PSEHB/MDED Notification No. 0328-1
March 28, 2022

To: Director-General of the Prefectural Health Department (Bureau)

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

Handling of Use-results Surveys and Re-examination of Regenerative Medical Products

The "Handling of Use-results Surveys and Re-examination of Regenerative Medical Products" (PSEHB/MDED Notification No. 0929-7, dated September 29, 2021, of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare [MHLW], hereinafter referred to as the "Re-examination Handling Notification") has been applied to periodic update reports on use results of regenerative medical products with conditional and time-limited approval granted based on Article 23-26, Paragraph 3 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 the "Act") and application for re-examination of regenerative medical products based on Article 23-29 of the Act.

Now, the following changes are made to handling of the periodic update reports on use results of regenerative medical products with conditional and time-limited approval in response to the amendment explained below: (a) handling of "the date designated by the Minister of Health, Labour and Welfare" is clarified as presented in the underlined part in Section 1.1 (1); and (b) the re-examination period of orphan regenerative medical products is specified as presented in the underlined part in Section 2.1 (1). Based on the Ministerial Ordinance Partially Amending the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHLW Ordinance No. 43 of 2022), "The reports prescribed in the preceding paragraph must be made annually (in the case of regenerative medicine products instructed by the Minister of Health, Labour and Welfare, the period instructed by the Minister) from the date when marketing of the regenerative medicine products concerning the investigation is approved" in Article 137-35, Paragraph 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 “Regulation”) is amended to read “The reports prescribed in the preceding paragraph must each be made to cover up to 1 year (in the case of regenerative medicine products instructed by the Minister of Health, Labour and Welfare, the period instructed by the Minister) from the date designated by the Minister of Health, Labour and Welfare when marketing of the regenerative medicine products concerning the investigation is approved.” Please understand the changes and ensure that relevant companies under your jurisdiction are thoroughly informed of them.

Of note, this notification supersedes the Re-examination Handling Notification.

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Section 1　Handling of regenerative medical products with conditional and time-limited approval

1　Periodic update reports on use results of regenerative medical products with conditional and time-limited approval

(1)　Reporting time frames

For regenerative medical products with conditional and time-limited approval, which requires investigations (surveillance) and reporting pursuant to the provisions of Article 23-26, Paragraph 3 of the Act, the reports each must be made to cover up to 1 year (in the case of regenerative medicine products instructed by the Minister of Health, Labour and Welfare, the period instructed by the Minister) (reporting interval) from the date designated by the Minister of Health, Labour and Welfare when marketing of the regenerative medicine products concerning the surveillance is approved and be submitted within 2 months after the expiry date (reporting deadline) of the reporting interval.

In principle, the "date designated by the Minister of Health, Labour and Welfare" is defined as follows:

A　The date when manufacture or sale of the concerned regenerative medical product is authorized for the first time in or outside Japan (hereinafter, referred to as the "International Birth Date [IBD]") (except for cases presented in B).

B　If the IBD is not the date of approval in Japan and is at least 6 months prior to the date of approval in Japan, the day that is after an integral multiple of 6 months counted from the IBD and immediately precedes the date of approval of the concerned regenerative medical product. If the day after an integral multiple of 6 months from the IBD is the date of approval in Japan, the concerned date of approval.

Or any day may be specified in view of the intention of the marketing authorization holder of regenerative medical products and/or efficiency of the management. If applicable, the applicant should propose the desired designation date using a format of their choice in a timely manner that matches the submission of data to the reviewing committee of the Pharmaceutical Affairs and Food Sanitation Council.

For new regenerative medical products first approved for marketing in Japan, the IBD may be specified on the last day of the month.

(2)　Format of periodic update reports on use results after conditional and time-limited approval

For regenerative medical products approved under Article 23-25, Paragraph 1 of the Act with a condition and time limit pursuant to the provisions in Article 23-26, Paragraph 1 of the Act (hereinafter, referred to as "conditional and time-limited approval"), the authorization holder should submit the reports defined in Article 23-26, Paragraph 3 of the Act (hereinafter, referred to as "periodic update reports on use results after conditional and time-limited approval") using Attachment Format 1.

Even after an application for approval defined in Article 23-25, Paragraph 1 of the Act is filed pursuant to the provisions in Article 23-26, Paragraph 5 of the Act, the periodic update reports on use results after conditional and time-limited approval should be continuously submitted until disposition of the concerned application is made.

(3) Submission of periodic update reports on use results after conditional and time-limited approval

A The current package insert should be attached.

B Periodic update reports on use results after conditional and time-limited approval should be addressed to the Chief Executive of the Pharmaceuticals and Medical Devices Agency (hereinafter, referred to as "PMDA") and submitted to the Review Administration Division II, Office of Review Administration, PMDA in person or by mail.

