Standard for Re-examination of New Drugs, etc.

Ministry of Food and Drug Safety Notice No. 2020-122, Dec. 14, 2020
Partially Amended and Enforced on Dec. 14, 2020

Article 1 (Purpose)

The purpose of this Standard is to set forth the matters regarding the number of surveillance subjects, the requirements of re-examination data and the preparation methods of surveillance data, etc. for the items requiring the re-examination of new drugs, etc. (hereinafter referred to as the 're-examination') in accordance with Articles 32, 37-3, 38, 42 and 69 of the Pharmaceutical Affairs Act (PAA), Articles 22, 23, 47, 48 (3, 14, 21), 60 (2) and Annex 4-3 of the Regulation on Safety of Medicinal Products, etc. and Article 57 of the Narcotics Control Act.

Article 2 (Definitions)

(1) The terms used in this Standard shall be defined as follows:

1. The term "Post-marketing Surveillance (PMS)" means a surveillance that the marketing authorization holder conducts during the re-examination period, such as the use-result surveillance, special surveillance and post-marketing clinical trial, etc. in order to collect, review, confirm, or verify the information regarding the safety, efficacy and the necessary information for the appropriate use of pharmaceutical drugs requiring the re-examination in accordance with Articles 32 and 42 (5) of the PAA.
2. The term "Standard of Work for PMS (hereinafter referred to as the "Standard of Work")" means the document that specifies all contents and specifications of all PMS activities to be performed during the re-examination period in order to appropriately conduct the PMS.
3. The term "Surveillance Table" means a table that includes the observation records for surveillance subjects who have taken the relevant pharmaceutical drug for the PMS such as the use-result surveillance, special surveillance and post-marketing clinical trial, etc.
4. The term "Raw Data" means the observation records for surveillance subjects described in the surveillance table and may include source data, if necessary.
5. The term "Use-result Surveillance" means one of PMS to be conducted to prepare data for the use-result of the pharmaceutical drug necessary for the re-examination application and to understand the safety and efficacy information, etc. of the pharmaceutical drug in the routine medical examination without setting the conditions of surveillance subjects.
6. The term "Special Surveillance" means one of PMS to be conducted for the information requiring the confirmation or verification after marketing based on the approved conditions or to be conducted to obtain

the additional information when a problem is found by the assessment and analysis results of the information acquired from the post-marketing pharmacovigilance (follow up research after authorization, pharmacoepidermiology research, post marketing database research, etc.).

7. The term "Post-marketing Clinical Trial" means one of PMS to be conducted for the clinical effect observation and adverse events surveillance on the approved information in accordance with Articles 31 and 42 (1) of the PAA in order to collect the safety and efficacy information.
8. The term "Post-marketing Surveillance Protocol (hereinafter referred to as the "Surveillance Protocol")" means the document that specifies the type, purpose, estimated period, number of subjects, designated institution, item and key item, method, interpretation item and method, etc. necessary for the PMS.
9. The term "Periodic Report on Post-marketing Surveillance (hereinafter referred to as the 'Periodic Report')" means the document that periodically reports the results of assessment/analysis and the safety data of the PMS, which are collected during the determined surveillance period, to the Minister of Ministry of Food and Drug Safety.
10. The term "Surveillance Institution" means the medical or research institution to conduct the PMS.
11. The term "Investigator" means the doctor, dental doctor, or oriental doctor who has a responsibility for the conduct of PMS in the surveillance institution.
12. The term "Inspection" means the activity of inspection by the Minister of Ministry of Food and Drug Safety of all facilities, documents and records, etc. of the marketing authorization holder and surveillance institution, etc., in order to confirm whether the PMS is conducted in accordance with this Notice and the surveillance protocol.

(2) The definitions of the terms that are used in this regulation but are not specified separately shall comply with Annex 4-3 of the Regulation on Safety of Medicinal Products, etc.

Article 3 (Application for Re-examination, etc.)

(1) The marketing authorization holder, who intends to receive the re-examination in accordance with Article 23 (1) of the Regulation on Safety of Medicinal Products, etc., shall submit to the Minister of Ministry of Food and Drug Safety a re-examination application made on Form No. 21 of the Regulation on Safety of Medicinal Products, etc. with the results of the periodic report under Subparagraph 8 (a) of the post-marketing safety control standard in Annex 4-3 of the Regulation on Safety of Medicinal Products, etc. and the data that have comprehensively analyzed and evaluated these within 3 months from the expiration date after conducting the PMS for each item during the re-examination period in accordance with Article 22 (2) of the Regulation on Safety of Medicinal Products, etc.

