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(Attachment)

## Reports of Adverse Drug Reactions, etc. of Pharmaceuticals

### 1 GLOSSARY

#### (1) Drugs, quasi-drugs, and cosmetics

##### -1- Related to Article 228-20, paragraph 1, item 1 of the Enforcement Ordinance

- a) “Of the occurrences of death, those suspected to have been caused by adverse reactions to the drug concerned” means cases where adverse reactions caused by the drug concerned are suspected as the reason for death.
- b) “Those suspected to have been caused by adverse reactions” means cases other than those where a causal relationship can be ruled out and includes cases where the causality is unknown.
- c) “Drugs which are confirmed to have the same ingredients as the drugs concerned and are used in foreign countries (hereinafter referred to as “Overseas Drugs”)” means drugs that are used in foreign countries (including those currently being studied in clinical trials), have the same ingredients as the drugs concerned, and may include the drugs with a different administration route, dosage and administration, indications, etc. Whether or not a case occurring in a foreign country corresponds to a case for which reporting is required should be judged pursuant to the provisions in Article 228-20, paragraph 1, item 1 of the Enforcement Ordinance. However, at least, cases where prompt reporting is required to the regulatory authorities of the country where the case occurred should be subject to reporting.
- d) “Those which cannot be predicted from the Precautions, etc.” means cases which are not described in “Warnings,” “Important precautions,” “Drug interactions,” “Adverse reactions,” etc., or are inconsistent with the contents of descriptions, in terms of nature, level of symptom, or specificity etc. even if they are described (hereinafter referred to as the “Unknown”). For instance, serious cases that can hardly be predicted from the



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descriptions, even if they are described in the Precautions, are regarded as subject to reporting within 15 days.

- e) “Cases where the tendency of the number, frequency, or conditions of occurrence (hereinafter referred to as the “onset tendency”) cannot be predicted from the Precautions, etc. of the drug concerned” means cases where the tendency of onset, such as the number, frequency, or conditions of the adverse reactions of the drug concerned, cannot be predicted from Precautions, etc. For instance, cases where serious adverse reactions or new adverse reactions occurred in association with new interactions with a drug not described in the Precautions correspond to this situation.

Also, cases where the frequency is clearly higher than the description in the Precautions correspond to this situation.

Incidentally, it is desirable to establish an internal system so that the number of shipments, estimated number of patients exposed, etc. can be monitored periodically or, at least, relevant data can be collected when necessary in order to assess the predictability of the frequency of occurrence.

- f) “Those with changes indicating the risk of occurrence or spread of hygienic hazards” means cases where changes in the tendency of occurrence may have the potential for the occurrence or spread of hygienic hazards regardless of whether the trend of the number, frequency, and conditions etc. of the occurrence of adverse reactions can be predicted from the Precautions of the drug concerned. For instance, where cases not reported previously occur in a specific group of patients or the frequency of the cases changes significantly from previously known correspond to this situation. Also, at least, cases where a consideration of some sort of safety measures has been initiated, including the revision of Precautions and alerting healthcare professionals, correspond to this situation.
- g) “Disability” means the onset of dysfunction to an extent which causes problems in daily life.



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- h) “Drugs that have ingredients different from the approved drugs” means drugs with new active ingredients approved as drugs having active ingredients different from the approved drugs specified in the Cabinet Order for Fees Related to the Act for Ensuring Quality, Efficacy, and Safety of Drugs and Medical Devices, etc. (Cabinet Order No. 91 of 2005). (The drugs for which an application for approval has been submitted as drugs having the same active ingredients as the drugs containing new ingredients and have been approved during the period of reevaluation.)
- i) “Those obtained from the early post-marketing phase vigilance” means cases suspected to be caused by adverse reactions to the drugs concerned and obtained from the early post-marketing phase vigilance. For the drugs currently under the early post-marketing phase vigilance due to additional indications, etc., the adverse reactions caused by the use in association with the indications subject to the early post-marketing phase vigilance correspond to this situation.
- j) “Infections suspected to be caused by the use of the drug concerned” means the cases of biological products where contamination of the drug concerned is suspected to have originated from pathogens contained in raw materials or substances derived from living organisms. For instance, viral hepatitis or HIV infection suspected to be caused by blood preparations corresponds to this situation. When virus markers, including HBV, HCV, and HIV, are determined to be positive, their reporting as infections is required.
- k) “Implementation of the measures to prevent the occurrence or spread of hygienic hazards, including the cessation of manufacturing, import, and marketing of overseas drugs or recall and disposal of the same” includes the cessation of manufacturing for reasons of efficacy and safety as well as changes in indications, dosage and administration, or manufacturing method and distribution of doctors’ letters or the equivalent revision of Important precautions in foreign countries.