C One each of the original copy and duplicate copy should be submitted. Furthermore, the data in electronic media should be submitted.

(4) Notifying the Minister of Health, Labour and Welfare of receipt of periodic update reports on use results after conditional and time-limited approval

PMDA should notify the Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare of receipt of periodic update reports on use results after conditional and time-limited approval in Attachment Format 8 where applicable.

Section 2 Re-examination of regenerative medical products

1 Designation of re-examination

(1) Re-examination period

The investigation (survey) period defined in Article 23-29, Paragraph 1, Item 1 of the Act (hereinafter, referred to as the "re-examination period") is as follows:

1) Orphan regenerative medical products

(A) For products granted the first approval for the designated indication or performance (except for conditional and time-limited approval), 10 years

(B) For products of which administration route is evidently different from that of regenerative medical products already granted marketing approval (except for conditional and time-limited approval) (hereinafter referred to as "approved regenerative medical products"), a period that is longer than 6 years but not longer than 8 years and instructed by the Minister of Health, Labour and Welfare

2) For new regenerative medical products of which constitutive cells or transgenes are evidently different from those of approved regenerative medical products (except for products defined in 1) above), 8 years

3) For regenerative medical products with specific intended use, a period that is not shorter than 4 years but less than 6 years and instructed by the Minister of Health, Labour and Welfare

4) For new regenerative medical products of which only the indication or performance is evidently different from that of approved regenerative medical products (except for products defined in 1) above)

(A) For pioneering regenerative medical products, a period that is longer than 6 years but not longer than 8 years and instructed by the Minister of Health, Labour and Welfare

(B) For approved orphan regenerative medical products only with the designated indication or performance (except for products defined in (A) above), 5 years and 10 months

(C) For products except for ones in (A) or (B) above, 4 years

5) For new regenerative medical products of which only the dosage and administration (except for administration routes) or method of use is evidently different from that of approved regenerative medical products, 4 years

6) For new regenerative medical products of which the structure is evidently different from that of approved regenerative medical products (except for ones defined in 2) above), 6 years

7) For new regenerative medical products of which the administration route is evidently different from that of approved regenerative medical products (except for ones defined in 2) above), 6 years

(2) Verification of establishment of dosage and administration or method of use in children

If post-marketing surveillance, etc. of an approved regenerative medical product indicates that a post-marketing clinical study or trial needs to be conducted to verify establishment of the dosage and administration or method of use in children, the re-examination period may be extended to not longer than 10 years pursuant to the provisions in Article 23-29, Paragraph 2 of the Act. Whether the re-examination period needs to be extended will be determined based on a post-marketing surveillance master plan (notification for addition) submitted by the marketing authorization holder. The concerned notification for addition should be submitted by 1 year prior to the expiry of the re-examination period. When the notification for addition is prepared, necessity, feasibility, and period of the surveillance should be fully examined.

2 Periodic update reports on use results of regenerative medical products during the re-examination period

(1) Reporting time frames

For regenerative medical products on which surveillance and reporting are required in accordance with Article 23-29, Paragraph 6 of the Act and the first sentence of Article 23-30, Paragraph 2 of the Act, the reports each must be prepared to cover up to 1 year (in the case of

regenerative medicine products instructed by the Minister of Health, Labour and Welfare, the period instructed by the Minister) from the date designated by the Minister of Health, Labour and Welfare when marketing of the regenerative medicine products concerning the investigation is approved and be submitted within 2 months after the end of the period covered by the report or reporting deadline.

Irrespective of this provision, however, if the last reporting deadline is on or after the expiry date of the re-examination period, an application for re-examination may supersede a periodic update report on use results as of the last reporting deadline.

In principle, the "date designated by the Minister of Health, Labour and Welfare" is defined as follows:

A IBD (except for cases defined in B)

B If the IBD is not the date of approval in Japan and is at least 6 months prior to the date of approval in Japan, the day that is after an integral multiple of 6 months counted from the IBD and immediately precedes the date of approval for the concerned regenerative medical product. If the day after an integral multiple of 6 months from the IBD is the date of approval in Japan, the concerned date of approval.

Or any day may be specified in view of the intention of the marketing authorization holder of regenerative medical products and/or efficiency of management. If applicable, the applicant should propose the desired designation date using a format of their choice in a timely manner that matches the submission of data to the reviewing committee of the Pharmaceutical Affairs and Food Sanitation Council.

For new regenerative medical products first approved for marketing in Japan, the IBD may be specified on the last day of the month.

