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- Safety Control after Releasing Medicinal Products etc. -

Guideline on re-examination affairs of new drugs etc.

(A guide for civil petitioner)

Nov 18, 2021

Ministry of Food and Drug Safety

This guide describes Ministry of Food and Drug Safety's position on 「re-examination standard for new drug etc.」 for post-market safety control of pharmaceuticals etc.

This guide does not have legal force and you need not observe even though there are some descriptions in this guide which are rigid such as you must ~. This guide was prepared based on scientific·technological fact and effective regulations as of December 2018 and therefore it is subject to change according to contents of revised regulations and specific facts.

※ "A guide for civil petitioner" describes regulations or notice・directive・published rulings in easy terms or Ministry of Food and Drug Safety's position on specific matters(Article 2 of Regulation on Control of Ministry of Food and Drug Safety's Guideline)

※ If you have any opinion or inquiry about this guide, feel free to inquire of Pharmaceutical Safety Evaluation Safety, Pharmaceutical Safety Bureau, Ministry of Food and Drug Safety.

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The history of enactment·revision

Serial number	Enactment·revision number	Approval date	Main content
1	Guide-0019-01	2011	enacted
2	Guide-0019-02	July 2012	revised
3	Guide-0019-03	Dec 27, 2018	revised (relevant provision update, adding items to be entered in a periodic report and re-examination application form, updating Q&A etc.)
4	Guide-0019-04	Dec 16, 2019	revised (extension of scope of PMS, adding analysis for the joint development product, Q&A update, etc.)
5	Guide-0019-05	Dec 2020	revised
6	Guide-0019-05	Nov 2021	Revised

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Ⅰ. Guideline on re-examination service of new drugs etc.

Chapter 1 Introduction

1. Purpose

The purpose of this guideline is to present recommendations and examples in determining matters that are required for methods and procedures of re-examination which aims to reflect the result of observation in approval by observing safety and efficacy of new drugs etc. which were previously approved and are on the market for designated period (4~6years).

2. Background

New drugs are put on the market after their safety and efficacy are proven through non-clinical trials and clinical trials. However, pre-market clinical trials have several problems such as limited observation period caused by a purpose of obtaining approval as soon as possible and limited number of Target product to observation and application of strict criteria for selecting Target product to observation, which makes it difficult to apply the result of pre-market clinical trials to all patients and thus serious adverse events which have not been found in clinical trial are likely to occur in case that lots of people take for a long time after pharmaceutical is put on the market. Accordingly, in Republic of Korea, since 1995 re-examination system has been implemented to reexamine factors influencing safety and efficacy, new adverse events and their appearance which were not found during development and approval process of pharmaceutical and manage approval for relevant pharmaceutical based on the result by closely examining efficacy and safety of new drugs etc. which are put on the market after obtaining marketing approval targeting a wide range of patients. According to above mentioned system, as a condition for marketing approval for new drugs etc. 4 years to 6 years of re-examination period are assigned depending on property of pharmaceutical and procedures and methods of pharmaceutical re-examination are based on 「Re-examination standard for new drugs etc.」(Notification of the Ministry of

Food and Drug Safety).

This ‘guideline on re-examination of new drugs etc.’ was enacted in 2011 and revised in July 2012 for the first time to reflect revisions of re-examination related provisions. In other words, In July 2015 Risk Management protocol was introduced and revision was made to minimize inconvenience of submitting overlapped data at the time of periodic report for re-examination and In January 2017「Regulation on Control of Safety Information of Pharmaceuticals」(Notification of the Ministry of Food and Drug Safety) was abolished and relevant content was enacted as 「 Pharmaceutical Affairs Act」, 「Regulations on Safety of Pharmaceuticals, etc.」(ordinance of the prime minister) [attached table 4-3] Standard for Post market Safety Control of Pharmaceutical. Accordingly, this guideline aims to improve efficiency of service by reflecting latest matters related to re-examination of new drugs etc. and clarifying matters for re-examination service procedure and required documents. The guideline was revised with the extension of special surveillance method under 「**Standard for Re-examination of New Drugs, etc**」(notified by MFDS) ,which was revised in December, 2020.

