PSEHB/PED Notification No. 1122-4
PSEHB/MDED Notification No. 1122-10
PSEHB/SD Notification No. 1122-7
PSEHB/CND Notification No. 1122-4
November 22, 2016

Attention to: Commissioner of Prefectural Health Supervising Department

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

Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
(Official seal omitted)

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

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

Amendments to the "Handling of Applications for Approval of Combination Products"

Handling of applications for approval of products that combine at least 2 different types of drug agents, instruments, and processed cells, which would be classified as drugs, medical devices, and regenerative medical products if distributed alone, and are marketed as united drugs, medical devices, or regenerative medical products has been specified in the "Handling of Applications for Approval of Combination Products" (PFSB/ELD Notification No. 1024-2, PFSB/ELD/OMDE/CMS Notification No. 1024-1, PFSB/SD Notification No. 1024-9, and

PFSB/CND Notification No. 1024-15, dated October 24, 2014, from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Counsellor to the Minister's Secretariat [in charge of review management of medical devices and regenerative medical products], from the Safety Division, Pharmaceutical and Food Safety Bureau, and from the Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare. Hereinafter referred to as "Combination Product Notification"). With this document, the Combination Product Notification is amended as shown below. Please ensure that related organizations under your jurisdiction are thoroughly informed.

The amended Combination Product Notification is provided in Appendix.

1 Amendments to Combination Product Notification

(1) 1 (2) [2] is amended as follows.

(2) [2] Kit products (refers to kit products defined in the "Handling of Kit and Other Products that Combine Solutions etc. to Injections" [PAB/ELD Notification No. 2-98, dated March 12, 1986, from the First Evaluation and Registration Division, the Second Evaluation and Registration Division, and the Biological Product Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare] [excluding those that are specified in Sections 1 and 3 of this notification and have a single container filled with drugs {limited to those without a device allowing injection into the body attached in advance} as well as those that are specified in Section 5 of this notification and have an inhaler filled with drugs {limited to those that would not be classified as medical devices if distributed alone}]. The same shall apply hereinafter.)

(2) Section 3 (7) is amended as shown below.

(7) For drugs that have been already approved and fall under combination products, "Combination products" should be entered in the column of remarks in the approval application form when the marketing authorization holder has any chance to submit it for an application for partial change approval or minor change notification. In addition, for drugs that fall under combination products but do not undergo change procedures by November 24, 2016, to have the above content entered in the column of remarks, the marketing authorization holder should submit the attached table filled with the brand name, approval number, etc. of the relevant drug to the Administrative Division I, Office of Review Administration, Pharmaceuticals and Medical Devices Agency by mail or in person by March 31, 2017.

Appendix

PFSB/ELD Notification No. 1024-2
PFSB/ELD/OMDE/CMS Notification No. 1024-1
PFSB/SD Notification No. 1024-9
PFSB/CND Notification No. 1024-15
October 24, 2014

Attention to: Commissioner of Prefectural Health Department (Bureau)

Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare
(Official seal omitted)

Counsellor of Minister's Secretariat of the Ministry of Health, Labour and Welfare
(for Medical Device and Regenerative Medicine Product Evaluation)
(Official seal omitted)

Director of the Safety Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare
(Official seal omitted)

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

Handling of Applications for Approval of Combination Products

Conventionally, handling of the products combining drugs with medical devices, which can be classified as kit products, has been instructed in the “Handling of Kit and Other Products that Combine Solutions etc. to Injections” (PAB/ELD Notification No. 2-98, dated March 12, 1986, from the First Evaluation and Registration Division, the Second Evaluation and Registration Division, and the Biological Product Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare [MHW]) and “Handling of Kit Products” (PFSB/ELD Notification No. 0213005, dated February 13, 2004, from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare [MHLW]). The recent enforcement of the Act for Partial Amendment of the Pharmaceutical Affairs Act, etc. (Act No. 84 of 2013)

(hereinafter referred to as the "Amendment Act") has come into effect, and a new approval system has established for cellular and tissue-based products. In association with this, the MHLW has decided to handle products combining drugs (except in vitro diagnostics. The same shall apply hereinafter.), medical devices, and/or regenerative medical products as provided below, with respect to applications for marketing approval and licensing, accreditation, and registration for marketing and manufacturing businesses as well as manufacturing control, quality control, and adverse reaction/malfunction reports. Please ensure that related parties under your jurisdiction are thoroughly informed.