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-2- Related to Article 228-20, paragraph 1, item 2 of the Enforcement Ordinance

- a) “There is a risk of occurrence of cancers or other serious diseases, disabilities, or deaths” means that the occurrence or the possibility of occurrence of serious diseases caused by adverse reactions to the drugs concerned or infections caused by the use of the drugs is indicated by epidemiological studies results or studies using animals, etc., physical studies, or chemical studies, etc. For instance, cancer, deafness, or blindness thus caused are included.
- b) “Significant changes in the trend of occurrence of cases which are caused by the adverse reactions of the drugs or overseas drugs concerned or infections caused by the use of these drugs” means distinct changes in the number, frequency, conditions of occurrence, symptoms or the level of the symptoms of adverse reactions, and infections regarding the drugs concerned or overseas drugs. For instance, it refers to an increase in the number of occurrences or frequency revealed by stratified assessment in specific ages, complications, or dosage and administration, while there may not be any significant changes in the overall number of occurrences or increases in frequency.
- c) “Not having efficacy for the approved indications” means that there is no efficacy for the approved indications with respect to the drugs concerned or their active ingredients as demonstrated by the clinical trials and animal studies.
- d) “Research reports” means research reports published in the academic journals of Japan or foreign countries or the studies conducted internally or by relevant companies.

-3- Related to Article 228-20, paragraph 1, item 3 of the Enforcement Ordinance

“New drugs regulated under Article 14-4, paragraph 1, item 1 of the Act and the drugs designated by the Minister of Health, Labour and Welfare pursuant to the provisions of Article 14-4, paragraph 1, item 2 of the Act” means drugs that are subject to reexamination as required at the time of approval.



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-4- Related to Article 228-20, paragraph 5, item 2-(b) of the Enforcement Ordinance

“There is a risk of adverse effects associated with quasi-drugs or cosmetics” means that the occurrence or the possibility of occurrence of adverse effects requiring caution for health and hygiene (e.g., cancer, hypersensitivity, skin disorders, etc.) caused by quasi-drugs, cosmetics, or ingredients contained in these products is indicated by epidemiological studies, results of studies using animals, etc., physical studies, or chemical studies. The adverse effects include infections suspected to be caused by the use of quasi-drugs and cosmetics.

(2) Medical devices

-1- Related to Article 228-20, paragraph 2, item 1 of the Enforcement Ordinance

- a) “Effects caused by malfunctions” means the effects caused by a wide range of undesirable conditions, including breakage and poor operating performance, irrespective of in which stages they occur, such as in design, manufacturing and marketing, distribution, or use.
- b) “Those suspected of being effects caused by malfunctions” means events other than those where a causal relationship can be ruled out, including those where the causal relationship is unknown.
- c) “Medical devices that are used in foreign countries and confirmed to be equivalent to the medical devices concerned in terms of form, structure, raw materials, usage, indications, and performance, etc.” means the devices used in foreign countries (including those being examined in clinical trials) and possess the same properties as the medical devices approved, certified, or notified in Japan.
- d) “Those that cannot be predicted based on Precautions, etc.” means cases that are not described in “Warnings,” “Important precautions,” “Drug interactions,” “Malfunction and adverse events,” etc. or that have imperfect



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descriptions such as inconsistency between the contents of descriptions and nature or level of symptoms even if they are described.