(2) The Minister of Ministry of Food and Drug Safety shall issue the re-examination result notice of pharmaceutical drug made on Form No. 22 of the Regulation on Safety of Medicinal Products, etc. for

each item after reviewing the re-examination application in accordance with Paragraph (1) and shall clearly state the details in case the amendment of the approval information such as efficacy and effectiveness, dose and administration, cautions in use, or pharmaceutical classification, etc. is necessary based on the re-examination results.

(3) In case of intending to change the pharmaceutical classification according to Paragraph (2), the Minister of Ministry of Food and Drug Safety may get opinions from the relevant marketing authorization holder, physician/dentist association established in accordance with Article 28 of the Medical Service Act, pharmacist association established in accordance with Article 11 of the PAA and consumer association registered in accordance with Article 29 of the Framework Act on Consumers.

Article 4 (Standard of Work)

The marketing authorization holder for an item subject to the re-examination shall prepare and place the standard of work including matters of the following subparagraphs in order to appropriately conduct the PMS and, if there is any change, shall amend the standard of work in advance and describe the date:

1. Matters regarding the collection of the information on pharmaceuticals
   (a) Collection targets including the information of the PMS, the domestic voluntary adverse events reports, the foreign information and the information from literatures and conferences;
   (b) Collection method and procedure.
2. Matters regarding the use-result surveillance and special surveillance
   (a) Surveillance methods (surveillance procedure, data collection method, data analytical procedure, etc.);
   (b) Subjects selection criteria and number of surveillance subjects;
   (c) Surveillance item and key surveillance item;
   (d) Interpretation item and statistical analysis method;
   (e) Form of the surveillance table;
   (f) Surveillance request procedures;
   (g) Other necessary matters (reference, safety control manager and contract information).
3. Clinical trial protocol in case of conducting a post-marketing clinical trial
   (a) Trial objective;
   (b) Trial method;
   (c) Interpretation item and statistical analysis method;
   (d) Trial procedures.
4. Matters regarding the assessment and analysis of the collected information and the measures according to the results
   (a) Confirmation method of information;
   (b) Specifications of assessment and analysis;
   (c) Measures according to assessment and analysis results.

5. Matters regarding the delivery of information on pharmaceuticals
   (a) Delivery target according to details of the delivered information;
   (b) Procedure deadline for the delivery completion and confirmation procedure.
6. Matters regarding the education and training of people who are engaged in the PMS
7. Other necessary matters to properly conduct the PMS

Article 5 (Responsibilities of Marketing Authorization Holder and Safety Control Manager)

(1) The marketing authorization holder shall appoint a safety control manager to conduct the PMS pursuant to Articles 37-3 and 42 (5) of the PAA.

(2) The marketing authorization holder shall deliver all pharmaceutical information collected to a safety control manager.

(3) The marketing authorization holder shall take necessary measures, such as the securing and support of sufficient human resources needed for the PMS, to avoid any difficulties on the task conduct of the safety control manager in order to appropriately and smoothly conduct the PMS and, when receiving any request from the safety control manager, shall not deny it without any justification.

(4) In case where a serious adverse event and adverse drug reactions emerges during the PMS, the marketing authorization holder shall let a surveillance investigator promptly notify it to him/her. A serious adverse drug reaction should be reported to the president of the Korean Institute of Drug Safety and Risk Management (KIDS) within 15 days from the date of receipt of report or recognition using the Form No.77-2 of the Regulation on Safety of Medicinal Products, etc. (including an electronic document) via the KIDS website or by phone, fax, post-mail, or electronic document, etc. In case where an unexpected adverse event and adverse drug reaction emerges, its result should be delivered to a doctor if necessary.

(5) When conducting the PMS, the marketing authorization holder shall request it in writing to a surveillance institution and investigator who can fully achieve the purposes of the PMS including the creditability of surveillances and are suitable according to the following subparagraphs. The request of the surveillance shall be documented:
   1. A surveillance institution shall secure the equipment and facilities and human resources to fully achieve the objectives of PMS.
   2. A surveillance investigator shall have the specific knowledge for the pharmaceutical drug, disease, etc., for which the PMS is conducted, and shall receive the education and training necessary to conduct the PMS tasks or have hands-on experiences.
   3. A surveillance institution and investigator shall maintain the records related to the private information of surveillance subjects as confidential.
   4. A surveillance investigator shall be fully aware of this Notice and surveillance protocol.