This notification is effective as of the day of enforcement of the Amendment Act (November 25, 2014).

1 Scope of this notification

(1) This notification shall apply to products that combine at least 2 different types of drug agents, instruments, and processed cells (hereinafter referred to as "Drug agents, etc."), which would be classified as drugs, medical devices, and regenerative medical products if distributed alone, and are marketed as united drugs, medical devices, or regenerative medical products (hereinafter referred to as "Combination products").

(2) Combination products shall include:

[1] Set products (refer to combination products comprised of drug agents, etc., that are not integral and can be independently distributed as drugs, medical devices, or regenerative medical products)

[2] Kit products (refers to kit products defined in the "Handling of Kit and Other Products that Combine Solutions etc. to Injections" [PAB/ELD Notification No. 2-98, dated March 12, 1986, from the First Evaluation and Registration Division, the Second Evaluation and Registration Division, and the Biological Product Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare] [excluding those that are specified in Sections 1 and 3 of this notification and have a single container filled with drugs {limited to those without a device allowing injection into the body attached in advance} as well as those that are specified in Section 5 of this notification and have an inhaler filled with drugs {limited to those that would not be classified as medical devices if distributed alone}]. The same shall apply hereinafter.)

[3] Products comprised of drugs agents, etc. that cannot be independently distributed, such as medical devices integral with drug agents (except kit products)

(3) Products that combine medical devices for puncture, such as catheters and syringes, with topical disinfectants, used as drugs for skin disinfection at the site of puncture, and are entirely packaged and sterilized should be subject to the "Handling of Marketing Approval application, Marketing Certification application, Marketing Notification for combination medical device" (PFSB/ELD/OMDE Notification No. 0331002, dated March 31, 2009, by the Director of the Office of Medical Device Evaluation, the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW) but not subject to this notification. Of note, set products that combine drug agents and instruments other than the above are subject to this notification.

(4) Products composed of marketed drugs, medical devices, and/or regenerative medical products made commercially available by distributors should be subject to the "Handling

of Combined Drugs, etc." (PMSB/CD Notification No. 104, dated December 25, 1997, from the Compliance Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare) but not subject to this notification.

(5) General medical devices integral with drug agents or ones constituting regenerative medical products that may fall under (2) [3] and are specified as containers in the definition section for generic name of the relevant general medical device should be regarded as containers. Drugs or regenerative medical products comprised of drug agents or processed cells potentially falling under (2) [3] and general medical devices integral with them (limited to ones specified as a container in the definition section for generic name of the relevant general medical device) do not fall under the combination products defined in this notification.

(6) The following products specified in the "Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (MHW Ordinance No. 1 of 1961. Hereinafter, referred to as the "Enforcement Regulation") should be regarded as combination products defined in this notification: Article 98, Paragraph 2 and Article 228-20, Paragraph 3 "Drugs approved for marketing as products integral with instruments, etc."; Article 114-60, Paragraph 2 "Medical devices approved for marketing as products integral with drug agents"; and Article 137-60 "Regenerative medical products approved for marketing as products integral with instruments, etc.".

2 The applicable category of combination products: drugs, medical devices, or regenerative medical products

Which category the products potentially falling under combination products are classified into, drugs, medical devices, or regenerative medical products should be determined on an individual basis in view of the main function and purpose of the product. The determination may be made with reference to the examples provided below.

If having difficulty determining whether the product falls under combination products or not or which category the product is classified into, drugs, medical devices, or regenerative medical products, the applicant should consult with the Evaluation and Licensing Division or Office of Review Management of Medical Devices and Regenerative Medical Products, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare.