- e) “Those, among the changes in the incidence of malfunctions relating to the medical devices that the minister of MHLW designates separately as those for which the incidence of malfunctions can be predicted [limited to the incidence or possibility of incidence of death or cases listed in the previous paragraph, item 1-(c), (1) to (5); the same applies to (d) and (f)] and that have exceeded such predictions previously made by the marketing authorization holders or exceptional authorization holders of foreign manufacturing of the medical devices concerned” means those medical devices and malfunctions designated by the minister of MHLW which have exceeded the incidence concerned as originally predicted by the marketing authorization holders, etc. (calculated using an appropriate statistical method)
- f) “Cases where the onset tendency cannot be predicted from Precautions, etc. of the medical devices concerned” means cases suspected to be the effects of malfunctions of the medical devices concerned where the tendency of the number, frequency, or conditions of occurrence cannot be predicted from the Precautions, etc. For instance, new cases, etc. that are not described in Precautions that have newly emerged in association with interactions with a medical device correspond to this situation.

Also, cases where the frequency is clearly higher than the one described in Precautions correspond to this situation.

It is desirable to establish an internal system so that the number of shipments, estimated number of patients exposed, etc. can be monitored periodically or, at least, relevant data can be collected when necessary to assess the predictability of the frequency of occurrence.

- g) “Those with changes indicating the possibility of occurrence or spread of hygienic hazards” means cases where changes in the tendency of occurrence may have the potential for the occurrence or spread of hygienic hazards regardless of whether the trend of the number, frequency, and conditions etc. of occurrence of cases suspected to be the effects of



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malfunctions can be predicted from the Precautions of the medical devices concerned. For instance, cases not reported previously occur in a specific group of patients or the frequency of the cases changes markedly from previously known correspond to this situation. Also, at least, cases where the consideration of some sort of safety measures has been initiated, including a revision of Precautions and alerting healthcare professionals correspond to this situation.

- h) “When the incidence of malfunctions concerning overseas medical devices can be predicted, cases where the incidence of malfunctions related to the medical devices concerned exceeds such predictions originally made by the marketing authorization holders or exceptional authorization holders of foreign manufacturing of the medical devices concerned” means the malfunctions that exceed the predictions by the marketing authorization holders or exceptional authorization holders of the foreign manufacturing of the medical devices concerned (calculated using an appropriate statistical method) made as reasonably based on the Precautions, etc. of the medical devices concerned, with the mechanism of occurrence, etc. known and measures to address the malfunctions concerned, etc. established.
- i) “Infections suspected to be caused by the use of the medical devices concerned” means the cases of biological products where the contamination of the medical devices concerned with pathogens contained in raw materials or substances derived from living organisms is suspected. When virus markers, including HBV, HCV, and HIV, are determined to be positive, reporting them as infections is required.
- j) “Implementation of measures to prevent the occurrence or spread of hygienic hazards, including the cessation of manufacturing, import, and marketing or recall and disposal of overseas medical devices” includes the cessation of manufacturing for reasons of efficacy and safety as well as changes in indications, operation method, usage, or manufacturing method, and distribution of doctors’ letters or equivalent revisions of Important precautions in foreign countries.





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-2- Related to Article 228-20, paragraph 2, item 2 of the Enforcement Ordinance

- a) “The occurrence of malfunctions in the medical devices or overseas medical devices concerned, which may cause deaths or the events described in the previous paragraph, item 1-(c), (1) to (5)” means the occurrence of malfunctions in medical devices that may predict deaths or disabilities, etc. although no deaths or disabilities, etc. have actually occurred.
- b) “There is a risk of occurrence of cancers or other serious diseases, disabilities, or death” means that the occurrence or the possibility of occurrence of serious diseases caused by the malfunctions of the medical devices concerned or infections derived from the use of the devices is indicated by epidemiological studies, results of studies using animals, etc., physical studies, chemical studies, or electrical tests, etc.
- c) “Significant changes in the onset tendency of cases caused by the malfunctions of the medical devices or overseas medical devices concerned or that of infections by the use of such devices” means cases where distinct changes are noted in the number of occurrences, frequency, conditions of occurrence, symptoms, or level of symptoms regarding the medical devices or overseas medical devices concerned.
- d) “No efficacy for the approved indications” means that clinical trials or animal studies have shown that the medical devices concerned or their form, structure, or principle, etc. or specifications, etc. do not have the efficacy for the approved indications.
- e) “Research reports” means research reports published in the academic journals of Japan or foreign countries or research reports, etc. published internally or by relevant business entities.