Chapter 2 Summary of re-examination

1. Relevant regulations

A.「Pharmaceutical Affairs Act」

Article32(Re-Examination of New Drugs, etc.)

Article37-3(Safety Control after Releasing Medicinal Products)

Article38(Production Control of Drugs, etc. and Reporting thereof)

Article42(Permission, etc. for Importation of Drugs, etc.)

Article69(Reporting, Inspection, etc.)

B.「Regulations on Safety of Pharmaceuticals, etc.」(ordinance of the prime ministry)

Article22(Target product to re-examination of new drug etc.)

Article23(Re-examination application etc. for new drugs etc.)

Article47(Matters to be observed by safety control managers)

Article48(Matters to be observed by manufacturers etc.)subparagraphs 3, 14, and 21
Article60(Matters to be observed by importers etc.) paragraph2
[Schedule 4] Good Clinical Practice(concerning Paragraph 1, Article 30)
[Schedule 4-3] Standard for Post Market Safety Control of Pharmaceutical etc.

C.「Act on the Control of Narcotics, etc.」Article 57(Application of Other Acts)

D.「Regulation on Approval·Examination of Biological Products」(Notification of the Ministry of Food and Drug Safety) Article 22(Approval conditions) paragraphs 3, 4

E.「Rare Disease Management Act」Article 19(Exceptions to Pharmaceuticals Affairs Act) Paragraph 4

F.「Re-examination standard for new drugs etc.」(Notification of the Ministry of Food and Drug Safety)

2. Definitions

A. "Re-examination" means system that reevaluates safety · efficacy by investigating and verifying adverse events which did not appear within the period in accordance with Article 32 of Pharmaceutical Affairs Act after date of original approval for prescription drugs etc. equivalent to new drugs determined by Minister of Ministry of Food and Drug Safety.

B. "Post market surveillance" means investigation conducted during the period of re-examination such as use result surveillance, special surveillance, and clinical trials after releasing which a person who has obtained marketing approval conducts to collect, examine, check or verify information on safety ·efficacy of pharmaceuticals subject to re-examination in accordance with Article 32 and Paragraph 5, Article 42 of「 Pharmaceutical Affairs Ac t」.

C. The term “Standard of Work for PMS” means the document that specifies all contents

and specifications of all Post market surveillance activities to be performed during the re-examination period in order to appropriately conduct the PMS.

D. "Surveillance table" means a table that includes the observation records for surveillance subjects who have taken the relevant pharmaceuticals for the PMS such as the use-result surveillance, special surveillance and post-marketing clinical trial, etc.

E. "Raw data" means the observation record for surveillance subjects described in the surveillance table and may include source data, if necessary.

F. "Use-result surveillance" means one of PMS to be conducted to prepare data for the use-result of the pharmaceuticals necessary for the re-examination application and to understand the safety and efficacy information, etc. of the pharmaceuticals in the routine medical examination without setting the conditions of surveillance subjects.

G. "Special surveillance" means investigation conducted to obtain additional information (further research required after approval, pharmacoepidemiology study, Post Market database research etc.) when any problem occurs based on a result of evaluation and analysis of information gained from post market pharmacovigilance activity and investigation performed based on conditions imposed at the time of approval in matters to be checked or verified after pharmaceutical is put on the market among post market surveillance.

H. " Post-marketing Clinical trial" means a test conducted to observe clinical effect and investigate adverse effect of matters approved in accordance with Article 31 and Paragraph 1, Article 42 of 「 Pharmaceutical Affairs Act」 to collect information safety ·efficacy among post market surveillance.

I. " Post market surveillance protocol " means a document that specifies types of surveillance needed for Post market surveillance, purpose of the surveillance, scheduled surveillance period, number of Target product to surveillance, scheduled investigation

agency, investigation items, main investigation items, surveillance method, analysis items and analysis methods.

J. "Periodic Report on post-marketing surveillance" means the document that periodically reports the result of assessment/analysis and the safety data of the post ‐ marketing surveillance, which are collected during the determined surveillance period, to the Minister of Ministry of Food and Drug Safety.

