



October 24, 2014

## Notification

PFSB/ELD Notification No. 1024-2  
PFSB/ELD/OMDE Notification No. 1024-1  
PFSB/SD Notification No. 1024-9  
PFSB/CND Notification No.1024-15

To: Commissioner of Prefectural Health Department (Bureau)

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

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

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

### Handling of Marketing Application for Combination Products

The handling of products that combine drugs and medical devices had been indicated for kit products in the *Handling of Kit and Other Products that Combine Solutions etc. to Injections* (PAB/ELD Notification No. 2-98 by the director of the First Evaluation and Registration Division, the director of the Second Evaluation and Registration Division, and the director of the Biological Products Division of the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated March 12, 1986) and the *Handling of Kit Products* (PFSB/ELD Notification No. 0213005 by the director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated February 13, 2004). The *Act for Partial Amendment of the Pharmaceutical Affairs Act, etc.* (Act No. 84, 2013) has come into effect, and a new approval system has established for cellular and tissue-based products. Therefore, the handling of products that combine drugs (excluding in vitro diagnostics; same hereinafter), medical devices or cellular and tissue-based products has been established as follows regarding product marketing approval application; license, certification, or registration for marketing authorization holders and manufacturers; quality management; and adverse drug reaction/malfunction reports. We ask you to inform marketing authorization holders and relevant organizations placed under your administration regarding this matter.

This notification shall be applied from the effective date of the revised act (November 25, 2014).



## 1. Scope of This Notification

(1) This notification applies to products marketed as a single drug, medical device, or cellular and tissue-based product that combine two or more types of drug, device, processed cell, etc. (hereinafter referred to as “drugs etc.”) that are expected to fall under the category of drugs, medical devices, or cellular and tissue-based products if marketed individually (hereinafter referred to as “combination products”).

(2) Combination products shall include the following products:

(a) Set products (combination products in which the constituting drugs etc. are not indivisible and each can be marketed individually as either a drug, medical device, or cellular and tissue-based product.)

(b) Kit products (“kit products” specified in the *Handling of Kit and Other Products that Combine Solutions etc. to Injections* (PAB/ELD Notification No. 2-98 by the director of the First Evaluation and Registration Division, the director of the Second Evaluation and Registration Division, and the director of the Biological Products Division of Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated March 12, 1986)

(c) Products in which the constituting drugs etc. cannot be marketed individually, such as medical devices etc. that cannot be separately used from drugs (excluding kit products)

(3) Products in which medical devices for puncture, such as catheters and injections, and external disinfectants used as drugs for disinfecting the skin at the puncture site are combined and then they are packaged together and sterilized shall be handled in accordance with the *Handling of Marketing Approval application, Marketing Certification application, Marketing Notification for combination medical devices* (PFSB/ELD/OMDE Notification No. 0331002 by the director of the Office of Medical Devices, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 31, 2009) and not be the subject of this notification. Other set products that combine drugs and devices are the subject of this notification.

(4) Products in which marketed drugs, medical devices, or cellular or tissue-based products are sold together by distributors shall be handled according to the *Handling of Combination Drugs etc.* (PMSB/IGD Notification No.104, by the director of Inspection and Guidance Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare, dated December 25, 1997) and not be the subject of this notification.

(5) “Drugs Approved for Integral Marketing with Devices” specified in Article 98-2, and Article 228-20-3; “Medical Devices Approved for Integral Marketing with Drugs” specified in Article 114-60-2; and “Cellular and Tissue-based Products Approved for Integral Marketing with Devices etc.” specified in Article 137-60 of



the *Ministerial Ordinance for Enforcement of the Act for Ensuring etc. the Quality, Efficacy, and Safety of Drugs, Medical Devices, etc.* (Ordinance of the Ministry of Health and Welfare No. 1 of 1961. Hereinafter referred to as the “Ministerial Ordinance for Enforcement”.) shall be the subject of combination products specified in this notification.

## 2. Judgment on Correspondence of Combination Products to Drugs, Medical Devices, or Cellular and Tissue-based Products

Products thought to correspond to combination products shall be individually judged as to whether they fall under the category of drugs, medical devices, or cellular and tissue-based products with the consideration of their primary function and purpose. Refer to the following examples when making a judgment.

In the case of difficulty in judging whether the product corresponds to combination product, or whether the combination product corresponds to either drugs, medical devices, or cellular and tissue-based products, consult the Evaluation and Licensing Division or the Office of Medical Device/Cellular and Tissue-based Products of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare.