-3- Related to Article 228-20, paragraph 2, item 3 of the Enforcement Ordinance

- a) “Regarding the occurrence of malfunctions in the medical devices concerned, the malfunctions which may cause deaths or events other than those described in paragraph 1, item 1-(c), (1) to (5)” means the occurrence





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of malfunctions in the medical devices that may result in non-serious events, etc.

(3) Combination products

-1- Related to Article 228-20, paragraph 3 of the Enforcement Ordinance

- a) “Drugs for integral marketing with devices” means drugs approved to be marketed in combination with devices that are expected to fall under the category of medical devices if distributed individually (hereinafter referred to as “combination products”).
- b) “Malfunctions in the devices of the drugs concerned” means malfunctions occurring in the devices of the combination products.

(4) Regenerative medicine products

-1- Related to Article 228-20, paragraph 4, item 1 of the Enforcement Ordinance

- a) “Effects caused by malfunctions” means effects originating from a wide range of malfunctions of regenerative medicine products, i.e., adverse reactions occurring in the human body caused by the cells, irrespective of in which stage they occur, such as in marketing, distribution, or use.
- b) “Those suspected to be caused by malfunctions” means malfunctions other than those where a causal relationship can be ruled out, including cases where the causal relationship is unknown.
- c) “Regenerative medicine products used in foreign countries and confirmed to be equivalent in the component cells, transferred gene, structure, manufacturing method, and usage, etc.” means regenerative medicine products used in foreign countries (including those being examined in clinical trials) having the same properties as the regenerative medicine products approved in Japan. Whether or not a case occurring in a foreign country is subject to reporting, it should be judged pursuant to the provisions in Article 228-20, paragraph 4, item 1 of the Enforcement Ordinance. However, at the very least, cases where prompt reporting is



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required to the regulatory authorities of the country where the case occurred should be subject to reporting.

- d) “Those that cannot be predicted from Precautions, etc.” means cases that are not described in “Warnings,” “Important precautions,” “Drug interactions,” “Malfunctions/adverse reactions,” etc. or which have an imperfect description such as inconsistency between the contents of descriptions and the nature or level of symptoms even if they are described.
- e) “Those for which onset tendency cannot be predicted from the Precautions, etc. of the regenerative medicine products concerned” means the tendency of the number, frequency, and conditions, etc. of the occurrence of cases suspected to be the effects of the malfunctions of the regenerative medicine products concerned cannot be predicted from Precautions, etc. For instance, cases occurring with new malfunctions that are not described in Precautions through interactions with other drugs, medical devices, and regenerative medicine products etc. correspond to this situation.

Also, cases where the frequency of occurrence is clearly higher than the description of Precautions correspond to this situation.

It is desirable to prepare an internal system so that the number of shipments, estimated number of patients exposed, etc. can be monitored periodically or, at least, relevant data can be collected when necessary to assess the predictability of the frequency of occurrence.

- f) “Those with changes indicating the possibility of occurrence or spread of hygienic hazards” means cases where changes in the tendency of occurrence may have the potential for the occurrence or spread of hygienic hazards regardless whether the trend of the number, frequency, and conditions etc. of the occurrence of the cases suspected to be the effects by malfunctions can be predicted from the Precautions of the cellular, tissue based products concerned. For instance, cases not reported previously occur in a specific group of patients or the frequency of the cases changes markedly from previously known to correspond to this



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situation. Also, at least, cases where a consideration of some sort of safety measures has been initiated, including a revision of Precautions and alerting healthcare professionals, correspond to this situation.

