(Attachment)

# Questions and Answers (Qs&As) on Handling of Applications for Approval of Combination Products

* The following abbreviations are used in this collection of questions and answers.

"Kit Product Notification"
"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])

"Combination Product Notification"
"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, MHLW)

"Amended Combination Product Notification"
"Amendment of the "Handling of Applications for Approval of Combination Products"" (PSEHB/PED Notification No. 1122-4, PSEHB/MDED Notification No. 1122-10, PSEHB/SD Notification No. 1122-7, and PSEHB/CND Notification No. 1122-4, dated November 22, 2016, from the Pharmaceutical Evaluation Division, the Medical Device Evaluation Division, the Safety Division, and the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)

"Components"
Drug agents, instruments, and processed cells constituting combination products

"Main component"
Part corresponding to drug agents in combination products classified as drugs, instruments in combination products classified as medical devices, and processed cells in combination products classified as regenerative medical products

"Sub-component"
Parts other than the main component

○ Scope of the Combination Product Notification and the applicable category of combination products (drugs, medical devices, or regenerative medical products)

Q1:
Is it acceptable to determine that drugs or regenerative medical products combined with an instrument which would not be classified as a medical device if distributed alone do not fall under combination products?

A1:
Yes.

Q2:
Is it acceptable to determine that drugs or regenerative medical products combined with an instrument which would be classified as a medical device if distributed alone all fall under combination products?

A2:
Not all are applicable. For example, a single-use infusion container (so-called single bag) consisting of a single tank with neither a pre-set device to inject a drug into the body nor a temporary connector and products using a dosing spray bottle as a sub-component do not fall under combination products.

Q3:
Do all the kit products (Cases 1 to 5) presented in the Kit Product Notification fall under combination products?

A3:
Not all are applicable. Of the kit products, the following ones do not fall under combination products: the kit products including the sub-component of a so-called single bag (see A2 above) and the kit products with drugs filled in an inhalator (corresponding to Case 5 in the Kit Product Notification) including the sub-component of an instrument that would not be classified as a medical device if distributed alone.

For the products that are described as a “Combination product (kit product)” in the column of remarks in the approval application form but do not fall under combination products, the relevant description should be changed to “Kit product” when any chance to submit an application for approval of partial changes in approved items for marketing (hereinafter referred to as “Application for partial change approval”) or minor change notifications occurs.

Q4:
What do “asthma agents with inhaler (with adjustable respiratory intake system)” presented as an example of combination products classified as drugs in the Combination Product Notification look like?

A4:
The product includes an instrument of an inhaler equipped with the adjustment function of inhalation dose, particle size, etc. (adjustable respiratory intake system, etc.), which would be classified as a medical device if distributed alone.

Q5:
Do prefilled syringe products fall under combination products regardless of the presence or absence of a needle?

A5:
Yes.

○ Handling of approval applications

Q6:
If an application for marketing approval of the combination product classified as a drug and uses the sub-component of an instrument, how should the sub-component be described?

A6:
The contents corresponding to the intended use and indications of the sub-component should be provided in the column of “Ingredients and quantities or nature,” and the following actions should be taken depending on whether approval, etc. has been granted or not.

(1) If the sub-component has been individually granted approval, certification, or acceptance of notification (hereinafter referred to as “Approval, etc.”) as a medical device, the brand name, generic name, name of the marketing authorization holder, approval number, etc., and date of approval, etc. should be provided in the column of manufacturing method in the approval application form. In addition, the information included in “Shape, structure and principle” should be provided in the Appendix where appropriate.

(2) If the sub-component is not individually granted approval, etc. as a medical device, the information included in the approval certificate of a general medical device should be provided in an appendix. More specifically, the information included in “Shape, structure and principle,” “Raw materials,” “Specifications for performance and safety,” and “Method of use,” the items in the approval certificate of a medical device, should be provided. For the “Manufacturing method,” the information on the manufacturing process is not required in principle, but if sterilized products are used, the information on the sterilization method should be provided. Information on sterilization validation

should be provided in the CTD. For the “Storage and shelf life,” if the shelf life of the relevant instrument is longer than that of the drug agent, the main component, the shelf life of the drug agent may be provided.

Q7:
If a description of the sub-component is abbreviated according to A6 (1) and information on the sub-component is provided in the approval certificate in place of the approval number according to A6 (2), what procedures should be taken?

A7:
In principle, applications for partial change approval should be utilized. If it is difficult to determine whether applications for partial change approval should be utilized or not or on which items the information should be provided in the approval certificate, a simple consultation option should be utilized for individual consultation.

Q8:
Is it acceptable to consider as follows?: if an appropriate procedure such as providing information on the sub-component in the approval certificate as shown above is taken, and then the marketing business license, manufacturing business license, etc. are withdrawn to organize the approval, etc. of the sub-component, no further procedures for the approval certificate would be required.

A8:
Yes. However, the marketing authorization holder of the combination product shall continuously and appropriately take measures to maintain the quality of the product including the sub-component.

Q9:
If an approval application is submitted for the combination product classified as a drug and has the sub-component of an instrument, which part of the CTD should the information on the instrument be provided in?

A9:
Regarding the information on the instrument, the outline should be provided in the approval application form, and the manufacturing method, storage and shelf life, manufacturing site of the product to be marketed, etc. should be provided in Section 2.3.P.7 of the CTD. In addition, data such as the attached data (corresponding to STED, certificates of analysis, etc.) should be attached to Section 3.2.P.7 of the CTD.

Q10:
For drugs that have been approved and fall under combination products, how and by when should the description be updated?