(2) Format of periodic update reports on use results during the re-examination period

For regenerative medical products defined in Article 23-29, Paragraph 1 of the Act, the reports defined in Article 23-29, Paragraph 6 of the Act (hereinafter referred to as "periodic update reports on use results during the re-examination period") should be prepared using Attachment Format 1 by the authorization holder.

(3) Submission of periodic update reports on use results during the re-examination period

A The current package insert should be attached.

B Periodic update reports on use results during the re-examination period should be addressed to the Chief Executive of the PMDA and submitted to the Review Administration Division II, Office of Review Administration, PMDA in person or by mail.

C One each of the original copy and duplicate copy should be submitted. Furthermore, the data on electronic media should be submitted.

3 Data attached to an application form for re-examination

Data on use results of regenerative medical products attached to an application form for re-examination defined in Article 137-40, Paragraph 1 of the Regulation should be as provided in an appendix and prepared as follows:

It should be noted that provisions in Article 137-23, Paragraphs 3 and 4 of the Regulation shall apply with modifications.

(1) Summary of products included in application for re-examination

For preparation, Attachment Format 9 should be referred to.

(2) Summary of use results

1) History from approval to application for re-examination

A Duplicate copy of approval certificate

For products included in an application for re-examination, duplicate copies of the approval certificates supporting re-examination should be attached.

B Approval conditions

Approval conditions, if any, should be described, and post-marketing actions should be briefly described.

C Prior partial changes in approved items

Prior partial changes in approved items, if any, should be briefly described in terms of the background and content.

D Prior changes in "Precautions" statements in package inserts

Prior changes in "Precautions" statements, if any, should be briefly described in terms of the background and content.

E Summary of post-marketing surveillance, etc. and prior changes

A summary of the post-marketing surveillance, etc. master plan should be provided. In addition, summaries of use-results surveys, post-marketing database surveillance, and post-marketing clinical studies should be prepared using Attachment Formats 10 to 12. If changes have been made to the surveillance plan, involving changes in these summaries, the prior changes should be briefly described in terms of the date and content. If any post-marketing non-clinical study has been additionally conducted for suspected safety issues of the product concerned, the non-clinical study should be briefly described in terms of the background and content.

2) Estimated changes in quantity used or released over time

Estimated changes in annual quantity used over time should be provided in a table format. Quantity released may be used if the quantity used is difficult to estimate.

3) Estimated number of patients with use and sampling rate

Estimated number of patients with use and a proportion of the patients subject to re-examination or sampling rate should be provided in a table format, including a method to estimate the number of patients.

4) Sales and action status of the regenerative medical products concerned in and outside Japan

A Sales status

Countries with the product commercially available should be listed in order of date (month and year) of launch along with the main intended use or indication in the labels including package inserts.

B Status of actions such as recall and discontinuation of sales

If actions such as recall and discontinuation of sales have been taken to ensure proper use, countries and time of the actions taken should be provided, including their details.

5) Post-marketing surveillance, etc.

Data addressing A to F should be attached. If the data addressing A to F are included in full reports such as clinical study reports prepared by the applicant, attachment of such reports can replace submission of the data.

A Data on surveillance, etc.

The master plan and protocols of post-marketing surveillance, etc. at the time of application for re-examination as well as implementation procedures, questionnaire forms, and registration forms for individual surveillance should be attached.

B Disposition of patients

Disposition of all the patients included in a post-marketing surveillance (overall surveillance population) should be provided, including the numbers of the overall surveillance population, patients subject to safety evaluation, and those not subject to safety evaluation as well as those subject to efficacy evaluation and those not subject to efficacy evaluation. Further detailed disposition of the patients not subject to safety or efficacy evaluation should be provided, including reasons for exclusion or dropout by patient characteristic parameter.

C Safety matters

Characteristics of the patients included in the surveillance for each objective should be provided in a table format. Of cases of malfunctions and infections collected, ones with a suspected relationship to the regenerative medical products concerned (ones for which a relationship cannot be ruled out) should be discussed in terms of details of the occurrence and factors potentially affecting safety. In addition, the “Cases of malfunctions and infections up to approval” (Attachment Format 2) and “List of cases of malfunctions and infections in post-marketing surveillance, etc.” (Attachment Format 3) should be prepared. For the cases deemed as serious adverse events, the “Serious adverse events up to approval” (Attachment Format 4) and “List of serious adverse events in post-marketing surveillance, etc.” (Attachment Format 5) should be prepared. The completed formats should be all attached.

D Efficacy matters

Results on efficacy should be described, and factors affecting efficacy should be discussed.

E Matters in patients with specific backgrounds

Based on the post-marketing surveillance master plan, efficacy and safety in patients with specific backgrounds such as children, elderly, and long-term use should be described.

F Summary

Views on results in post-marketing surveillance, etc. and actions should be described.