- g) “Infections suspected to be caused by the use of the regenerative medicine products concerned” means cases where the contamination of the regenerative medicine products concerned is suspected to originate from pathogens contained in raw materials or substances derived from living organisms is suspected. When virus markers, including HBV, HCV, and HIV, are determined to be positive in the manufacturing and use of similar regenerative medicine products, reporting them as infections is required.
- h) “Implementation of measures to prevent the occurrence or spread of hygienic hazards, including the cessation of manufacturing, import, and marketing or recall and disposal of overseas regenerative medicine products” includes the discontinuation of manufacturing for reasons of efficacy and safety as well as changes in the indications, operation method, usage or manufacturing method, and distribution of doctors’ letters or equivalent revisions of Important precautions in foreign countries.

-2- Related to Article 228-20, paragraph 4, item 2 of the Enforcement Ordinance

- a) “The occurrence of malfunctions in the regenerative medicine products or the overseas regenerative medicine products concerned, which may cause deaths or the events described in paragraph 1, item 1-(c), (1) to (5)” means the occurrence of malfunctions in the regenerative medicine products which may predict deaths or disabilities although no deaths or disabilities have actually occurred.
- b) “There is a risk of occurrence of cancers or other serious diseases, disabilities, or deaths” means that the occurrence or possibility of the occurrence of serious diseases caused by the malfunctions of the regenerative medicine products concerned or infections derived from the use of these products is indicated by epidemiological studies, results of studies using animals, etc., in vitro biological and chemical studies, or physical studies.



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- c) “Significant changes in the onset tendency of cases caused by the malfunctions of the regenerative medicine products or the overseas regenerative medicine products concerned or of infections caused by the use of these products” means that distinct changes are noted in the number of occurrences, frequency, conditions of occurrence, symptoms or the level of symptoms, etc. of cases or infections caused by the malfunction or use of the regenerative medicine products or the overseas regenerative medicine products concerned (referring to the overseas regenerative medicine products stipulated in Article 228-20, paragraph 4, item 1, b) of the Enforcement Ordinance).
- d) “No efficacy for the approved indications” means that clinical trials and animal studies, etc. have shown that the regenerative medicine products concerned do not have the efficacy or performance for approved indications.
- e) “Research reports” means research reports published in the academic journals of Japan or foreign countries or the research reports, etc. published internally or by relevant business entities.

-3- Related to Article 228-20, paragraph 5, item 3 of the Enforcement Ordinance

- a) “Regarding the occurrence of malfunctions in the regenerative medicine products concerned, those which may result in deaths or events other than those described in paragraph 1, item 1-(c), (1) to (5)” means the occurrence of malfunctions in the regenerative medicine products concerned that may cause non-serious events, etc.



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## 2 Reporting Time Frames, etc.

### (1) Drugs, quasi-drugs, and cosmetics

- 1- Reporting adverse drug reactions should be made within 15 days for those corresponding to Article 228-20, paragraph 1, item 1 of the Enforcement Ordinance and within 30 days for those corresponding to Article 228-20, paragraph 1, item 2.

Reporting infections suspected to be caused by the use of drugs should be made within 15 days where they correspond to Article 228-20, paragraph 1, item 1 of the Enforcement Ordinance.

When the manufacturing, importing, or marketing of overseas drugs was discontinued, these drugs were recalled and disposed of or measures were taken to prevent the occurrence or spread of hygienic hazards, reporting should be made within 15 days.

When there is a risk of occurrence of cancers or other serious diseases, disabilities, or deaths due to the adverse reactions of the drugs or overseas drugs concerned or infections caused by their use, or when significant changes are noted in the onset tendency of the cases of adverse reactions caused by the drugs or overseas drugs concerned or infections by their use, or when it is known through research reports that the drugs concerned do not have the efficacy for approved indications, reporting should be made within 30 days.

Furthermore, when the investigation of matters that should be reported before the reporting time frame is not completed, reporting should be made with the investigation results obtained in that time together with the reason why the investigation needs more time to complete.

