

Provisional Translation (as of August 2025).

This English document has been prepared for reference purpose only. In the event of inconsistency and discrepancy between the Japanese original and the English translation, the Japanese text shall prevail.

PSEHB Notification No. 0831-10

August 31, 2020

To: Prefectural Governors

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

Reporting of Malfunctions, etc. in Clinical Trials Related to Processed Cells, etc.

Handling of reports of malfunctions and adverse events during clinical trials related to processed cells, etc. for the approval application of regenerative medical products (hereinafter referred to as “reports of malfunctions, etc. in clinical trials”) has been shown in “Reporting of Malfunctions, etc. in Clinical Trials Related to Processed Cells, etc.” (PFSB Notification No. 1002-23 of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated October 2, 2014).

With the enforcement of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 63 of 2019) and the Ministerial Ordinance on the Development of Related Ministerial Ordinances in Accordance with Enforcement of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ordinance No. 155 of Ministry of Health, Labour and Welfare in 2020), handling of reporting of malfunctions, etc. in clinical trials on processed cells, etc. has been specified as follows. Please be aware of this and inform related businesses under your jurisdiction of this matter and provide instructions to them.

Note

1 The terms in Article 275-3 used with modifications in Article 279 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ministry of Health and Welfare Ordinance No. 1 of 1961) are defined as follows.

- (1) “Products considered to have the same component cells or transgenes as that of the study product concerned” refer to products with the same component cells, transgenes, structure, raw materials, etc. as those of the study product concerned. It

should be determined whether a case occurring overseas is subject to reporting according to the provisions of Article 275-3 of the Regulation. However, the cases that need to be reported urgently to the government at least in the country where they occurred should be reported.

- (2) “Events suspected to be caused by the effect of use” are events other than those for which a causal relationship can be ruled out. The events for which the causal relationship is unknown are also included. For combination products that are regenerative medical products, adverse events suspected to have been caused by the effect of drugs or machines/equipment are also subject to reporting.
- (3) “Infections suspected to be caused by their use” refer to infections including those for which contamination of the study product, etc. (referring to the study product concerned or the products with the same component cells, transgenes, structure, raw materials, etc. as the study product concerned; the same applies hereinafter) with pathogens is suspected based on the raw materials or materials of biological origin or their raw materials. In addition, in manufacturing, use, etc. of human (allogenic) study products, etc., tests of markers for viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) turning positive are subject to reporting.
- (4) “Events not expected from the Investigator’s Brochure of the test product concerned or existing scientific findings on the study products, etc. other than the test product concerned” are events not described in the materials used for the latest judgment of expectedness at the time of evaluation of malfunctions, etc. (the Investigator’s Brochure or documents describing scientific findings on the study products other than the test product, such as package inserts and academic papers [hereinafter referred to as “Investigator's Brochure, etc.”]) or events that are described in these materials, but are not consistent with the description in nature, severity of symptoms, or occurrence tendency. For example, an unexpected serious case of an event should be reported even if the event is listed in the Investigator's Brochure, etc.
- (5) “Disability” refers to the onset of incapacity that interferes with daily life.
- (6) “Malfunctions” refer to a wide range of unwell states such as dysfunction of test products, etc. and adverse reactions, etc. to cells in the human body, regardless of the stage where they occur, such as manufacturing, delivery, storage, and use.
- (7) “Occurrence of malfunctions of the study product, etc. that may result in cases, etc. in (a) or (b) of Item 1 or (a), (1) to (5) of the preceding item” refers to occurrence of malfunctions of the study product concerned, etc. that are considered to possibly result in death, disability, etc. although death, disability, etc. have not occurred in reality.
- (8) “Situations involving no risk of affecting safety judgment related to subject protection in the clinical trial concerned” refer to the situations including those where the obtained safety information does not include sufficient information that contributes to medical evaluation and it is difficult to obtain additional information that contributes to the evaluation in consideration of the information sources,

occurrence status, etc., or where the contents of the obtained safety information are significantly different from the status of use in subjects of the clinical trial concerned and therefore there is no risk of affecting the safety judgment related to subject protection.

Specifically, the situations where it is difficult to judge whether the safety information is true or not as it has been derived from anonymous posting of adverse events on the internet or provision of information or inquiries from consumers or other non-healthcare professionals to the call center, which makes medical discussion or collection of additional information difficult, or the cases of malfunctions, etc. that occurred with the method of use different from those used in the clinical trial and are unique to the method of use concerned are applicable. However, even in the case of such information, if the accumulation of information indicates an increase in the number, frequency, etc. of diseases, etc. suspected to be caused by the effect of the use of the test product concerned, etc. or infections suspected to be caused by their use, the change in such tendency needs to be reported separately.