6) Malfunctions (including adverse reactions, hereinafter the same)

A Serious malfunctions

Of cases of malfunctions collected in post-marketing surveillance, etc. or spontaneously reported, serious ones should be described.

B Unknown malfunctions

Of cases of malfunctions collected in post-marketing surveillance, etc. or spontaneously reported, ones unexpected from the precautions at the time of application for re-examination should be described.

C Summary

Views on cases of serious or unknown malfunctions and actions should be described.

7) Infections

A Serious infections

Of cases of infections collected in post-marketing surveillance, etc. or spontaneously reported, serious ones should be described.

B Summary

Views on cases of serious infections and actions should be described.

8) Research reports

A search should be conducted for research reports that question the approved indication or performance or safety of the regenerative medical products concerned, and the outline and search results should be provided.

9) Survey of package inserts outside Japan

For the regenerative medical products concerned, contents of package inserts in major countries should be tabulated for comparisons of the indication or performance, dosage and administration or method of use, and precautions. Results on the comparisons and discussions should be provided.

10) Summary

A Views and actions

Comprehensive views on results in post-marketing surveillance, malfunction reports, and research reports as well as actions should be described.

B Proposed changes to indication or performance, dosage and administration or method of use, and precautions

If results in post-marketing surveillance and malfunction reports indicate that indication or performance, dosage and administration or method of use, or precautions need to be changed at the time of application for re-examination, the proposed changes should be provided in a manner allowing comparison with the current statements.

(3) Other data to be attached

1) List of patients included in post-marketing surveillance, etc.

All the patients included in post-marketing surveillance, etc. should be listed. If multiple surveys have been implemented, the list should be prepared for each survey. The list of patients should include information appropriate for the regenerative medical products concerned. Appropriate information may include, for example, the patient number, sex, age, inpatient or outpatient, primary disease, severity before use, duration of disease, complications, period of use, amount used, details of concomitant therapies, efficacy measures, malfunctions (including seriousness, relationship, and outcome), excluded or dropout status and the reason, and usefulness (overall evaluation) as well as safety and efficacy endpoints for the regenerative medical products concerned. Because the information obtained from medical information databases without a table linking to the original medical information is not required to include adverse reactions and infections for each patient in reports, omission of the concerned information is allowed.

2) List of cases of malfunctions and infections

Of cases of malfunctions and infections collected in post-marketing surveillance, etc. or spontaneously reported, ones based on Article 228-20, Paragraph 4 of the Regulation (excluding ones outside Japan) should be listed using Attachment Format 6 and Attachment Format 7.

3) List of research reports

Research reports doubting the approved indication or performance of the regenerative medical products concerned should be listed.

4) Current package insert

4 Others

If multiple products have been subjected to evaluation on use results in the same plan, data to be attached to an application form for re-examination may be included in a single format covering all the products. To products under joint development, the same handling shall apply.

Appendix

(1) Summary of products included in application for re-examination (Attachment Format 9)

(2) Summary of use results

1) History from approval to application for re-examination

A Duplicate copy of approval certificate

B Approval conditions or instructions

C Prior partial changes in approved items

D Prior changes in “Precautions” statements in package inserts

E Summary of post-marketing surveillance, etc. (Attachment Formats 10-12) and prior changes

2) Estimated changes in quantity used or released over time

3) Estimated number of patients with use and sampling rate

4) Sales and action status of the regenerative medical products concerned in and outside Japan

A Approval and sales status

B Status of actions such as recall and discontinuation of sales

5) Post-marketing surveillance, etc.

A Data on surveillance, etc.

B Disposition of patients

C Safety matters (Attachment Formats 2-5)

D Efficacy matters

E Matters in patients with specific backgrounds

F Summary

6) Malfunctions

A Serious malfunctions

B Unknown malfunctions

C Summary

7) Infections

A Serious infections

B Summary

8) Research reports

9) Survey of package inserts outside Japan

10) Summary

A Views and actions

B Proposed changes to indication or performance, dosage and administration or method of use, and precautions

(3) Other data to be attached

1) List of patients included in post-marketing surveillance, etc.