- 2- As for cases to be reported within 15 days, the first report should be made promptly by facsimile, etc. to the Office of Safety II, Pharmaceuticals and Medical Devices Agency (PMDA) with respect to the occurrence of deaths suspected to be caused by unknown adverse drug reactions among deaths in Japan, all cases of infections by drugs, and all the measures taken when the cessation of manufacturing, importing, or marketing overseas drugs, recalling



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and disposing overseas drugs, or preventing the occurrence or spread of hygienic hazards.

- 3- When marketing authorization holders receive reports not only from physicians, etc. but also from the proprietors of a pharmacy, distributors of drugs, etc. referring to suspected occurrences of cases pursuant to Article 228-20, paragraph 1 of the Enforcement Ordinance, they should make efforts to seek a determination from physicians, etc. promptly as to whether the cases correspond to Article 228-20, paragraph 1.
- 4- The initial date and the frequency of periodic reporting stipulated in Article 228-20, paragraph 1, item 3 of the Enforcement Ordinance are as follows.
  - a) Drugs regulated under Article 228-20, paragraph 1, item 3-a)

Counting from the date that the minister of MHLW designates for periodic safety reporting at the time of the marketing approval of the drugs concerned, reporting should be made within 70 days after the expiration date of the reporting time frame period (hereinafter referred to as “the expiration date for reporting”) (3 months when materials obtained from the investigation are not written in Japanese under Article 63, paragraph 1 of the Enforcement Ordinance) every 6 months for the first 2 years and every 1 year after the first 2 years (or once in every period designated by the minister of MHLW for drugs designated by the minister of MHLW).

- b) Drugs regulated under Article 228-20, paragraph 1, item 3-b)

Regarding the reporting of drugs other than those mentioned in “a)” above, the initial date for reporting shall be the date that the manufacturing or marketing of the drug concerned is first approved in Japan or foreign countries (hereinafter referred to as “the international birthdate”) or the date, etc. when the drug is approved, and reporting should be made within 2 months after the expiration date of the period (every year).



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However, for drugs for which approval is not necessary, the initial date for reporting is April 1, 2014, and reporting should be made within 2 months after the expiration date of the period every year.

(2) Medical devices

- 1- Reporting the malfunctions of medical devices should be made within 15 days for those corresponding to Article 228-20, paragraph 2, item 1 of the Enforcement Ordinance and within 30 days for those corresponding to Article 228-20, paragraph 2, item 2.

Reporting infections caused by medical devices should be made within 15 days for those corresponding to Article 228-20, paragraph 2, item 1 of the Enforcement Ordinance.

When the cessation of the manufacturing, import, or marketing of overseas medical devices or other measures to prevent the occurrence or spread of hygienic hazards have been taken, reporting should be made within 15 days.

When there is a risk of occurrence of cancer or other serious diseases, disabilities, or deaths due to the malfunctions of medical devices or overseas medical devices concerned or infections by in their use or when significant changes are noted in the onset tendency of cases caused by the malfunctions of the medical devices or overseas medical devices concerned, or infections by their use, or when it is known through research reports that the medical devices concerned do not have the efficacy for approved indications, reporting should be made within 30 days.

Furthermore, when the investigation of matters that should be reported before the reporting time frame is not completed, reporting should be made with the investigation results obtained by that time together with the next projected date of reporting and the reason why the investigation needs more time to complete.

- 2- The first report should be made by facsimile, etc. promptly to the Medical Device Safety Division, the Office of Safety I, PMDA for all cases of deaths and infections in Japan as well as the details of all measures taken to prevent the





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occurrence or spread of hygienic hazards such as the cessation of the manufacturing, import, or marketing of overseas medical devices.

- 3- When marketing authorization holders receive reports not only from physicians, etc. but also from the distributors of medical devices, etc. referring to the suspected occurrence of cases corresponding to Article 228-20, paragraph 2 of the Enforcement Ordinance, the marketing authorization holders are to make efforts to promptly seek a determination from physicians, etc. as to whether the cases correspond to Article 228-20, paragraph 2.
- 4- Regarding the initial date and frequency of periodic reporting pursuant to Article 228-20, paragraph 2, item 3 of the Enforcement Ordinance, reporting should be made annually after the date of marketing approval/certification/notification for the medical device concerned within 2 months after the end of the period every year.