(6) In case that the marketing authorization holder or the safety control manager comes to know the private information of surveillance subjects, they shall maintain it as confidential.

(7) A safety control manager shall conform to matters falling under the following subparagraphs in order to properly conduct the PMS:

1. Should control PMS tasks overall;
2. Should prepare and retain a surveillance protocol describing the surveillance method and assessment method, etc. for each pharmaceutical drug based on standard of work;
3. Should amend a surveillance protocol in case that it is recognized as necessary based on the review results for the safety and efficacy information of pharmaceuticals;
4. Should take the necessary measures through reviewing and confirming whether the PMS is appropriately conducted and recorded based on standard of work, surveillance protocol, this Notice, etc.;
5. Should perform the education and training for an individual who is engaged in the PMS tasks;
6. Should confirm the accuracy and integrity of the described details on the surveillance table right after collecting them and, if necessary, should amend or make up for it through properly revising or correcting it with the signature of surveillance investigator.
7. Should present the opinion in writing to the marketing authorization holder in case of being judged as necessary to conduct the PMS and should retain the relevant document or the copy

Article 6 (Surveillance Protocol, etc.)

(1) The marketing authorization holder, who intends to conduct the PMS in accordance with Article 2 (1) 1, shall submit to the Minister of Ministry of Food and Drug Safety a surveillance protocol made on Form No. 1 by one month prior to the initial marketing and shall conduct the PMS according to the surveillance protocol submitted. However, in case where the risk management plan submitted in accordance with Article 4 (1) 11 of the Regulation on Safety of Medicinal Products, etc. meets Paragraphs (2) through (4), the submission of separate post-marketing surveillance protocol may not be required.

(2) A surveillance protocol of Paragraph (1) shall include the information of following subparagraphs:

1. Overview of the product subject to re-examination
2. Safety information
   (a) Issues in development;
   (b) Issues of similar products;
   (c) Issues considered from experiences used in foreign countries;
   (d) Foreign approval and marketing status.
3. Use-result surveillance and special surveillance protocol
   (a) Objective of surveillance;
   (b) Subject group of surveillance;
   (c) Number of surveillance subjects;
   (d) Expected period of surveillance;

(e) Expected institution of surveillance;

(f) Surveillance item and method;

(g) Assessment item and method and interpretation method;

(h) Form of surveillance table;

(i) Other necessary matters.

4. Clinical trial protocol in case of conducting a post-marketing clinical trial

(a) Trial objective;

(b) Trial method;

(c) Interpretation item and statistical analysis method;

(d) Trial procedure.

(3) The total number of surveillance subjects required for the re-examination shall be determined through the calculation per item based on the properties such the indication of relevant drug. However, in case where the Minister of Ministry of Food and Drug Safety admits it is appropriate to unify the number of surveillance subjects due to the properties of product/formulation, it can be unified per item.

(4) The marketing authorization holder, who intends to conduct PMS, should submit the objective and appropriate rationale on the calculation of the number of surveillance subjects in accordance with Paragraph (3).

1. Deleted

2. Deleted

(5) The re-examination period of an item, which the Minister of Ministry of Food and Drug Safety authorizes as unnecessary for a separate re-examination because the quantity of drug substances, efficacy/effectiveness and administration route, etc. are similar to pharmaceuticals designated as the target of the re-examination in accordance with Articles 32 and 42 (5) of the PAA, shall be the remaining period of re-examination period for the designated drug. In this case, the total number of surveillance subjects in the report may be determined as the number of surveillance subjects considering the re-examination period and remaining period.

(6) In case of requiring the amendment of matters including the surveillance subject group, total number of surveillance subjects, surveillance period and surveillance method, etc. in the surveillance protocol submitted in accordance with Paragraph 1, the surveillance protocol amendment shall in advance be submitted according to Form No.1 to the Minister of Ministry of Food and Drug Safety. However, in case of minor changes such as the change on the number or names of surveillance institutions and the change of 20% less on the number of surveillance subjects (only for a case where the number of surveillance subjects is increased), it may not be required.

(7) The Minister of Ministry of Food and Drug Safety may request the correction or complement in any

necessary case through reviewing the surveillance protocol submitted.

Article 7 (Periodic Report, etc.)

