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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 Defects or Adverse Events Relevant to Processed Cells, Etc. in Clinical Studies

Handling of reports on defects or adverse events during clinical studies related to processed cells, etc. for application for approval of regenerative medical products (hereinafter referred to as "reports on defects or adverse events during clinical studies") has been specified in "Reporting of Defects or Adverse Events Relevant to Processed Cells, Etc. in Clinical Studies" (PFSB Notification No. 1002-23, by the Director-general of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (hereinafter referred to as MHLW), dated October 2, 2014).

Recently, in association 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 Maintenance, Etc. of Related Ministerial Ordinances in Association With Enforcement of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHLW Ordinance No. 155 of 2020), handling of reports on defects or adverse events of processed cells, etc. in clinical studies has been specified as follows. Please be aware of the following and give considerations, including providing notifications and guidance, to relevant business vendors, etc. under your jurisdiction.

1 The definitions of terms in Article 275-3 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, hereinafter referred to as the "Enforcement Regulation of the Act") applied in Article 279 of the Enforcement Regulation of the Act shall be as follows.

(1) The term "products with component cells and transgenes which is recognized as identical to the investigational product or control/concomitant products used in the clinical study (hereinafter referred to as “products used in the clinical study”)" refers to products that are identical to the product used in the clinical study in the aspect of component cells, transgenes, structure, raw materials, etc. Whether or not cases occurring in foreign countries are subject to reporting should be judged according to the provisions of Article 275-3 of the Enforcement Regulation of the Act. At least, cases that were subject to urgent reporting to the relevant government of the country where the cases occurred should be reported.

(2) The term "those suspected to be affected by the use of the product used in the clinical study." refers to events other than those for which a causal relationship can be ruled out, including events for which the causal relationship is unknown. In the cases of combination products as regenerative medical products, if the occurrence of an adverse event due to the use of a drug or device is suspected, it shall be subject to reporting.

(3) The term "infectious diseases caused by their use" shall include cases where contamination of pathogens from biologics raw and ancillary materials of the products used in clinical trials (including those identical to them in the aspect of component cells, transgenes, structure, raw materials, etc.; the same shall apply hereinafter) is suspected. In the manufacturing or use of the products etc. used for human (allogeneic) clinical trials, etc., positive conversion of virus markers such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) shall also be subject to reporting.

(4) The term "those that cannot be predicted from the investigator's brochure of the investigational product or from the existing scientific findings for the products used in the clinical study other than investigational products"

- Defects or adverse events not described in the latest material used for the

judgment of expectedness at the time of evaluation of defects or adverse events (investigator's brochure or documents such as package insert and scientific papers that describe the scientific findings for the products used in clinical trials other than the investigational product (hereinafter referred to as "investigator's brochure, etc.")).

- Those with difference in nature, severity, or tendency of occurrence from the description in the investigator's brochure, etc.

For example, an unexpected serious case of defects or adverse events that are described in the investigator's brochure, etc. is subject to reporting.

(5) The term "disability" refers to the onset of dysfunction to an extent which causes problems in daily life.

(6) The term "defects or adverse events" refers to a wide range of unwell states such as dysfunction of the investigational products, etc. and adverse reactions of cells to the human body, regardless of the timing of occurrence such as during manufacturing, supply, storage, or use.

(7) The phrase "occurrences of defects or adverse events of the products used in the clinical study that may cause diseases, etc. set forth in item (i), (a) or (b), or (a), (1) through (5) of the preceding item" shall mean occurrence of defects or adverse events of the products used in the clinical study that have the possibility of causing death, disability, etc. in spite of no cases of death, disability, etc.in reality.

(8) The phrase "when it is considered that there is no possibility of affecting the safety judgment concerning the protection of subjects in the clinical trial" refers to the cases where the information for medical evaluation of the obtained safety information is insufficient and it is difficult to obtain additional information that contribute to the evaluation in terms of the source of information, occurrence status, etc., or when the contents of the obtained safety information are significantly different from the status of use in subjects in the clinical trial and there is no possibility of affecting the safety judgment concerning the protection of subjects.