2) List of cases of malfunctions and infections (Attachment Formats 6 and 7)
3) List of research reports
4) Current package insert

Attachment Format 1

(Periodic update reports on use results during re-examination period after conditional and time-limited approval)

<table>
<tr><td rowspan="4">Brand name</td><td rowspan="4"></td><td>Approval number</td><td colspan="2"></td></tr>
<tr><td rowspan="3">Date of approval</td><td>Conditional and time-limited</td><td></td></tr>
<tr><td>Approval</td><td></td></tr>
<tr><td>Date of designation</td><td colspan="2"></td></tr>
<tr><td rowspan="2">Non-proprietary name</td><td rowspan="2"></td><td>Classification</td><td colspan="2"></td></tr>
<tr><td>IBD</td><td colspan="2"></td></tr>
<tr><td colspan="2">Product outline</td><td colspan="3"></td></tr>
<tr><td colspan="2">Indication or performance</td><td colspan="3"></td></tr>
<tr><td colspan="2">Dosage and administration or method of use</td><td colspan="3"></td></tr>
<tr><td colspan="2">Time limit</td><td></td><td rowspan="2">Number of reports</td><td rowspan="2"></td></tr>
<tr><td colspan="2">Re-examination period</td><td></td></tr>
<tr><td colspan="2">Reporting interval</td><td></td><td>Quantity used</td><td></td></tr>
<tr><td colspan="2">Surveillance status</td><td colspan="3"></td></tr>
<tr><td colspan="2">Summary of surveillance results</td><td colspan="3"></td></tr>
<tr><td colspan="2">Occurrences of malfunctions</td><td colspan="3">(Attachment Formats 2-7)</td></tr>
<tr><td colspan="2">Safety measures to be taken based on surveillance results</td><td colspan="3"></td></tr>
<tr><td colspan="2">Remarks</td><td colspan="3"></td></tr>
</table>

As shown above, I hereby report surveillance results including use results.

MM DD, YYYY

Address: (in the case of corporation, location of the main office)
Name: (in the case of corporation, names of the corporation and its representative)

To: Chief Executive of the Pharmaceuticals and Medical Devices Agency

(instructions)

(1) Print the form on A4 (Japanese Industrial Standards) paper.
(2) Submit one each of the original and duplicate copies of the completed form.
(3) For regenerative medical products manufactured outside Japan, the name of the marketing authorization holder should be given under the “Name” field, and information on the designated foreign marketing authorization holder of regenerative medical products manufactured outside Japan should be provided in the “Remarks” field.
(4) The “Conditional and time-limited” field and “Approval” field under the “Date of approval” field should be given “None” if it is not applicable. For products that were granted a conditional and time-limited approval and then unconditionally approved in response to an application for approval re-submitted on or before the time limit, date of the approval concerned should be entered in the “Approval” field, and date of the conditional and time-limited approval should be entered in the “Conditional and time-limited” field.
(5) The “Date of designation” field should be given the date when a period covered by the first report started.

(6) The “IBD” field should be given the date when the first marketing approval for a product containing the active substance was granted to any company in any country across the world.

(7) The “Time limit” field and “Re-examination period” field should be given “None” if it is not applicable. For products that were granted a conditional and time-limited approval and then unconditionally approved in response to an application for approval re-submitted on or before the time limit, the re-examination period of the approval concerned should be entered in the “Re-examination period” field, and the time limit specified by the conditional and time-limited approval should be entered in the “Time limit” field.

(8) The “Number of reports” field should be given the number of periodic update reports on use results submitted for each product. For products that were granted a conditional and time-limited approval and then unconditionally approved in response to an application for approval re-submitted on or before the time limit, the cumulative number of reports submitted after receipt of the conditional and time-limited approval should be entered.

(9) The “Surveillance status” field should be given a brief description including progress and future implementation plan of post-marketing surveillance as well as the numbers of centers and patients included in the surveillance.

(10) The “Summary of surveillance results” field should be given a summary of results from post-marketing surveillance, etc. For use-results surveys and post-marketing database surveillance, factors potentially affecting incidences of malfunctions and infections and safety should be investigated for each objective of the surveillance, and the results should be described. For each of completed post-marketing clinical studies, investigation results should be provided, and for ongoing post-marketing clinical studies, the information on efficacy or safety warranting special mention, if any, should be provided.

(11) To the “Occurrences of malfunctions” field, the following documents should be prepared and attached: (a) cases of malfunctions and infections that were collected in post-marketing surveillance, etc. and suspected to be related to regenerative medical products concerned (ones for which a relationship cannot be ruled out) should be described in the “Cases of malfunctions and infections up to approval” (Attachment Format 2) and “List of cases of malfunctions and infections in post-marketing surveillance, etc.” (Attachment Format 3); (b) of the above cases, ones deemed as serious adverse events (serious health hazards caused by malfunctions in use-results surveys and post-marketing database surveillance) should be described in the “Serious adverse events up to approval” (Attachment Format 4) and “List of serious adverse events in post-marketing surveillance, etc.” (Attachment Format 5). Of cases of malfunctions and infections collected in post-marketing surveillance, etc. or spontaneously reported, ones based on Article 228-20, Paragraph 4 of the Regulation (excluding ones outside Japan) should be listed using Attachment Format 6 and Attachment Format 7.