A10:
The description should be updated when an application for partial change approval or minor change notification is submitted in accordance with 3 (7) in the Combination Product Notification and the Amended Combination Product Notification. In addition, if the column of remarks in an approval application form has a remark "Classified as a kit product," the Combination Product Notification with the brand name, approval number, etc. of the product filled in the attached table in it should be submitted to the Administrative Division I, Office of Review Administration, Pharmaceuticals and Medical Devices Agency by March 31, 2017.

Of note, as the above deadline is related to description update, reporting of adverse reactions and malfunctions related to the product should be appropriately implemented on and after November 25, 2016.

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

Q11:
Is the following understanding correct? Drug agents, instruments, and processed cells that would be marketed as combination products all fall under investigational combination products, and clinical trial notifications, in any case, should be submitted with "Clinical trial for combination products" entered in the column of remarks.

A11:
Clinical trial notifications for such products should all have the remark "Clinical trial for combination products."

This does not preclude the handling according to 5 (2) of the Combination Product Notification.

Q12:
How should adverse reactions or malfunctions related to sub-components occurring during clinical trials for combination products be reported?

A12:
In clinical trials conducted under the clinical trial notifications for drug agents, adverse events and malfunctions (including malfunctions that may cause serious cases, etc. The same shall apply hereinafter.) attributable to the instrument part should be reported as investigational device malfunction reports. In such reports, the date when the clinical trial notification for the combination product using the drug agent as the main component was submitted should be provided in the column of date of clinical trial notification, and a

statement “The clinical trial notification has been submitted for the investigational combination product. Investigational ingredient code: XXXXXX Receipt number of clinical trial notification: XX-XXXX” should be provided in the column of remarks, while entry of the clinical trial identification code is optional.

In clinical trials conducted under clinical trial notifications for instruments, adverse reactions related to the drug agent part as well as adverse events and malfunctions attributable to the processed cell part should be reported as investigational device malfunction reports.

In clinical trials conducted under clinical trial notifications for processed cells, etc., adverse reactions related to the drug agent part as well as adverse events and malfunctions attributable to the instrument part should be reported as investigational device malfunction reports.

If a clinical trial notification has been separately submitted in accordance with 5 (2) of the Combination Product Notification, adverse reactions or malfunctions related to the sub-component should be reported according to the category of the notification.

Q13:

Regarding adverse reactions and malfunctions occurring during clinical trials for combination products using drug agents as the main component, which reports should be made, adverse reaction reports or malfunction reports?

A13:

If the event is considered applicable to either adverse reactions related to the main component of drug agents or malfunctions related to the sub-components, but which is more appropriate remains to be decided because of the responsible part being unclear, both adverse reaction reports and malfunction reports should be submitted.

Q14:

Regarding adverse reactions and malfunctions occurring during clinical trials for combination products using drug agents as the main component, is submission of adverse reaction reports required in the following case?: events have occurred but the symptoms are clearly caused by malfunctions related to the sub-component (such as needle breakage), and there are no adverse reactions related to drug agents.

A14:

Only the malfunction reports should be submitted.

Q15:

Regarding clinical trials for combination products using drug agents as the main component, how should foreign corrective action reports and research reports from ongoing clinical trials for the sub-component be submitted?

A15:

The foreign corrective action reports and research reports on the drug agents may be submitted collectively.

Q16:

How should annual reports on the sub-component of a combination product using drug agents as the main component be made, if applicable?

A16:

The annual reports on combination products classified as drug agents should be prepared in accordance with the "Points to consider for Enforcement of the Ministerial Ordinance Partially Amending Regulation for Enforcement of the Pharmaceutical Affairs Act, etc." (PFSB/ELD Notification No. 1228-11, dated December 28, 2012, from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW), and the column of "Remarks" in Attached Form 1 should be provided with a statement "Report on investigational combination products." In this report, the malfunction reports should be collectively included.

In Attached Form 2, lists of the occurrence of events should be separately prepared for each of the adverse reaction reports, investigational device malfunction reports, and investigational product malfunction reports.

○ Post-marketing adverse reaction reports and malfunction reports

Q17:

Should periodic safety update reports on combination products classified as drugs include the content in the malfunction reports, if applicable?

A17:

It should be included. When such report is prepared, Attached Form 1 in the "Periodic Safety Update Report System for New Prescription Drugs and Enforcement of the Ministerial Ordinance Partially Amending the Enforcement Regulation of the Pharmaceutical Affairs Act" (PFSB Notification No. 0517-2, dated May 17, 2013, of the Pharmaceutical and Food Safety Bureau, MHLW) should be filled to include a statement "The product is a combination product" in the column of "Remarks" as well as the content in the malfunction reports and the comments in the column of "Other Safety Management Information" (or the column of "Other Proper Use Information," if Attached Form 1 in the "Periodic Safety Update Report System for New Prescription Drugs" [PAB Notification No. 437, dated March 27, 1997, of the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare] is used) but not in the column of "Occurrence of Adverse Reactions, etc."

If there are no malfunction reports to be described, the applicable column should be provided with a statement to this effect and should not be left blank.

Q18:

If an application for reexamination of combination products classified as drugs is submitted, should the content in the malfunction reports be included in the application data for reexamination?

A18:

It should be included. When such data are prepared, a statement "The product is a combination product" should be included in the column of "Remarks" in Attached Form 1 in the "Data to be Attached for Applications for Reexamination of New Prescription Drugs" (PFSB/ELD Notification No. 1027004, dated October 27, 2005, from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW), and appropriate information should be provided to Section 2, 1. Summary of Data for Reexamination Applications (5) Safety Investigations, k. Others (nothing should be provided to the preceding a. to j.) in this notification.

If there are no malfunction reports to be described, the applicable column should be provided with a statement to this effect and should not be left blank.