Specifically, it includes the following cases:

- Cases where the safety information is derived from the anonymous description about adverse events on the Internet or information and inquiries to the call center from general consumers or other non-healthcare

professionals, thereby making it difficult to judge the authenticity, to make medical consideration, or to collect additional information

- Cases where a defect or an adverse event is caused by a method that is different from the method of use in the clinical trial and its occurrence is specific to the method of use

However, even for such information, if an increase in the number of cases, incidence, etc. of diseases, etc. suspected to be due to the use of the investigational product, etc. or infections suspected to be due to the use of the investigational product, etc. is observed as a result of accumulation of information, the change in the tendency concerned needs to be reported separately.

(9) The phrase "implementation of suspension of manufacturing, import, or sales, the recall, abandonment, or other measures taken for the products used in a foreign country with component cells and transgenes identical to the products used in clinical trials in order to prevent the occurrence or spread of a hazard in health and hygiene" shall include, in addition to the discontinuation of manufacturing, etc. in foreign countries from the viewpoint of efficacy or safety, changes in indications or performance, dosage and administration, directions for use, manufacturing methods, etc., as well as distribution of Dear Healthcare Professional Letters or relevant revision of the important precautions.

(10) The phrase "measures for the products used in clinical trials other than the investigational product in order to prevent the occurrence or spread of health and hygiene hazards when used in combination with the investigational product" refers to measures to prevent the occurrence or spread of health and hygiene hazards related to the products used in clinical trials other than the investigational product, which are likely to occur when these products are used in combination with the investigational product in the clinical trial.

(11) The phrase "risks of cancers, other serious diseases, disabilities, or death" refers to the onset or possible onset of serious diseases caused by the use of the investigational products, etc. or infections due to its use indicated by the results of epidemiological survey reports, studies in animals, in vitro biological/chemical studies, physical studies, etc.

(12) The phrase "the marked change in the trend of occurrence, such as the

change in the occurrence number, frequency, and conditions for occurrence of diseases affected by the use of the products or infectious diseases suspected to be caused by the use of the product" shall indicate a clear change in the number, frequency, onset conditions (for example, cases where the number or frequency of occurrence increases at a particular age, complication, method of use, etc. when stratified, although the change in the number of overall events or frequency is not large), symptoms, severity, etc. of diseases or infections suspected to be due to the use of the investigational products, etc.

(13) The phrase "the investigational products, etc. have no performance for the target disease to be investigated" shall mean that the investigational product, etc. does not have the performance for the target disease to be investigated based on clinical studies, animal studies, etc.

(14) The term "research reports" means research reports published in academic journals, etc. in Japan and overseas, and research reports, etc. prepared by a sponsor or affiliated companies.

(15) The term "research reports that are considered not to affect the evaluation of the efficacy and safety of the investigational product, etc. for the diseases to be investigated in the clinical trial" is supposed to include, for example, defects or adverse events that are expected in the clinical trial for which safety measures have already been taken for subjects (e.g., patients who may develop the defects or adverse events are excluded from the trial subjects, appropriate examination plans have been drawn up in the clinical trial) and diseases or infections, etc. that are suspected to be due to the use of the investigational product, etc. for which an increase in the number, frequency, etc. of occurrence has not been observed.

2 Reporting time frame, etc.

(1) Reports on defects or adverse events during clinical studies shall be made within 7 days in cases falling under Article 275-3, Paragraph 1, Item 1 and Paragraph 2, Item 1 of the Enforcement Regulation of the Act, within 15 days in cases falling under the same article, Paragraph 1, Item 2 and Paragraph 2, Item 2 of the Enforcement Regulation of the Act, and within 30 days in cases falling under the same article, Paragraph 1, Item 3 and Paragraph 2,

Item 3 of the Enforcement Regulation of the Act.