(12) In the “Safety measures to be taken based on surveillance results” field, future safety measures should be described based on results in post-marketing surveillance, etc.

(13) The “Remarks” field should include the following information.

1) Name of person in charge and contact information
2) If there is a product under joint development, the name of the regenerative medical product concerned and the company name should be provided.
3) If conditions and time limit or re-examination period relating to an approval of the regenerative medical products concerned are separately instructed owing to addition of indication or performance, etc., the time limit or re-examination period should be also provided.

(14) If a field in the attachment format is too small to fill all the required information, a document filled with the information may be separately attached by entering “See Attachment ()” in this field.

Attachment Format 2

Malfunctions and infections reported up to approval

	Cases reported up to approval
Number of centers included in the surveillance	
Number of patients included in the surveillance	
Number of patients with malfunctions	( )
Number of malfunctions	( )
Incidence of malfunctions	( )
Type of malfunctions	Percentage of patients with malfunctions (number of cases) by type (%)
	• • •

(instructions)

(1) Print the form on A4 paper.

(2) Lists should be prepared for each type of surveillance. The type of applicable surveillance should be provided to the table.

(3) For the number of centers included in the surveillance, each center should be counted only once. If the number of centers included in the surveillance is determined based on the number of agreements (e.g., the number of departments), this matter should be described.

(4) For the total number of patients included in the surveillance, each patient should be counted only once.

(5) If multiple cases of malfunctions and/or infections have occurred in a single patient, each case should be counted once.

(6) In the “Type of malfunctions and infections” field for malfunctions and infections unexpected from precautions at the time of reporting, * should be prefixed to the term expressing the corresponding type.

(7) The number of cases collected or reported as infections should be separately provided in parentheses ( ) as the number inclusive of the total. The entry may be omitted if they are not collected or reported as infections.

(8) Because the information obtained from medical information databases without a table linking to the original medical information is not required to include adverse reactions and infections for each patient in reports, omission of the concerned information is allowed.

(9) If the control group is included in the surveillance or study, information in this group should be also entered by adding rows as appropriate.

Attachment Format 3

List of cases of malfunctions and infections in post-marketing surveillance, etc.

Period	Use-results surveys/post-marketing clinical studies based on post-marketing database surveillance				
	MM DD, YYYY to MM DD, YYYY	MM DD, YYYY to MM DD, YYYY	MM DD, YYYY to MM DD, YYYY	• • •	Total
Number of centers included in the surveillance				• • •	
Number of patients included in the surveillance					
Number of patients with malfunctions	( )	( )	( )	• • •	( )
Number of malfunctions	( )	( )	( )	• • •	( )
Incidence of malfunctions	( )	( )	( )	• • •	( )
Type of malfunctions	Percentage of patients with malfunctions (number of cases) by type (%)				
				• • •	
	• • •	• • •	• • •	• • •	• • •

(instructions)

(1) Print the form on A4 paper.

(2) Lists should be prepared for each type of surveillance. The type of applicable surveillance should be provided to the table.

(3) Depending on completed or ongoing post-marketing surveillance, etc., results up to the reporting time point should be tabulated by appropriate period, and the completed table should be provided. Or if follow-up is performed according to characteristics of the product, the tabulation period may start from the day when the product is used in a patient but not from the specific date.

(4) For the total number of centers included in the post-marketing surveillance, each center should be counted only once. If the number of centers included in the surveillance is determined based on the number of agreements (e.g., the number of departments), this matter should be described.

(5) For the total number of patients included in the surveillance, each patient should be counted only once.

(6) If multiple cases of malfunctions and/or infections have occurred in a single patient, each case should be counted once.

(7) In the “Type of malfunctions and infections” field for malfunctions and infections unexpected from precautions at the time of reporting, * should be prefixed to the term expressing the corresponding type.

(8) The number of cases collected or reported as infections should be separately provided in parentheses ( ) as that included in the total. The entry may be omitted if they are not collected or reported as infections.

(9) Because the information obtained from medical information databases without a table linking to the original medical information is not required to include adverse reactions and infections for each patient in reports, omission of the concerned information is allowed.

(10) If the control group is included in the surveillance or study, information in this group should be also entered by adding rows as appropriate.

Attachment Format 4

Serious adverse events reported up to approval

	Cases reported up to approval
Number of centers included in the surveillance	
Number of patients included in the surveillance	
Number of patients with adverse events	( )
Number of adverse events	( )
Incidence of adverse events	( )
Type of adverse events	Percentage of patients with adverse events (number of events) by type (%)
	• • •

(instructions)

(1) Print the form on A4 paper.

(2) Lists should be prepared for each type of surveillance. The type of applicable surveillance should be provided to the table.