- (9) “Implementation of actions that prevent the occurrence or spread of public health hazards including discontinuation of manufacturing, import, or marketing, recall, and disposal of products used overseas with the same component cells or transgenes as those of the study product” includes discontinuation of manufacturing, etc. overseas in light of efficacy or safety, changes in indications, performance, dosage and administration, directions for use, manufacturing methods, etc., and distribution of doctor letters and associated revision of important precautions.
- (10) “For study products other than test products, actions that prevent the occurrence or spread of public health hazards in combined use with the test products” refer to measures to prevent public health hazards related to study products other than test products that are likely to occur or spread in concomitant use with the test products in the clinical trial concerned.
- (11) “There is a risk of cancer or other serious diseases, disabilities, or death” indicates the onset or possible onset of clinically significant diseases attributable to the use of the test product concerned, etc. or infections due to the use, which is shown in the epidemiological survey reports or results, etc. of studies in animals, etc. *in vitro* biological/chemical tests, and physical tests, etc.
- (12) “Marked changes in the tendency of occurrence such as the number of cases, frequency, and conditions of occurrence of diseases, etc. suspected to be caused by the effect of their use or infections suspected to be caused by their use” are clear changes that are observed in the number of cases, frequency, conditions of occurrence (for example, the number of cases or frequency as a whole has not changed so greatly, but the number of cases or frequency is found to have particularly increased for specific ages, complications, use methods, etc. when stratified), symptoms, or severity, etc. of diseases suspected to be caused by the effect of the use of the test products concerned, etc. or infections suspected to be caused by their use.

- (13) The phrase, a test product “does not have the efficacy, effect, or performance on the disease investigated in the clinical trial,” refers to the absence of efficacy, effect, or performance on the disease targeted in the clinical trial in the test product concerned based on clinical studies, animal studies, etc.
- (14) “Research reports” refer to reports such as research reports published in academic journals, etc. in Japan or overseas or reports of in-house research or research conducted by related companies.
- (15) “Research reports considered not to affect the evaluation of efficacy and safety of the test product concerned, etc. for the diseases investigated in the clinical trial” refers to research reports intended for malfunctions, etc. expected in the clinical trial for which safety measures for subjects have already been taken (exclusion of certain subjects in whom the malfunctions, etc. concerned may occur, appropriate examination plans developed in the trial, etc.), or for diseases, etc. suspected to be caused by the effect of the use of the test products concerned, etc. or infections suspected to be caused by their use showing no increase in the number of cases, frequency.

2 Reporting deadline, etc.

- (1) Reports of malfunctions, etc. in clinical trials should be made within 7 days if they correspond to Article 275-3, Paragraph 1, Item 1 and Paragraph 2, Item 1, within 15 days if they correspond to Paragraph 1, Item 2 and Paragraph 2, Item 2 of the same article, and within 30 days if they correspond to Paragraph 1, Item 3 and Paragraph 2, Item 3 of the same article of the Regulation.
- (2) The matters specified in Article 275-3, Paragraph 4 of the Regulation must be reported every year starting from the date of the first clinical trial notification for the test product concerned, within 2 months after the expiration of the period.
- (3) If all clinical trials related to the test product have been completed and an application for marketing approval of a regenerative medical product related to the test product is pending or an application for marketing approval is being prepared, reporting is required until the marketing approval is granted.

3 Report forms

- (1) For reports based on Article 275-3, Paragraph 1, Paragraph 2, Item 1, Item 2, (a) and (b) and Item 3 of the Regulation (reports of cases of malfunctions/infections), use Attached Form 1.
- (2) For reports based on Item 2, (c) and (d) (research reports and foreign corrective action reports) of the same paragraph, use Attached Form 2.
- (3) For reports based on Paragraph 4 of the same article (periodic safety reports), use Attached Form 3.

4 Where to submit

The reports of malfunctions, etc. in clinical trials shall be submitted to the Review Planning Division, Office of Review Management, Pharmaceuticals and Medical Devices Agency.

5 Handling of extremely significant safety information obtained during clinical trials

If the sponsor obtains extremely significant safety information such as the information on unknown serious malfunctions, etc. which are reasonably considered attributable to the use of study products with component cells or transgenes different from those of the regenerative medical products marketed by the sponsor (including test products to be marketed) (hereinafter referred to as “other companies’ study products”) that would be considered to be the reason for suspension/discontinuation of clinical trials, it is desirable to appropriately provide the information to the marketing authorization holders, etc. of the study products concerned in Japan from the perspective of subject protection and improvement of public health safety in Japan, in addition to making above reports of malfunctions, etc. based on the laws and regulations.

6 Application timing, etc.

This notification shall apply from September 1, 2020. However, in cases where a clinical trial notification was submitted in accordance with previous rules, based on “Handling, etc. of Notifications of Clinical Trial Plans, etc. Related to Processed Cells, etc.” (PSEHB/MDED Notification No. 0831-9 of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020), reports on clinical trials should be made according to the previous rules.

7 Abolition of notification

With the application of this notification, the “Reporting of Malfunctions, etc. in Clinical Trials Related to Processed Cells, etc.” (PFSB Notification No. 1002-23 of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated October 2, 2014) shall be abolished as of August 31, 2022.