[1] Examples of combination products classified as drugs

Prefilled syringes for injection, injections with injector pen (with adjustable dosing system), asthma agents with inhaler (with adjustable respiratory intake system)

[2] Examples of combination products classified as medical devices

Drug-eluting stents, heparin-coated catheters, and bone cement containing antibacterial agents

[3] Examples of combination products classified as regenerative medical products

Cell suspensions in prefilled syringe, a set product of cell suspension and scaffolding material used by impregnating at clinical settings

3 Handling of approval applications

(1) Combination products shall be submitted for application as a single product corresponding to either drugs, medical devices, or cellular and tissue-based products.

(2) For drug agents, etc. constituting combination products (for combination products classified as drugs, instruments or processed cells; for combination products classified as medical devices, drug agents or processed cells; and for combination products classified as regenerative medical products, drug agents or instruments. The same shall apply hereinafter), no individual approval, certification, or acceptance of notification (hereinafter referred to as "Approval, etc.") for marketing of drugs, medical devices, or regenerative medical products is required, even if they are manufactured at manufacturing sites other than those of the combination products, the final products.

(3) To market drug agents, etc. constituting combination products as drugs, etc. corresponding to the final products, marketing business license and marketing approval would be required separately.

(4) If drug agents, etc. constituting a combination product have been granted approval, etc. as drugs, medical devices, or regenerative medical products, they may be described as ingredients or component parts in the approval application form of the combination product with the brand name, non-proprietary name, name of the marketing authorization holder, approval number, certification number, or notification number, and date of approval, etc. of the drug agents, etc. entered, and entries in the other columns in the approval application form may be abbreviated.

(5) For approval application, set products should be demonstrated to be clinically relevant, otherwise they may not be accepted in general.

(6) For combination products classified as drugs, "Combination products" should be entered in the column of remarks in the approval application forms. However, if the combination product falls under a "Kit product" defined in the "Handling of Kit and Other Products that Combine Solutions etc. to Injections" (PAB/ELD Notification No. 2-98, dated March 12, 1986, from the First Evaluation and Registration Division, the Second Evaluation and Registration Division, and the Biological Product Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare), "Combination products (kit product)" should be entered.

(7) For drugs that have been already approved and fall under combination products, "Combination products" should be entered in the column of remarks in the approval application form when the marketing authorization holder has any chance to submit it for an application for partial change approval or minor change notification. In addition, for drugs that fall under combination products but do not undergo change procedures by November 24, 2016, to have the above content entered in the column of remarks, the marketing authorization holder should submit the attached table filled with the brand name, approval number, etc. of the relevant drug to the Administrative Division I, Office of

Review Administration, Pharmaceuticals and Medical Devices Agency by mail or in person by March 31, 2017.

4 Licensing, accreditation, or registration of manufacturing business, and manufacturing control and quality control

(1) For combination products classified as drugs, medical devices, and regenerative medical products, license or accreditation, registration, and license or accreditation, respectively, of manufacturing business should be obtained. In this case, manufacturers of drug agents, etc. constituting combination products may not have to obtain license, accreditation, or registration.

(2) Inspections for compliance with the good manufacturing practice should be implemented in accordance with the Ministerial Ordinance on Good Manufacturing Practice for Drugs and Quasi-drugs for the combination products classified as drugs, the Ministerial Ordinance on Quality Management System for Medical Devices and In Vitro Diagnostics for ones classified as medical devices, and the Ministerial Ordinance on Good Gene, Cellular, and Tissue-based Products Manufacturing Practice for ones classified as regenerative medical products. Drug agents, etc. constituting combination products are not separately required to comply with the different ordinance from that applied to the combination products, the final products. However, for drug agents, etc. constituting combination products, appropriate purchasing control, etc. should be implemented in accordance with the good manufacturing practice applied to the relevant combination products.

5 Clinical Trial Notifications as well as Handling of Adverse Reactions and Malfunctions

(1) If a clinical trial notification is submitted for products that would be marketed as combination products (hereinafter referred to as “Investigational combination product”), it should be handled as a document for one of drug agents, instruments, and processed cells, and “Clinical trial for combination product” should be entered in the column of remarks.