(3) Serious adverse events reported up to approval should be provided.

(4) For the number of centers included in the surveillance, each center should be counted only once. If the number of centers included in the surveillance is determined based on the number of agreements (e.g., the number of departments), this matter should be described.

(5) For the number of patients included in the surveillance, each patient should be counted only once.

(6) If multiple adverse events have occurred in a single patient, each event should be counted once.

(7) In the “Type of adverse events” field for events not listed in precautions at the time of reporting, * should be prefixed to the term expressing the corresponding type.

(8) The number of cases collected or reported as infections should be separately provided in parentheses ( ) as the number inclusive of the total. The entry may be omitted if they are not collected or reported as infections.

(9) The number of adverse events for which a relationship to the product is ruled out should be separately provided in parentheses ( ) as the number inclusive of the total.

(10) Because the information obtained from medical information databases without a table linking to the original medical information is not required to include adverse reactions and infections for each patient in reports, omission of the concerned information is allowed.

(11) If the control group is included in the surveillance or study, information in this group should be also entered by adding rows as appropriate.

Attachment Format 5

List of serious adverse events in post-marketing surveillance, etc.

Period	Use-results surveys/post-marketing clinical studies based on post-marketing database surveillance				
	MM DD, YYYY to MM DD, YYYY	MM DD, YYYY to MM DD, YYYY	MM DD, YYYY to MM DD, YYYY	• • •	Total
Number of centers included in the surveillance				• • •	
Number of patients included in the surveillance					
Number of patients with adverse events	( )	( )	( )	• • •	( )
Number of adverse events	( )	( )	( )	• • •	( )
Incidence of adverse events	( )	( )	( )	• • •	( )
Type of adverse events	Percentage of patients with adverse events (number of events) by type (%)				
				• • •	
	• • •	• • •	• • •	• • •	• • •

(instructions)

(1) Print the form on A4 paper.

(2) Lists should be prepared for each type of surveillance. The type of applicable surveillance should be provided to the table.

(3) Depending on completed or ongoing post-marketing surveillance, etc., results up to the reporting time point should be tabulated by appropriate period, and the completed table should be provided. Or if follow-up is performed according to characteristics of the product, the tabulation period may start from the day when the product is used in a patient but not from the specific date.

(4) Serious adverse events reported in post-marketing surveillance, etc. should be provided.

(5) For the total number of centers included in the surveillance, each center should be counted only once. If the number of centers included in the surveillance is determined based on the number of agreements (e.g., the number of departments), this matter should be described.

(6) For the total number of patients included in the surveillance, each patient should be counted only once.

(7) If multiple adverse events have occurred in a single patient, each event should be counted once.

(8) In the “Type of adverse events” field for events not listed in precautions at the time of reporting, * should be prefixed to the term expressing the corresponding type.

(9) The number of cases collected or reported as infections should be separately provided in parentheses ( ) as the number inclusive of the total. The entry may be omitted if they are not collected or reported as infections.

(10) The number of adverse events for which a relationship to the product is ruled out should be separately provided in parentheses ( ) as the number inclusive of the total.

(11) Because the information obtained from medical information databases without a table linking to the original medical information is not required to include adverse reactions and infections for each patient in reports, omission of the concerned information is allowed.

(12) If the control group is included in the surveillance or study, information in this group should be also entered by adding rows as appropriate.

Attachment Format 6

Cases of malfunctions and infections reported up to approval

Type of malfunctions and infections	Cases reported up to approval
	( )
	( )
	( )
	( )
	• • •

(instructions)

(1) Print the form on A4 paper.

(2) If multiple cases of malfunctions and/or infections have occurred in a single patient, each reportable case should be counted once.

(3) In the “Type of malfunctions and infections” field for malfunctions and infections unexpected from precautions at the time of reporting, * should be prefixed to the term expressing the corresponding type.

(4) The number of cases of malfunctions and infections that were collected up to approval and reported to PMDA should be given along with the incidence.

(5) The number of cases of malfunctions and infections that were reported to PMDA and originally collected or reported as infections should be separately provided in parentheses ( ) as the number inclusive of the total. The entry may be omitted if they are not collected or reported as infections.

Attachment Format 7

List of cases of malfunctions and infections

Type of malfunctions and infections	Number of cases of malfunctions and infections reported to PMDA				
	MM DD, YYYY to MM DD, YYYY	MM DD, YYYY to MM DD, YYYY	MM DD, YYYY to MM DD, YYYY	• • •	Remarks
	( )	( )	( )	• • •	( )
	( )	( )	( )	• • •	( )
	( )	( )	( )	• • •	( )
	( )	( )	( )	• • •	( )
	• • •	• • •	• • •	• • •	• • •
Quantity used (quantity released)					

(instructions)

(1) Print the form on A4 paper.