Study Product Malfunction/Infection Case Report Form

1. Management information										
1) Control number	Identification number		Number of reports to PMDA			Report category	[1] 7 days	[2] 15 days	[3] 30 days	
	Report type	[1] Malfunctions (including adverse events)	[2] Infections		Site of occurrence of malfunction, etc.		[1] Japan [2] Overseas ()			
2) Date on which the first report was received		Month DD, YYYY			3) Date of most recent information		Month DD, YYYY			
4) Scheduled date of next report		Month DD, YYYY								
5) Status of malfunction of investigational product			[1] Yes		[2] No		[3] Unknown			
6) Status of health damage in the subject, etc.			[1] Yes		[2] No		[3] Unknown			
7) Contact information of the person in charge	Name of the person in charge					Name of corporation				
	Department									
	Address									
	Tel				Fax			E-mail		
2. Information on the subject, etc.										
1) Abbreviated name of subject, etc.		2) Age	years old	3) Sex	Male/ Female	4) Body weight	kg	5) Height	cm	
6) Status of subject, etc. at the time of occurrence of malfunction, etc.	Malfunction									
	Name of malfunction					Known or unknown		[1] Known [2] Unknown		
	Date of occurrence			Month DD, YYYY						
	Status of health damage in the subject									
	Name of adverse event/infection					Known or unknown		[1] Known [2] Unknown		
	Onset date			Month DD, YYYY		End date		Month DD, YYYY		
	Seriousness					Outcome				
	Causality assessment		Attending physician, etc.							
			Reporter							
7) Course of occurrence status of malfunction, etc.										

3. Information on investigational product			
1) Clinical trial identification code		2) Category	
3) Generic name			
4) Date of clinical trial notification submitted			
5) Outline of clinical trial			
6) Details of investigational product			
7) Classification	[1] Regenerative medical products	[2] Designated regenerative medical products	
8) Status of use of investigational product	months,	days, or	hours after the start of use
9) Current status of investigational product	[1] Recall of actual product	[2] Product not recalled (disposed, remaining in the body, recall planned, recall impossible)	
10) Concomitant therapies			
11) Remarks			
4. Investigation results and actions, etc.			
1) Investigation results			
2) Comments from the attending physician, etc.			
3) Reporter's comments			
4) Previous actions			
5) Future actions			

I hereby report a case of malfunction/infection related to the investigational product as described above.

Month DD, YYYY

Address

Name

To: Chief Executive, Pharmaceuticals and Medical Devices Agency

**Report on Investigation of Research Reports of Investigational Product
Report on Investigation of Actions Overseas Including Discontinuation of
Manufacturing, etc., Recall, and Disposal of Investigational Product**

1. Management information							
1) Control number	Identification number		Number of reports to PMDA		Report type	[1] Research reports	[2] Action reports
2) Date on which the first report was received		Month DD, YYYY		3) Date of most recent information		Month DD, YYYY	
4) Scheduled date of next report		Month DD, YYYY					
5) Status of malfunction of investigational product			[1] Yes	[2] No	[3] Unknown		
6) Status of health damage in the subject, etc.			[1] Yes	[2] No	[3] Unknown		
7) Contact information of the person in charge	Name of the person in charge		Name of corporation				
			Department				
	Address						
	Tel			Fax			E-mail
2. Information on investigational product							
1) Clinical trial identification code				2) Category			
3) Generic name							
4) Date of clinical trial notification							
5) Outline of clinical trial							
6) Details of investigational product							
7) Investigational product classification		[1] Regenerative medical products			[2] Designated regenerative medical products		
8) Remarks							

3. Report contents and actions, etc.		
1) Details of research report or action	Source of research report	
	Country where action is taken	
	Action category	
2) Previous actions		
3) Future actions		

I hereby report the investigation results of the investigational product as described above.

Month DD, YYYY

Address

Name

To: Chief Executive, Pharmaceuticals and Medical Devices Agency

Attached Form 3-1

Investigational Product Periodic Safety Report

1) Clinical trial identification code		2) Category	
3) Generic name			
4) Date of the first clinical trial notification submitted		5) Base date for reporting	
6) Outline of clinical trial			
7) Details of investigational product			
8) Investigational product classification	[1] Regenerative medical products	[2] Designated regenerative medical products	
9) Reporting period		10) Number of reports to PMDA	
11) Information on changes in investigational product			
12) Approval status overseas			
13) Occurrence status of malfunction, etc.			
14) Comments and safety measures based on accumulation			
15) Remarks			

I hereby submit a periodic safety report for the investigational product as described above.

Month DD, YYYY

Address

Name

To: Chief Executive, Pharmaceuticals and Medical Devices Agency

List of Occurrence Status of Cases of Investigational Product Malfunctions/Infections

Category	Clinical trials in Japan		Overseas clinical studies		Overseas post-marketing spontaneous reports	
	Within reporting period	Total	Within reporting period	Total	Within reporting period	Total
Approximate number of subjects						
Type of malfunction (including adverse event)	Number of malfunctions by type					
Type of infection	Number of infections by type					
Remarks						