K. "Surveillance institution" means the medical or research institution to conduct the post-marketing surveillance.

L. "Investigator" means physician, dentist and oriental medical doctor who are responsible for carrying out Post market surveillance in investigation agency .

M. "Research on the actual condition" means that Minister of Ministry of Food and Drug Safety investigates a person who has obtained marketing approval, investigation agencies, facilities, documents, record etc. to check whether surveillance after releasing has been conducted in accordance with this notice and a surveillance protocol.

N. "Safety information" means various information related to safety · efficacy of medicinal products etc. such as side effects caused by medicinal products etc. efficacy · effectiveness, administration · dosage, precautions.

O. "Pharmacovigilance" means scientific activity about detection, evaluation, analysis and prevention of adverse events or safety related problems.

P. "Safety information" means all information on relevant pharmaceutical etc. collected through pharmacovigilance.

Q. "Side effect" means all unintended effect that occurs when pharmaceutical with normal

dosage is administered and includes unintended desirable effect.

R. "Adverse Event (AE)" means undesirable and unintended sign (ex: abnormality in examination value in terms of laboratory), symptom or disease that occurs while pharmaceutical is being administered or used and does not need causal relationship with relevant pharmaceutical.

S. "Adverse Drug Reaction (ADR)" means harmful and unintended reaction that occurs when a medicinal product is administered and used normally and that causal relationship with relevant medicinal product cannot be excluded and among voluntarily reported adverse events, a case which causal relationship with relevant medicinal product is not known is considered as adverse drug reaction. Provided, however, that reporter and manufacturer/clients all find that a case is not related to medicinal products etc. the case is excluded from adverse drug reaction.

T. "Risk Management protocol (RMP)" means comprehensive medicinal products safety control protocol including methods of relieving risk determined by Minister of Ministry of Food and Drug Safety such as instruction for patients and measures for safe use.

U. "Korea Institute of Drug Safety & Risk Management" means institution that aims to conduct collection, management, analysis, evaluation of information related to safety of pharmaceutical such as side effect caused by pharmaceutical, marketing approval information·notification information and ti provide service efficiently and systematically.

3. The target product and period of re-examination and number of surveillance subjects.

The subject of re-examination is limited to medicinal products prescribed in Article 32 and Paragraph 5, Article 42 of Pharmaceutical Affairs Act and re-examination period ranges from 4 to 6 years according to products from a date when manufacture or import is approved.

A. The subject and period of re-examination

* Legal Background : Paragraph 1, Article 22 (subject of re-examination of new drugs etc.) 「Regulations on Safety of Pharmaceuticals, etc.」

Paragraphs 4 and 5, Article 22 (approval conditions etc.) of 「Regulation on pharmaceuticals approval notification & review」

Classification of subject	Re-examination period
○ New drugs ○ Prescription drugs which types or composition ratio of active pharmaceutical ingredient are different ○ Prescription drugs which active pharmaceutical ingredient is same but route of administration is different	for 6 years after approval
○ Prescription pharmaceuticals which active ingredient and administration route are same but distinctly different efficacy · effect are added ○ Pharmaceuticals that need re-examination - In case where there is consent of applicant, pharmaceuticals falling under any one of the following shall be designated as the subject of re-examination · Pharmaceuticals that administration and dosage for children are approved through clinical trial conducted in Republic of Korea · Orphan drug주1)	for 4 years after approval

Note[1] In case where an applicant applies orphan drug which is used for disease that proper therapy and pharmaceutical has not been developed as pharmaceutical subject to re-examination Subparagraph 4, Article 19 of 「Rare Disease Management Act」, Minister of Ministry of Food and Drug Safety may consult Central Pharmaceutical Affairs Council about its adequacy if needed and assign 10 years of re-examination. In such case, pharmaceutical that adds children indication can extend re-examination period by one year.