(2) For the matters specified in Article 275-3, Paragraph 4 of the Enforcement Regulation of the Act, reporting must be made for every 1-year period starting from the date of the first notification of the clinical trial plan for the investigational product within 2 months after the expiration of the period.

(3) If all clinical trials of the investigational product have been completed and an application for marketing approval of the regenerative medical product is being made or is being prepared, the information shall be subject to reporting until the marketing approval is obtained.

3 Report forms

(1) Reporting under Article 275-3, Paragraph 1, Paragraph 2, Item 1, and Paragraph 2, Item 2 (a) and (b), and Paragraph 2, Item 3 of the Enforcement Regulation of the Act (case reporting of defect or adverse event/infection) shall be made using Attached Form 1.

(2) Reporting under Item 2 (c) and (d) of the same paragraph (research report and foreign measure report) shall be made using Attached Form 2.

(3) Reporting under Paragraph 4 of the same article (periodic safety report) shall be made using Attached Form 3.

4 Submission destination

Reports on investigational product defects or adverse events should be submitted to the Review Planning Division, Office of Review Management, the Pharmaceuticals and Medical Devices Agency.

5 Handling of extremely significant safety information obtained in clinical studies

If the sponsor obtains extremely significant safety information, such as an unknown and serious defect or adverse event that is reasonably considered to be attributable to the use of the products used in clinical trials whose component cells or transgenes are different from those in the regenerative medical product (including an investigational product to be marketed) manufactured and marketed by the sponsor (hereinafter referred to as "products used in clinical trials of other companies") and that leads to suspension/discontinuation of the clinical trial, it is desirable to appropriately provide the information to the marketing authorization holder, etc. of the investigational products in Japan in

addition to the report of a defect or adverse event under the above laws and regulations, from the viewpoint of protection of subjects and improvement of public health safety in Japan.

6 Timing of application, etc.

This notification shall come into effect as from September 1, 2020. However, for clinical trials for which a clinical trial notification was submitted in accordance with the previous cases under "Handling of Clinical Trial Plan Notification Relevant to Processed Cells, Etc." (PSEHB/MDED Notification No. 0831-9 issued by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated August 31, 2020), a clinical trial product defect or adverse event case report should be submitted in accordance with the previous cases.

7 Abolition of notification

In association with the implementation of this notification, "Reporting of Defects or Adverse Events Relevant to Processed Cells, Etc. in Clinical Studies" (PFSB Notification No. 1002-23, by the Director-general of Pharmaceutical and Food Safety Bureau, MHLW, dated October 2, 2014) shall be abolished as of August 31, 2022.

Attached Form 1

Investigational Product Defect or Adverse Event/Infection Case Report Form

1. Management Information								
1) Control No.	Identification No.		Number of times of reporting to PMDA		Reporting category	[1] 7 days	[2] 15 days	[3] 30 days
	Reporting type	[1] Defect or adverse events	[2] Infection	Location of occurrence of defects or adverse events	[1] Japan	[2] Overseas ( )		
2) Date of receipt of initial report	MM DD, YYYY	3) Date of receipt of latest information	MM DD, YYYY					
4) Scheduled date of next reporting	MM DD, YYYY							
5) Status of defect or adverse event of investigational product	[1] Available	[2] Not available	[3] Unknown					
6) Health injury status of subject, etc.	[1] Available	[2] Not available	[3] Unknown					
7) Contact information of person in charge	Name of person in charge		Corporate name					
			Department					
	Address							
	Tel		Fax		E-mail			

2. Information on Subjects, etc.								
1) Abbreviated name of subject, etc.		2) Age	years old	3) Gender	Male/ Female	4) Weight	kg	5) Height	cm

6) Status of subject, etc. at the time of occurrence of defect or adverse event,					
	Defect or adverse event				
	Name of defect or adverse event		Known/ Unknown	[1] Known	[2] Unknown
	Occurrence date	MM DD, YYYY			
	Health injury status of subject				
	Name of adverse event/infection		Known/ Unknown	[1] Known	[2] Unknown
	Date of onset	MM DD, YYYY	Date of resolution	MM DD, YYYY	
	Seriousness		Outcome		
	Evaluation of causal relationship	Attending physician, etc.			
		Reporter			