### (a) Example of combination products that correspond to drugs

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

### (b) Example of combination products that correspond to medical devices

Drug-eluting stents, heparin-coated catheters, antibacterial bone cements

### (c) Example of combination products that correspond to cellular and tissue-based products

Cell suspensions in pre-filled syringe; a set product of cell suspension and scaffolding used by impregnating at clinical settings

## 3. Handling of Marketing Application

(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) Drugs, etc. constituting a combination product (devices, processed cell, etc. for combination products that correspond to drugs; drugs, processed cell, etc. for combination products that correspond to medical devices;



drugs, devices etc. for combination products that correspond to cellular and tissue-based products. The same hereinafter.) shall not require individual marketing approval, certification, or notification (hereinafter referred to as “approval etc.”) of drug, medical device, or cellular and tissue-based product even if they are manufactured at a manufacturing site other than where the final combination product is manufactured.

(3) The drug etc. constituting the combination product requires a separate license for marketing authorization holder, marketing approval, etc., if the drug etc. is marketed as a final product.

(4) If the drug etc. constituting the combination product is already approved, etc., as a drug, medical device, or cellular and tissue-based product, specify in the application form for the combination product the brand name, generic name, the name of marketing authorization holder, approval number, certification number or notification number, and the date of approval etc. of that drug etc. as the active ingredients or component parts, and other entries into that application form etc. may be abbreviated.

(5) Because set products are generally not approved other than those with clinical necessity, indicate their clinical necessity when submitting their marketing approval application.

(6) State “combination product” in the Comments column of the application form for combination products that correspond to drugs. However, state “combination product (kit product)” if the combination product corresponds to the “kit products” specified in the *Handling of Kit and Other Products that Combined Solutions etc. to Injections* (PAB/ELD Notification No. 2-98 by the director of the First Evaluation and Registration Division, the director of the Second Evaluation and Registration Division, and the director of the Biological Products Division of Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated March 12, 1986).

(7) For approved drugs corresponding to combination products, seek an opportunity to submit either the application for partial change or the minor change notification, and state “combination products” in the Comments column of the application form. For drugs that correspond to combination products in which their changes have not been submitted by November 24, 2016, fill in the brand name and approval number of the drug in the table of the attachment of this notification and submit it to the Administration Division I, Office of Review Administration, Pharmaceuticals and Medical Devices Agency by the above date in order to enter the above details in the Comments column of the application form. However, this notification is not necessary if the “kit product” has already been stated in the Comments column of the marketing application form.



#### 4. License, Accreditation, or Registration, and Manufacture and Quality Management

(1) The manufacturer of combination products shall obtain: license or accreditation for manufacturer of drugs if the combination product is a drug; registration for manufacturer of medical devices if the combination drug is a medical device; or license or accreditation for manufacturer of cellular and tissue based-products if the combination product is a cellular and tissue-based product. License, accreditation, or registration is not required for manufacturers who manufacture the drugs etc. that constitute the combination product.

(2) Compliance assessment concerning the standards for manufacture and quality management shall be conducted according to: the Ministerial Ordinance on Good Manufacturing Practice (GMP) for Drugs and Quasi-drugs for combination products that are drugs; the Ministerial Ordinance on Quality Management System (QMS) for Medical Devices and In Vitro Diagnostics for combination products that are medical devices; or the Ministerial Ordinance on QMS for Cellular and Tissue-based Products for combination products that are cellular and tissue-based products. The drugs etc. that constitute the combination product do not require any other compliance to standards different from those applied to the final combination product. However, an appropriate purchasing control etc. shall be conducted for drugs etc. that constitute the combination product in accordance with the GMP and QMS applicable to the combination product.

#### 5. Clinical Trial Notification, and Handling of Adverse Drug Reactions and Malfunctions

(1) When submitting a Clinical Trial Notification for a product that is expected to correspond to a combination product after launch for the market (hereinafter referred to as “investigational combination product”), state in the Comments column “clinical trial on combination product” and submit as a single notification for either a drug, device, or processed cell, etc.