B. The number of surveillance subjects

The number of Target product to surveillance shall be determined by products considering property such as indication of relevant pharmaceutical in accordance with Paragraphs 3 and 4, Article 6 of「Re-examination standard for new drugs etc.」and objective and valid supportive data needed for calculation shall be submitted. At this time, as objective and valid supportive data, domestic prevalence of relevant indication, number of actual patients, number of prescription of relevant and mimetic pharmaceutical or the amount claimed for pay, adverse drug reaction falling under safety main examination items and incidence may be submitted. For the following number of Target product to surveillance, separate supportive data don't have to be submitted and in such case, adjusting number of subject by products is possible considering property of pharmaceutical.

Classification of subject	Number of Target product to surveillance
○ New drugs - New drug which has been developed in Republic of Korea for the first time in the world - New drug which is being developed in a foreign country(new drug which has not been approved) - New drug which has been developed and approved in a foreign country and three years has not elapsed after it was approved from a country in which it was developed	3000 or more
- New drug which has been developed and approved in a foreign country and has not been used other than a country in which it was developed	600 or more
○ Other new drugs and pharmaceuticals that data were submitted	

4. Post market Surveillance(PMS)

The subject of re-examination shall conduct post market surveillance during the period of re-examination according to products after a date that approval is made and then within three

months of expiration of such period undergo re-examination by Minister of Ministry of Food and Drug Safety and post market surveillance in accordance with 「Re-examination standard for new drugs etc.」 is as follows.

A. Use-result Surveillance

- Select Target product to surveillance systematically according to surveillance protocol. (continuous surveillance method, total surveillance method, central registration method etc.)
- Understanding information on safety immediately after a product is put on the market is necessary and thus surveillance protocol shall be made before a product is put on the market (surveillance protocol shall be submitted to Ministry of Food and Drug Safety one month before a product is put on the market) and it is recommended that surveillance should be started at the same time as marketing[1)].
- Unlike clinical trial, use-result surveillance shall be conducted in non-interventioal way under ordinary medical treatment.
- It is recommenced that pharmaceutical which is likely to be used for a long term include surveillance result of patients who used the pharmaceutical for a long term in use-result surveillance and period may be set based on clinical trial at the time of approval.
- Use cases of special patients such as children, the aged, pregnant women, patients with renal disorder and patients with hepatopathy in clinical trials at the time of approval is small and thus you need to understand them as much as possible.

B. Special Surveillance

- This means surveillance conducted investigation conducted to obtain additional information (further research required after approval, pharmacoepidemiology study, Post Market database research etc.) when any problem occurs based on a result of evaluation and analysis of information gained from post market pharmacovigilance

activity and investigation performed based on conditions imposed at the time of approval.

※ Post Market Database research refers to classification and analysis by organs of an array of incidences caused by the adverse event and diseases by utilizing medical database provided by the medical database information manager to detect or identify the information on quality, efficacy and safety of the product.

* Medical Database Information: systematically computerized information including medical records, health insurance claims data, patient registration system, and other data on the patient's health status collected over a period of time.

· Post market database study can be considered the situation as follows.

- If the database study for the item is conducted abroad under the conditional approval
- If the database study recommended from the regulator is carried out to evaluate the identified risks and potential risks for the item abroad
- If it is judged that the separate study to identify the adverse drug reaction which is less frequent than 0.1% is necessary, considering the subject population to identify the reaction with a frequency of 1 of 1000 person at the 95% confidence level to three thousand persons.

If it is not necessary to carry out the supplement study based on the database study as the number of the subject is too small to identify with the use result surveillance due to a lower prevalence and incidence rate in Korea (e.g. cholangiocarcinoma or cancer that has a lower annual incidence rate compared than the cholangiocarcinoma in cancer prevalence statistics by the Ministry of Health and Welfare).

C. Post-marketing Clinical Trial

· This means a test conducted to verify estimation obtained by examining clinical trials or result of use-result surveillance among post market surveillance or collect information on efficacy and safety that cannot be obtained from medical treatment in accordance with directions · volume, efficacy · effect permitted pursuant to 31 and Paragraph 5, Article 42 of 「 Pharmaceutical Affairs Act」.