(2) Cases of malfunctions and infections reported to PMDA (except for cases outside Japan) should be described. Cases collected in post-marketing surveillance, etc. up to the time of reporting should be also included.

(3) If multiple cases of malfunctions and/or infections have occurred in a single patient, each reportable case should be counted once.

(4) In the “Type of malfunctions and infections” field for malfunctions and infections unexpected from precautions at the time of reporting, * should be prefixed to the term expressing the corresponding type.

(5) If malfunctions and infections reported have been additionally listed in the precautions, the “Remarks” field should be given “Action taken on MM YYYY.”

(6) The number of cases of malfunctions and infections that were reported to PMDA and originally collected or reported as infections should be separately provided in parentheses ( ) as the number inclusive of the total. The entry may be omitted if they are not collected or reported as infections.

Attachment Format 8

Notification of receipt of periodic update report on use results

Period covered by report	MM DD, YYYY to MM DD, YYYY
Result of receipt	
Remarks	

As shown above, I hereby notify receipt of the periodic update report on use results.

MM DD, YYYY

Chief Executive of the Pharmaceuticals and Medical Devices Agency

To: Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

Attachment Format 9

Summary of products included in application for re-examination

<table>
<tr><td rowspan="3">Brand name</td><td rowspan="3"></td><td>Approval number</td><td colspan="2"></td></tr>
<tr><td rowspan="2">Date of approval</td><td>Conditional and time-limited</td><td></td></tr>
<tr><td>Approval</td><td></td></tr>
<tr><td>Non-proprietary name</td><td></td><td>Classification</td><td colspan="2"></td></tr>
<tr><td colspan="2">Name of applicant</td><td colspan="3"></td></tr>
<tr><td colspan="2">Product outline</td><td colspan="3"></td></tr>
<tr><td colspan="2">Indication or performance</td><td colspan="3"></td></tr>
<tr><td colspan="2">Time limit</td><td colspan="3"></td></tr>
<tr><td colspan="2">Re-examination period</td><td colspan="3"></td></tr>
<tr><td colspan="2">Date of inclusion in insurance coverage</td><td colspan="3"></td></tr>
<tr><td colspan="2">Date of launch</td><td colspan="3"></td></tr>
<tr><td colspan="2">Date of partial changes in approved items and description</td><td colspan="3"></td></tr>
<tr><td colspan="2">Remarks</td><td colspan="3"></td></tr>
</table>

(instructions)

(1) Print the form on A4 paper.

(2) If multiple regenerative medical products have been subjected to surveillance using the same surveillance plan, a single application form for re-examination should have attached data covering all the products, and each field should be given information on all the regenerative medical products concerned. If data on each product to be attached to an application form are omitted, this matter should be described.

(3) For each item, text entered should be kept within the format frame in principle.

(4) The “indication or performance” field should be given the whole content approved. If a part of the approved content is subject to re-examination, the concerned part should be underlined.

(5) The “Date of partial changes in approved items and description” field should be given matters only related to indication or performance.

(6) The “Remarks” field should be given the information that includes name of the person in charge, department, and contact information (telephone number); prior re-examination performed on the regenerative medical products concerned where applicable and date of notification of re-examination result; and brand names of products under joint development where applicable and name of the company.

Attachment Format 10

Outline of use-results survey

Name of survey:	
Objectives	
Safety specification	
Efficacy specification	
Survey method	
Population	
Survey period	
Target sample size	
Observation period	
Number of centers	
Number of cases to be collected	
Sample size for safety analysis	
Sample size for efficacy analysis	
Remarks	

(instructions)

1. The use-results survey subject to re-examination (general use-results survey, specified use-results survey, use-results comparison survey) should be briefly described.
2. This format should be completed for each survey.

Attachment Format 11

Outline of post-marketing database surveillance

Name of survey:	
Objectives	
Safety specification	
Efficacy specification	
Database used in surveillance	
Period covered by data used in surveillance	
Surveillance design	
Exposure and control of interest	
Outcome definition	
Number of patients included in analysis	
Remarks	

(instructions)

1. The post-marketing database surveillance subject to re-examination should be briefly described.
2. This format should be completed for each survey.

Attachment Format 12

Outline of post-marketing clinical study

Name of study:	
Objectives	
Safety specification	
Efficacy specification	
Study design	
Population	
Survey period	
Dosage and administration or method of use (control group, if any, should be included)	
Observation period	
Planned sample size	
Endpoints	
Number of patients administered	
Sample size for safety analysis	
Sample size for efficacy analysis	
Remarks	

(instructions)

1. The post-marketing clinical study subject to re-examination should be briefly described.
2. This format should be completed for each study.