7) Course of occurrence of defects or adverse events

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3. Information on Investigational Product			
1) Study identification code		2) Category	
3) Nonproprietary name			
4) Date of clinical trial plan notification			
5) Outline of clinical trial			
6) Details of investigational product			
7) Classification	[1] Regenerative medical product		[2] Designated regenerative medical product
8) Status of use of investigational product	Months, days, or hours after the start of use		
9) Current status of investigational product	[1] Actual product is recalled.	[2] Actual product is not recalled (disposed of, remaining in the body, recall is planned, recall is impossible)	
10) Concomitant therapy			
11) Remarks			
4. Investigation Results and Actions, etc.			
1) Investigation results			
2) Opinions from the attending physician, etc.			
3) Opinion from the reporter			
4) Past actions			
5) Future plans			

I hereby report a case of a defect or adverse event/infection related to the investigational product.

MM DD, YYYY
Address
Name
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Attached Form 2

Investigation Report on **Research Report** **Measures such as Discontinuation of Manufacturing, Recall, and Disposal in Foreign Countries** **for Investigational Product**

1. Management Information							
1) Control No.	Identification No.		Number of times of reporting to PMDA		Reporting type	[1] Research Report	[2] Report on measures
2) Date of receipt of initial report	MM DD, YYYY		3) Date of receipt of latest information	MM DD, YYYY			
4) Scheduled date of next reporting	MM DD, YYYY						
5) Status of defect or adverse event of investigational product	[1] Available	[2] Not available	[3] Unknown				
6) Health injury status of subject, etc.	[1] Available	[2] Not available	[3] Unknown				
7) Contact information of person in charge	Name of person in charge		Corporate name				
			Department				
	Address						
	Tel		Fax		E-mail		
2. Information on Investigational Product							
1) Study identification code		2) Category					
3) Nonproprietary name							
4) Date of clinical trial plan notification							
5) Outline of clinical trial							
6) Details of investigational product							

7) Classification of investigational product	[1] Regenerative medical product	[2] Designated regenerative medical product
8) Remarks		

<table>
<tr><td colspan="3">3. Report Contents and Actions, etc.</td></tr>
<tr><td rowspan="3">1) Research report or details of measures</td><td>Source of research report</td><td></td></tr>
<tr><td>Country where measures were taken</td><td></td></tr>
<tr><td>Measure category</td><td></td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>2) Past actions</td><td colspan="2"></td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>3) Future plans</td><td colspan="2"></td></tr>
<tr><td colspan="3"></td></tr>
</table>

I hereby report the investigation results related to the investigational product.

MM DD, YYYY

Address
Name

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Attached Form 3-1

Investigational Product Periodic Safety Report

1) Study identification code		2) Category	
3) Nonproprietary name			
4) Date of initial clinical trial plan notification		5) Initial date of reckoning for reporting	
6) Outline of clinical trial			
7) Details of investigational product			
8) Classification of investigational product	[1] Regenerative medical product	[2] Designated regenerative medical product	
9) Reporting period		10) Number of times of reporting to PMDA	
11) Information on changes in the investigational product			
12) Approval status in foreign countries			
13) Occurrence status of defects or adverse events			
14) Opinions and safety measures based on the accumulation			
15) Remarks			

I hereby submit a periodic safety report related to the investigational product.
MM DD, YYYY

Address
Name

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Attached Form 3-2

Listing of Investigational Product Defects or Adverse Events/Infection Cases

Category	Clinical trial in Japan		Overseas clinical trial		Overseas post-marketing spontaneous reports	
	Within the reporting period	Cumulative	Within the reporting period	Cumulative	Within the reporting period	Cumulative
Approximate number of subjects, etc.						
Type of defect or adverse events	Number of cases by type of defect or adverse event					
Type of infection	Number of cases by type of infection					
Remarks						