask your cooperation in making this information widely known to related businesses and medical institutions in your jurisdiction.

Furthermore, this notification describes the current perception towards DNA sequencers, etc., and is subject to modification based on further future technological advancements or accumulation of knowledge, etc.

1. Scope

This notification describes the regulation of DNA sequencers, etc. manufactured and marketed for the purpose of diagnosing, treating, or preventing diseases in accordance with the Pharmaceuticals and Medical Devices Law.

2. Definitions

(1) DNA sequencer

Device and operating program which determines and outputs the DNA sequence of nucleic acid extracted from biological specimens or specific DNA region amplified or concentrated from the extracted nucleic acid, .

(2) Sequencing sample preparation reagent

A set of reagents that are required when determining the base sequence of genes, etc. using a DNA sequencer regardless of genetic variations, etc. to be tested. Includes reagents that are required to prepare libraries for bioinformatics analysis of sequencers.

(3) Template DNA preparation reagent

Primer set and related reagents (excluding sequencing sample preparation reagents) used to amplify or concentrate specific DNA region from nucleic acid extracted from biological specimens for the purpose of diagnosing diseases, etc.

(4) Software for bioinformatics analysis

Software that determines variants of clinical significance (including fusion genes, insertions, deletions, and genetic polymorphisms) by referring to and comparing the sequence information of genes with internal and external databases.

(5) DNA sequencer diagnostic system

An entire diagnostic system composed of above-mentioned DNA sequencer, sequencing sample preparation reagents, template DNA preparation reagents, and software for bioinformatics analysis.

3. Regulation of DNA Sequencer Diagnostic Systems in Accordance with the Pharmaceuticals and Medical Devices Law

DNA sequencers, etc. which are manufactured and marketed for the purpose of diagnosing, treating, or preventing diseases are considered medical devices or in vitro diagnostic

products in compliance with the Pharmaceuticals and Medical Devices Law, and the regulation of each is outlined as in the following items.

Applicability of medical devices, etc. is determined comprehensively as well as individually based on factors such as genetic variations and display of products, package inserts, and claims in advertisements. For example, devices, etc. used for genetic testing for genes that cause diseases or that are related to targeted population of certain pharmaceuticals, or devices, etc. that make claims related to certain diseases including future risk of acquiring the disease are, as a general rule, considered to be medical devices or in vitro diagnostic products in which the law applies.

Furthermore, even if the device, etc. does not claim use in diagnosing diseases, etc., it will be considered as a medical device, etc. if the device is considered to be used for the purpose of diagnosing diseases, etc during review.

(1) DNA sequencers are considered as medical devices. Furthermore, if it is to be used in combination with software for bioinformatics analysis, it will not be considered a "gene analysis equipment", which is a class I medical device, since it is an active medical device that is meant to identify variants of clinical significance. Therefore, an application for marketing authorization must be submitted if such devices are to be manufactured and marketed. Moreover, the MHLW will deliberate on adding a new non-proprietary name in such circumstances.

(2) Given that sequencing sample preparation reagents are reagents required when using a DNA sequencer regardless of the genetic variations, etc. to be tested, it is acceptable to consider such reagents to be a component of DNA sequencers.

(3) Given that template DNA preparation reagents are reagents used for the purpose of diagnosing diseases, etc. in combination with DNA sequencers and software for bioinformatics analysis, it is appropriate to consider such reagents to be in vitro diagnostic products.

(4) Given that software for bioinformatics analysis is used for the purpose of diagnosing diseases, etc., it is appropriate to consider such software to be software for medical devices.

(5) If DNA sequencers, sequencing sample preparation reagents, template DNA preparation reagents, and software for bioinformatics analysis are to be manufactured and marketed by one marketing authorization holder, it will be acceptable to submit an application for marketing authorization for all these combined as one combination medical device.

4. DNA Sequencers for Research

If a DNA sequencer diagnostic system is to be used in a medical institution, etc. in order to diagnose diseases, etc., approved DNA sequencer, template DNA preparation reagents, and software for bioinformatics analysis which have been approved are recommended to be used.

In the case where a DNA sequencer, template DNA preparation reagents, and software for bioinformatics analysis are approved as components of a new DNA sequencer diagnostic system, if the medical institution, etc. would like to establish a DNA sequencer diagnostic system using the approved template DNA preparation reagents and the software for bioinformatics analysis with the DNA sequencer that has already been used for research use (hereinafter referred to as "DNA sequencer for research"), the medical institution, etc. needs to confirm whether the DNA sequencer for research can be used with the template DNA preparation reagents and the software for bioinformatics analysis.

Furthermore, for maintenance management of DNA sequencers for research, sales or repair of consumable parts or component parts are not considered as sales or repair of medical devices.

5. Genetic Variations of Uncertain Clinical Significance

DNA sequencer diagnostic system is capable of detecting multiple genetic variations simultaneously, including genetic variations of uncertain clinical significance. Although detecting genetic variations of uncertain clinical significance is not eligible for approval, providing the results as reference information is acceptable only when the physician considers it necessary. In such circumstances, caution must be exercised so that physicians are appropriately informed that the clinical significance of those genetic variations and analytical validity of the system for those variations are unknown.

Furthermore, displaying the clinical significance, etc. of genetic variations that have not been approved on the product or in the package insert, or using it in advertisement claims conflicts with Article 54 or Article 66 as applied mutatis mutandis pursuant to Article 64 of the Pharmaceuticals and Medical Devices Law, and should be taken into consideration.