(1) The marketing authorization holder intending to conduct PMS pursuant to Article 2 (1) 1 shall submit to the Minister of Ministry of Food and Drug Safety the periodic PMS report made on Form No. 2 with the PMS results, etc. for 6 months in the first 2 years from the approval date, for 1 year thereafter within 2 months after the expiration of the surveillance period. However, the final Periodic report may be replaced with the re-examination application and any adverse events and adverse drug reactions, of which expedite report is not made pursuant to Article 5 (4) among data attached to the Periodic reports, shall be reported to the president of the KIDS using Form No. 77-2 of the Regulation on Safety of Medicinal Products, etc. via the KIDS website, or by phone, fax, post-mail, or electronic document, etc.

(2) The following subparagraphs include data to be attached to the Periodic report of Paragraph (1):

1. PMS results

   Overview of the results and interpretation, incidence of adverse events, and raw data of surveillance subjects of the PMS conducted at the relevant surveillance period.

2. In case of post-marketing clinical trials, report on data results reviewed per trial on the completed trials. However, even if the post-marketing clinical trial is still in the process of being conducted, in case of acquiring the noteworthy information, which needs to be considered for the safety and efficacy, it shall be included in the periodic report.

3. Other domestic and foreign data reported on safety such as adverse effects, etc. than Subparagraph 1.

   An adverse event and incidence status collected from domestic clinical trials and voluntary adverse events report, etc. Analyzed and evaluated data of reported event on adverse drug reaction for a pertinent drug collected from abroad during a re-examination period.

4. Reports on safety, including domestic and abroad literatures and academic data.

   Data on adverse drug reactions including the status and examples of adverse drug reactions for a relevant drug and an incidence status, etc. by type which are obtained from domestic and overseas safety data, literature, or academic data.

5. Data on domestic and abroad marketing and license status.

   As data on marketing and licensing status in foreign countries to help understanding the yearly production or import performance (including shipment records, etc.) of a relevant drug and its safety and efficacy, data concerning the status of registration, etc. in foreign pharmacopoeia, and data containing the latest information about measures taken in foreign countries with regard to the safety and efficacy.

(3) Notwithstanding paragraph (1), periodic report may be waived for a product for which surveillance protocol has not been submitted pursuant to proviso to Article 6 (1), if the results of the implementation and examination of the risk management plan submitted pursuant to Article 7-2 (6)

of the Regulation on Approval, Notification and Review of Pharmaceuticals, Article 7-2 (6) of the Regulation on Approval and Review of Biological Products, etc. and Article 8-2 (6) of the Regulation on Approval and Notification of Herbal (crude) Medicinal Preparations, etc. comply with paragraphs (1) and (2). A periodic report of an item, of which the re-examination is conducted during the remaining period of the pharmaceutical product of which the re-examination period is already determined pursuant to Article 6 (5), shall be submitted during the period of periodic report of the pharmaceutical product which is already determined.

(4) The Minister of Ministry of Food and Drug Safety may request the correction or complement in any necessary case through reviewing the periodic report submitted.

(5) The president of the KIDS shall report the summary of adverse events and adverse drug reactions, which are submitted in accordance with Article 5 (4) and 7 (1), to the Minister of Ministry of Food and Drug Safety within one month from the end of quarter.

Article 8 (Investigation, etc. of Reliability of PMS)

(1) In order to confirm matters of the following subparagraphs, the Minister of Ministry of Food and Drug Safety may let a relevant official and an expert or a surveillance investigator designated by the Minister of Ministry of Food and Drug Safety conduct the inspection including the document verification for all matters related to the PMS:

1. Validity of the PMS which is being performed or has already been completed;
2. Reliability of the surveillance institution to conduct the PMS by the manufacturer's request.

(2) In case of conducting the inspection of Paragraph (1), the Minister of Ministry of Food and Drug Safety shall notify it to the marketing authorization holder and the relevant surveillance institution at least 7 days before the inspection, and the marketing authorization holder and the director of surveillance institution shall cooperate it.

(3) If judged as necessary for adverse events reported to the KIDS in accordance with Articles 5 and 7, the Minister of Ministry of Food and Drug Safety may request the relevant data from the president of the KIDS or order the president of the KIDS to analyze and evaluate them and the president of the KIDS shall accept it.

Article 9 (Retention of Documents and Data, etc.)