(2) When evaluating drugs etc. that constitute the investigational combination product regardless of the rule specified in the above section (1), the rule shall not hinder the applicant to submit the investigational plan of the drugs etc. constituting the investigational combination product in addition to the investigational plan of the investigational combination product. In this case, the Comment column of the Clinical Trial Notifications shall each include the date of submission, number of submission, and investigational ingredient code or clinical trial identification code regarding the clinical trial whose notification will be submitted separately. The applicant of the Clinical Trial Notification for the investigational combination product can be different from the applicant for drugs etc. that constitute the investigational combination product.

(3) Adverse drug reactions and malfunctions shall be reported by the applicant of the Clinical Trial Notification for investigational combination product. However, in the cases of the above section (2), adverse



drug reactions and malfunctions related to the investigational combination product (excluding adverse drug reactions and malfunctions related to drugs etc. constituting the investigational combination product) shall be reported by the applicant of the Clinical Trial Notification for the investigational combination product, and adverse drug reactions and malfunctions related to the drugs etc. that constitute the investigational combination product shall be reported by the applicant of the Clinical Trial Notification for that drug etc.

## 6. Handling of Post-marketing Adverse Drug Reactions and Malfunctions

(1) Regarding combination products that correspond to drugs, malfunctions caused by the device that constitutes the product shall be reported by the marketing authorization holder of the combination product in accordance with Article 68-10-1 of the *Act for Ensuring etc. the Quality, Efficacy, and Safety of Drugs, Medical Devices, etc.* (Act No. 145 of 1960. Hereinafter referred to as “Act on Drugs, Medical Devices etc.”) and Article 228-20-3 of the *Ministerial Ordinance for Enforcement*. However, previously approved combination products shall be required this reporting starting from November 25, 2016 in accordance with Article 7 of the Supplementary Provisions the *Ministerial Ordinance Regarding Development etc. of Related Ministerial Ordinance* (MHLW Ordinance No. 87, 2014) for Enforcement of the *Cabinet Order on the Development etc. of Related Cabinet Order and Interim Measures for Enforcement of the Act on Partial Amendment of the Pharmaceutical Affairs Act etc.* Efforts shall be made to submit these reports in accordance with Article 68-10-1 of the Act on Drugs, Medical Devices etc. as well as Article 228-20-3 of the Ministerial Ordinance for Enforcement, and to develop a necessary system for this even before November 24, 2016.

(2) Regarding combination products that correspond to medical devices or cellular and tissue-based products, adverse drug reactions and malfunctions caused by drugs etc. that constitute the product shall be reported by the marketing authorization holder of the combination product in accordance with Article 68-10-1 of the Act on Drugs, Medical Devices etc. and Article 228-20-2 or 4 of the Ministerial Ordinance for Enforcement.

(3) Refer to the “Reporting on Adverse Drug Reactions etc. of Drugs etc.” (PFSB Notification No. 1002-20, dated December 2, 2014) regarding the method of reporting adverse drug reactions etc. related to combination product etc.

## 7. Miscellaneous

(1) Because marketing authorization holders are required to manage and obtain knowledge of the quality, efficacy, and safety (hereinafter referred as “quality etc.”) of the entire combination product, a system shall be ensured to obtain knowledge of important information regarding the drugs etc. including quality etc. and any change etc. in product information, regardless of whether the drugs etc. constituting the combination product have been approved etc. as a drug, medical device, or cellular and tissue-based product.



(2) If the drugs etc. constituting the combination product have received approval etc., and the marketing authorization holder of the drugs etc. is to change the content of that approval etc. (excluding minor changes that will not influence the quality etc. of the product), a notification must be sent in advance to the marketing authorization holder of the combination product. Any information that may largely influence the quality etc. of the drug, must also be promptly reported to the marketing authorization holder of the combination product upon obtaining that information.

(3) After the effective date of this notification, an application for partial change or minor change notification can be submitted in accordance with this notification. If there is no change in the actual status of manufacturing etc., minor change notification may be acceptable by writing the same information on specifications and use as the approved product information in the form; however, specific handling will be notified via separate notification. Approved product information can be maintained without submitting an application for partial change or minor change application; however, necessary procedures shall be taken in accordance with the details of the approval document, for example, updating the license for marketing authorization holder, at an appropriate time and via an appropriate method.



## Attachment

### List of Combination Products (Drugs)

Date of Submission	month day year			
Marketing Authorization Holder				
Marketed Combination Product	Brand Name	Generic Name	Approval Number	Approval Date
Person in Charge	Name:  Address:  (Phone)  (E-mail)			
Comments				