### (3) Combination products

Reporting the malfunctions of the devices of combination products should be made in accordance with the reporting of malfunctions in medical devices mentioned (2) above.

### (4) Regenerative medicine products

- 1- Reporting the malfunctions of regenerative medicine products should be made within 15 days for those corresponding to Article 228-20, paragraph 4, item 1 of the Enforcement Ordinance and within 30 days for those corresponding to Article 228-20, paragraph 4, item 2.

Reporting the infections suspected to be caused by regenerative medicine products should be made within 15 days for those corresponding to Article 228-20, paragraph 4, item 1 of the Enforcement Ordinance.

When the cessation of manufacturing, import, or marketing of overseas regenerative medicine products or other measures to prevent the occurrence or spread of hygienic hazards have been implemented, reporting should be made within 15 days.



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When there is a risk of occurrence of cancers or other serious diseases, disabilities, or deaths due to the malfunctions of the regenerative medicine products or overseas regenerative medicine products concerned or infections through their use or when significant changes are noted in the onset tendency of cases caused by the malfunctions of the regenerative medicine products or overseas regenerative medicine products concerned or infections in association with their use or when it is known through research reports that the regenerative medicine products concerned do not have the efficacy for approved indications”, reporting should be made within 30 days.

Furthermore, when the investigation of matters to be reported is not completed before the reporting time frame, reporting should be made with the investigation results obtained by that time together with the next projected date of reporting and the reason why the investigation needs more time to be completed.

- 2- The first report should be made by facsimile, etc. promptly to the Medical Device Safety Division, the Office of Safety I, PMDA for all the cases of death and infection in Japan as well as the details of all the measures taken to prevent the occurrence or spread of hygienic hazards, such as cessation of manufacturing, import, or marketing of overseas medical devices.
- 3- When marketing authorization holders receive reports not only from physicians, etc. but also from the distributors of regenerative medicine products, etc. referring to the suspected occurrence of cases pursuant to Article 228-20, paragraph 4 of the Enforcement Ordinance, the marketing authorization holders are to make efforts to promptly seek a determination from physicians, etc. on whether the cases correspond to Article 228-20, paragraph 4.
- 4- Regarding the initial date and frequency for periodic reporting pursuant to Article 228-20, paragraph 4, item 3 of the Enforcement Ordinance, reporting should be made annually after the date of marketing approval or international birthdate for the regenerative medicine products within 2 months after the end of the period every year.



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### 3 Reporting form

#### (1) Drugs, quasi-drugs, and cosmetics

-1- For reporting the adverse reactions, etc. of drugs, quasi-drugs, and cosmetics pursuant to the provisions in Article 228-20, paragraph 1 and paragraph 5 of the Enforcement Ordinance, the forms mentioned below should be used.

a) For reporting pursuant to the provisions in Article 228-20, paragraph 1, item 1, a)–g) or Article 228-20, paragraph 1, item 2, a), Form 1 and Form 2 from (1)–(5) should be used.

b) For reporting pursuant to the provisions in Article 228-20, paragraph 1, item 2, b) or Article 228-20, paragraph 5, item 2, b), Form 3 and Form 4 should be used.

c) For reporting pursuant to the provisions in Article 228-20, paragraph 1, item 1, h), Form 5 and Form 6 should be used.

d) For reporting pursuant to the provisions in Article 228-20, paragraph 1, item 3, Form 7 and should be used.

-2- Reporting using the forms pursuant to Article 228-20, paragraph 1 (except for paragraph 1, item 3) or paragraph 5, may be made with CD-R (ROM) etc. that records the matters requested in each form concerned and documents that include the name of the reporter, address, date of reporting, and other necessary matters.