- Cases of Post market clinical trials conducted according to clinical trial protocol examined by Ministry of Food and Drug Safety to be included in re-examination application as " a test conducted to observe clinical effect of pharmaceutical that is put on the market and investigate adverse events" in accordance with Subparagraph 1, Paragraph 8, Article 24 of 「Regulations on Safety of Pharmaceuticals, etc.」 may be included in post market surveillance.
- In case where Post market clinical trial for re-examination is conducted, Post market clinical trial protocol shall be submitted to Ministry of Food and Drug Safety and examined and Post market clinical trial shall be conducted in accordance with Article 30 of 「Regulations on Safety of Pharmaceuticals, etc.」 and [attached table 4] Good Clinical Practice.

* Note : post market surveillance shall be conducted within the scope of economic benefit permitted in accordance with Paragraphs 2 and 3 Article 47 of 「Pharmaceutical Affairs Act」 (scope of economic benefit permitted pursuant to Paragraph 4 Article 44 of 「Enforcement Regulations of the Pharmaceutical Affairs Act」 [schedule 2])

5. Review of re-examination data and notification of result of re-examination

On receiving re-examination application, Minister of Ministry of Food and Drug Safety shall conduct re-examination of relevant pharmaceutical and research on actual condition and consultation from Central Pharmaceutical Affairs Council and issue a notice of result of reexamination of pharmaceutical in accordance with 「Regulations on Safety of Pharmaceuticals, etc.」 [annexed paper no. 22 form] to an applicant (manufacturer·importer) of relevant pharmaceutical. If Minister of Ministry of Food and Drug Safety deems it necessary to change efficacy ·effectiveness, administration ·dosage, precautions in use or drug categorization based on the result of re-examination, he/she shall specify it.

6. Flow diagram of re-examination

service stage	Ministry of Food and Drug Safety		business enterprise	description
designation stage	Designating the subject of re-examination (departments in charge of approval[1])			
Submitting a protocol	Receiving a protocol (departments in charge of management[2])	⇦	drawing post market surveillance protocol	▷ Submitting at least 1 month before releasing · use-result surveillance, special surveillance, post-marketing clinical trials ▷ Data to be submitted : 「Re-examination standard for new drugs etc. (Notification of the Ministry of Food and Drug Safety)」data in accordance with Paragraphs 1-5 Article 6 (including annexed paper no. 1 form)
examining a protocol	Sending a result of examining a protocol (departments in charge of examination[3], departments in charge of management)	⇔	correcting or supplementing if needed	
conducting Post market surveillance (periodic report)	Sending a result of examining a periodic report (departments in charge of examination, departments in charge of management) ※if needed, investigate reliability	⇔	conducting Post market surveillance (preparing a periodic report)	▷ Submitting post market surveillance result conducted for 6 months for 2 years from the date of approval and thereafter conducted for 1 year within 2 months after surveillance period expires ▷ Data to be submitted : Paragraph 2 Article 7 of「Re-examination standard for new drugs etc. (Notification of the Ministry of Food and Drug Safety)」
applying for re-examination	Examining re-examination application (departments in charge of examination, departments in charge of management) ※ if needed, investigate reliability and consult advisory council, Central Pharmaceutical Affairs Council	⇔	reporting the final result (applying for re-examination)	▷ 'Re-examination application' replaces the final periodic report ▷ Submitting post market surveillance result during the period of re-examination within 3 months after re-examination period expires ▷ Data to be submitted : Paragraph 1 Article 3 of「Re-examination standard for new drugs etc. (Notification of the

			Ministry of Food and Drug Safety)」
follow-up	Follow-up based on re-examination result (departments in charge of management)	⇨ Fulfilling follow-up	▷ Notifying re-examination result ▷ Directing a change in matters approved ▷ Administrative measures ▷ Other matters required

※ Investigation of reliability may be conducted and advice from the experts of Central Pharmaceutical Affairs Council (CPAC), if necessary may be received.

1) departments in charge of approval : Director for Approval Management of Pharmaceutical and herbal (medicinal) product, Director for Novel Products Approval of biologics.