(2) Notwithstanding (1), if evaluation of drug agents, etc. constituting the investigational combination products is separately planned, a clinical trial notification for the drug agents, etc. constituting the investigational combination products may be submitted in addition to that for the investigational combination products. In this case, in the column of remarks of the clinical trial notification, the information on the separately submitted clinical trial notification should be provided each other to allow cross-reference, including date of notification, the number of submissions of the notification, and the investigational ingredient code or clinical trial identification code. The person who submits clinical trial notifications for an investigational combination product may be different from one who submits clinical trial notifications for drug agents, etc. constituting the investigational combination product.

(3) Adverse reactions or malfunctions during clinical trials should be reported by the person who submitted the clinical trial notification for the investigational combination product. However, in the case of (2), adverse reactions or malfunctions related to the investigational combination product (except for those related to drug agents, etc. constituting the investigational combination product) should be reported by the person who submitted the clinical trial notification for the concerned investigational combination product, while those related to drug agents, etc. constituting the investigational combination product should be reported by one who submitted the clinical trial notification for the relevant drug agents, etc.

6 Handling of adverse reactions and malfunctions in post-marketing settings

(1) For combination products classified as drugs, malfunctions attributable to the constitutive instrument, if any, should be reported by the marketing authorization holder of the relevant combination products in accordance with Article 68-10, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (Act No. 145 of 1960. Hereinafter referred to as "PMD Act") and Article 228-20, Paragraph 3 of the Enforcement Regulation. However, for the combination products currently approved, such reporting shall be required on and after November 25, 2016, in accordance with Article 7 of the Supplementary Provisions of the Ministerial Ordinance for Development of Relevant Ministerial Ordinances Associated with the Enforcement of the Act Partially Amending the Pharmaceutical Affairs Act and the Cabinet Order for Development of Relevant Cabinet Orders and Transitional Measures Associated with the Enforcement of the Act Partially Amending the Pharmaceutical Affairs Act (MHLW Ordinance No. 87 of 2014). In addition, if the above provisions are applied, efforts shall be made to implement reporting in accordance with Article 68-10, Paragraph 1 of the PMD Act and Article 228-20, Paragraph 3 of the Enforcement Regulation and to develop the necessary systems even on or before November 24, 2016.

(2) For combination products classified as medical devices or regenerative medical products, adverse reactions or malfunctions attributable to the constitutive drug agents, etc., if any, should be reported by the marketing authorization holder of the relevant combination products in accordance with Article 68-10, Paragraph 1 of the PMD Act and Article 228-20, Paragraph 2 or 4 of the Enforcement Regulation.

(3) For the reporting method of adverse reactions, etc. related to combination products, the "Reporting of Adverse Reactions, etc. of Drugs, etc." (PFSB Notification No. 1002-20, dated October 2, 2014, of the Pharmaceutical and Food Safety Bureau, MHLW) should be referred to.

7 Others

(1) Because marketing authorization holders of combination products are required to control and understand the quality, efficacy, and safety of the products overall (hereinafter, referred to as "Quality, etc."), they should establish systems to collect important information about the drug agents, etc. constituting combination products, including the quality, etc. and changes to the products, regardless of whether the relevant drug agents, etc. are approved as drugs, medical devices, or regenerative medical products or not.

(2) If drug agents, etc. constituting a combination product have been granted approval, etc., and the contents in the approval, etc. are subject to changes (except minor changes not affecting the quality, etc. of the product), the marketing authorization holder of the relevant drug agents, etc. should notify the marketing authorization holder of the combination product of the changes in advance. In addition, the information considerably affecting the quality, etc. of the relevant drug agents, etc., if obtained, should be also reported to the marketing authorization holder of the combination product without delay.

(3) Applications for partial change approval in approved items or minor change notifications may be submitted in accordance with this notification on and after the date of its application. The changes not affecting the actual status of manufacturing, etc. may be implemented through minor change notifications, which keep the necessary specifications, usage, etc. unchanged from the approved matters, but more specific handling should be separately notified. Or the approved matters may be maintained without submission of applications for partial change approval or minor change notifications. In this case, necessary procedures such as renewal of business license shall be taken in a timely and appropriate manner according to the contents of the approval certificate.