A marketing authorization holder, surveillance institution, and surveillance investigator shall retain all documents and data including the PMS records, raw data, standard of, PMS protocol and PMS assessment/analysis results, etc. which are prepared during the re-examination period, for 3 years from the date of completion of re-examinations

Article 10 (Information Delivery, etc.)

Any other matters for the collection, report, assessment, follow-up measures and delivery of the

information, protection and reward of reporters, etc., which are not specified in this standard, shall be governed by matters specified in the Annex 4-3 of the Regulation on the Safety of Medicinal Products, etc. established by the Minister of Ministry of Food and Drug Safety.

Article 11 (Consultation, etc.)

The Minister of Ministry of Food and Drug Safety may receive a consultation for the review of re-examination, periodic reporting and PMS protocol, etc. pursuant to this regulation with the Central Pharmaceutical Affairs Council (CPAC) if necessary.

Article 12 (Re-examination of Regulation)

The Minister of Ministry of Food and Drug Safety shall review the appropriateness of this Notice every three years beginning on January 1, 2014 (meaning by December 31 every third year) pursuant to Article 8 of the Framework Act on Administrative Regulation and the Regulation on the Issuance and Management of Orders, Rules, etc. and take proper measures for improvement, etc.

ADDENDUM <Standard No. 2017-95, Nov. 21, 2017>

Article 1 (Enforcement Date)

This Notice will be effective on the date of its announcement.

Article 2 (Interim Measures)

Re-examinations being conducted pursuant to previous laws and regulation at the time of the enforcement of this notice, previous regulation shall be applicable.

[Form No. 1]

(Front)

<table>
<tr><td colspan="5">Post-Marketing Surveillance (PMS) Protocol (Amendment)</td></tr>
<tr><td rowspan="4">Reporter</td><td>Business License No.
(Importer Confirmation)</td><td colspan="3"></td></tr>
<tr><td>Name of Manufacturing
(Business) Site</td><td colspan="3"></td></tr>
<tr><td>Address of Manufacturing
(Business) Site</td><td colspan="3"></td></tr>
<tr><td>Name</td><td></td><td>Birth Date</td><td></td></tr>
<tr><td rowspan="2">Manufacturer</td><td>Name of Manufacturing Site</td><td></td><td>Manufacturing Country</td><td></td></tr>
<tr><td>Address</td><td colspan="3"></td></tr>
<tr><td colspan="2">Product Name for Re-examination</td><td></td><td>Re-examination Period</td><td></td></tr>
<tr><td colspan="2">Approval Number</td><td></td><td>Approval Date</td><td></td></tr>
<tr><td colspan="5">I submit the PMS protocol (amendment) like the attached form in accordance with Article 6 of Standard for Re-examination of New Drugs Etc.
_____Year_____Month_____Day

Applicant: (Sign or Stamp)
Safety Control Manger:
Person in Charge:
Telephone:

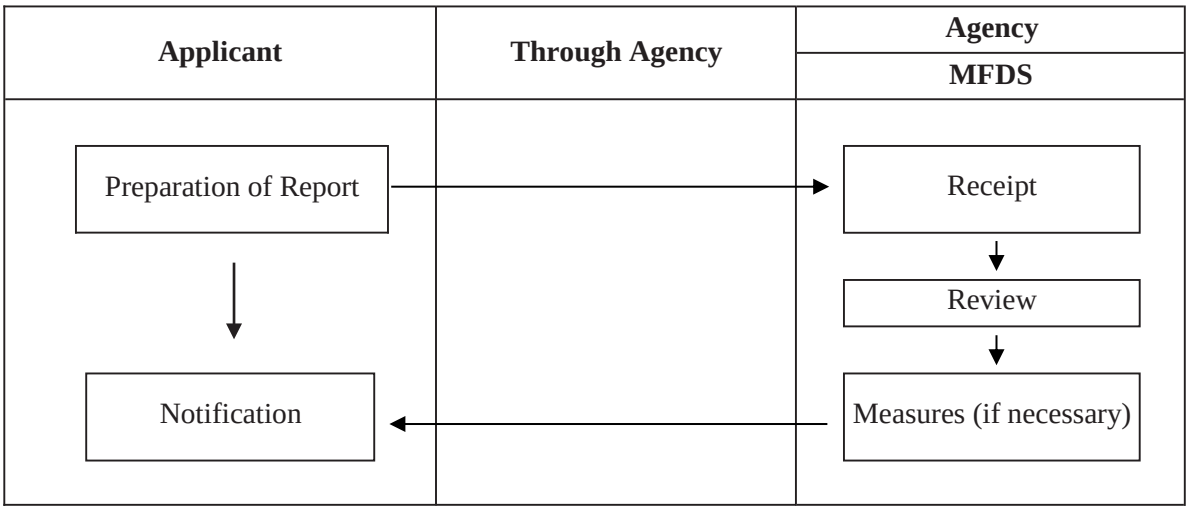
To Minister of Food and Drug Safety</td></tr>
<tr><td colspan="5">Required Documents
1. Summary of Re-examination Items
2. Safety Information
3. Use-result Surveillance & Special Surveillance Protocol
4. Post-Marketing Clinical Trial Protocol (only if conducted)
5. One copy of Summary of Changes on Surveillance Protocol Amendment (only if amended)</td></tr>
</table>