Reporting pursuant to Article 228-20, paragraph 1 (except for paragraph 1, item 3) and paragraph 5, item 2, b) may be made with an electronic data processing system pursuant to the “Ordinance for Enforcement of the Act on Use of Information and Communication Technology in the Administrative Procedures pertaining to Acts and Regulations under the MHLW” (MHLW Ministerial Ordinance No. 40 of 2003).



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## (2) Medical devices

- 1- For the reports of the malfunctions, etc. of medical devices pursuant to the provisions in Article 228-20, paragraph 2 of the Enforcement Ordinance, the forms mentioned below should be used.
  - a) For reporting pursuant to the provisions in paragraph 2, item 1, a), b), c), e), g), or h) or paragraph 2, item 2, a) or b), Form 8 should be used.
  - b) For reporting pursuant to the provisions in paragraph 2, item 1, d) or f), Form 9 should be used.
  - c) For reporting pursuant to the provisions in paragraph 2, item 1, i), or paragraph 2, item 2, c), Form 10 should be used.
  - d) For reporting pursuant to the provisions in paragraph 2, item 3, a), Form 11 should be used.
  - e) For reporting pursuant to the provisions in item 3, b) or c), Form 12 should be used.
- 2- Reporting using Form 8 and Form 10 pursuant to Article 228-20, paragraph 2, reporting may be made with an electronic data processing system pursuant to the “Ordinance for Enforcement of the Act on Use of Information and Communication Technology in the Administrative Procedures pertaining to Acts and Regulations under the MHLW”.

## (3) Combination products

- 1- For reporting the malfunctions, etc. of the devices of combination products pursuant to the provisions in Article 228-20, paragraph 3 of the Enforcement Ordinance, which Article 228-20, paragraph 2 shall apply mutatis mutandis to the forms mentioned below should be used.
  - a) For reporting pursuant to the provisions in paragraph 3, item 1, a), b), c), e), g), or h) or paragraph 3, item 2, a) or b), Form 8 should be used.
  - b) For reporting pursuant to the provisions in paragraph 3, item 1, f), Form 9 should be used.



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- c) For reporting pursuant to the provisions in paragraph 3, item 1, i), Form 5 and Form 6 should be used.
  - d) For reporting pursuant to the provisions in paragraph 3, item 2, c), Form 3 and Form 4 should be used.
  - e) For reporting pursuant to the provisions in paragraph 3, item 3, b), c), Form 12 should be used.
- 2- Regarding reporting pursuant to Article 228-20, paragraph 3 of the Enforcement Ordinance (which Article 228-20, paragraph 2, item 1, a), b), c), e), g) or h), or paragraph 2, item 2, a), or paragraph 2, item 3, b) shall apply mutatis mutandis to), when health damage has occurred, the report on the adverse reactions of (1) should also be submitted (except for the case where the malfunctions of the devices is evidently the cause of the health damage, and no health damage caused by the drugs is noted).
- 3- Regarding the reports using Form 3, 4, 5, 6, and 8 pursuant to Article 228-20, paragraph 3 of the Enforcement Ordinance, which Article 228-20, paragraph 2 shall apply mutatis mutandis to, reporting may be made with an electronic data processing system pursuant to the “Ordinance for Enforcement of the Act on Use of Information and Communication Technology in the Administrative Procedures pertaining to Acts and Regulations under the MHLW”.
- (4) Regenerative medicine products
- 1- For the reporting of malfunctions, etc. pursuant to the provisions in Article 228-20, paragraph 4 of the Enforcement Ordinance, the forms mentioned below should be used.
    - a) For reporting pursuant to the provisions in paragraph 4, item 1, a)–f) or paragraph 4, item 2, a) or b), Form 13 should be used.
    - b) For reporting pursuant to the provisions in paragraph 4, item 1, g) or item 2, c), Form 14 should be used.
    - c) For reporting pursuant to the provisions in paragraph 4, item 3, a) or b), Form 15 should be used.



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#### 4 The office to which reports are to be submitted

The above-mentioned reports (except the reports of 2 (1) -2-, (2) -2- and (4) -2- by facsimile, etc.) should be submitted to the Safety Information Division, the Office of Safety I, PMDA.