210 mm x 297 mm

Printing paper (Grade 2) 60g/m^3

This application shall be processed like the following:

(Reverse)



[Form Template]

<table>
<tr><th colspan="4">Overview of Post-Marketing Surveillance (PMS) Protocol</th></tr>
<tr><td rowspan="8">Use-result Surveillance</td><td colspan="2">Overview of Surveillance</td><td></td></tr>
<tr><td rowspan="2">General Use-result Surveillance</td><td colspan="2" rowspan="2"></td></tr>
<tr></tr>
<tr><td colspan="2">Overview of Surveillance</td><td></td></tr>
<tr><td rowspan="5">Surveillance for Special Patients</td><td>Surveillance for Pediatric Population</td><td></td></tr>
<tr><td>Surveillance for Elderly</td><td></td></tr>
<tr><td>Surveillance for Pregnant Women</td><td></td></tr>
<tr><td>Surveillance for Patients with Renal impairment</td><td></td></tr>
<tr><td>Surveillance for Patients with Hepatic impairment</td><td></td></tr>
<tr><td>Special Surveillance</td><td colspan="2"></td><td></td></tr>
<tr><td>Post-Marketing Clinical Trial</td><td colspan="2"></td><td></td></tr>
<tr><td colspan="4">Safety Issue</td></tr>
<tr><td colspan="3">Issues in Development Phase</td><td></td></tr>
<tr><td colspan="3">Issues with Similar Products</td><td></td></tr>
<tr><td colspan="3">Issues from Using Experiences in Other Countries</td><td></td></tr>
<tr><td colspan="4">Overview of Protocol Amendment</td></tr>
<tr><td colspan="4"></td></tr>
</table>

[Form No. 2]

<table>
<tr><th colspan="5">Post-Marketing Surveillance (PMS) Periodic Report (th)</th></tr>
<tr><td rowspan="4">Reporter</td><td>Business License (Importer Confirmation)</td><td colspan="3"></td></tr>
<tr><td>Name of Manufacturing</td><td colspan="3"></td></tr>
<tr><td>Address of Manufacturing</td><td colspan="3"></td></tr>
<tr><td>Name</td><td></td><td>Birth Date</td><td></td></tr>
<tr><td rowspan="2">Manufacturer</td><td>Name of Manufacturing Site</td><td></td><td>Manufacturing Country</td><td></td></tr>
<tr><td>Address</td><td colspan="3"></td></tr>
<tr><td colspan="2">Product Name for Re-examination</td><td></td><td>Re-examination Period</td><td></td></tr>
<tr><td colspan="2">Approval Number</td><td></td><td>Approval Date</td><td></td></tr>
<tr><td rowspan="2">Surveillance Results</td><td>Period and Number of Subjects</td><td colspan="3"></td></tr>
<tr><td>Summary and Interpretation of Results</td><td colspan="3"></td></tr>
<tr><td colspan="2">Production Results (Release Results)</td><td colspan="3"></td></tr>
<tr><td colspan="5">I submit the regular PMS report like the above information in accordance with the provision of Article 7 (1) of Standard for Re-examination of New Drugs, etc.
_____Year_____Month_____Day

Reporter : (Sign or Stamp)
Safety Control Manager:
Person in Charge:
Telephone:

To The Minister of Ministry of Food and Drug Safety</td></tr>
<tr><td colspan="5">Required Documents
1. PMS results
2. Report on data results per trial
3. Domestic/foreign safety data in addition to Subparagraph 1</td></tr>
</table>

210 mm x 297 mm

Printing paper (Grade 2) 60g/m^3

This application shall be processed like the following:

(Reverse)