2) departments in charge of management : (pharmaceutical) Pharmaceutical Safety Evaluation Division, (biologics) biopharmaceutical Quality Management Division, (Korean traditional medicine (herbal medicine) preparations) Herbal Medicine Policy Division

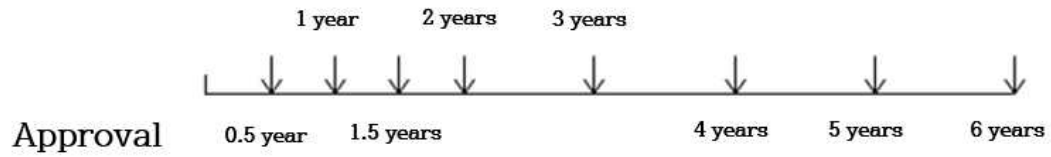
3) departments in charge of examination : (pharmaceutical) Cardiovascular and Neurology Products Division, Oncology and Antimicrobial Products Division, Bioequivalence Evaluation Division

(biologics) Bio Preparation Division, Gene Preparation Combination Pharmaceutical Division, Cell Gene Therapy Products Division,

(Korean traditional medicine (herbal medicine) preparations) Herbal Medicine Preparation Division

※ Time for periodic report to be submitted

- Submit within 2 months of relevant surveillance period expiring



Chapter 3 Preparation of Post market surveillance (change) protocol

1. General information

A. Post market surveillance (change) protocol (「Re-examination standard for new drugs et c.」 annexed paper no. 1 form, hereinafter referred to as "surveillance protocol".) shall be reported to Minister of Ministry of Food and Drug Safety one month before a product subject to re-examination is released . In case where a product subject to re-examination is not released until first periodic report, reason for which market surveillance is not conducted shall be submitted.

B. For a product that has obtained approval for change such as addition of efficacy · effectiveness which Post market surveillance has been already conducted, part subject to re-examination and its reason shall be stated additionally and changed surveillance protocol shall be made and submitted. In case where re-examination period is assigned separately, special surveillance protocol shall be submitted.

C. For matters which require discussion with Ministry of Food and Drug Safety when submitting surveillance protocol, they shall be stated briefly at the bottom of 「summary of post market surveillance protocol」 and then submitted.

D. In case where cases of Post market clinical trials are included when applying for re-examination, Post market clinical trial shall be submitted to Ministry of Food and Drug Safety separately from surveillance protocol.

E. In case where risk management protocol submitted in accordance with Subparagraph 11, Paragraph 1, Article 4 of 「Regulations on Safety of Pharmaceuticals, etc.」 includes content set forth in Paragraphs 2-4 Article 6 of 「Re-examination standard for new drugs etc.)」, special post market surveillance protocol may not be submitted.

2. Preparing post market surveillance (change) protocol and report

Post market surveillance (change) protocol and its annexed paper form shall be prepared as follows in accordance with 「Re-examination standard for new drugs etc.」 and [annexed paper no. 1 form] .

A. Post-market surveillance (change) protocol (「Re-examination standard for new drugs etc.」 annexed paper no. 1 form)

1) Reporter(applicant)

A) In case where medicinal product subject to re-examination comes under manufactured medicinal product, business license number shall be stated. In case where medicinal product subject to re-examination comes under imported medicinal products, the importing business notification number shall be stated and in case where there is no importing business notification number, it may not be stated.

B) For name and location of production facility(business office), name and location approved by Minister of Ministry of Food and Drug Safety, name and date of birth of representative shall be stated.

2) Manufacturer

A) For manufactured articles, name and location of production facility approved by Minister of Ministry of Food and Drug Safety shall be stated. For a branch factory, name and location of branch factory shall be stated as approved(ex. : Seoul Factory of ○○ Pharmaceutical. Ltd.).

B) For imported goods, name and location of production facility and country of origin recorded on written permission shall be stated.

3) Information on medicinal products subject to re-examination(product name, re-examination period, approval number and date of approval)

A) Name of pharmaceutical subject to re-examination, re-examination period, approval

number and date of approval shall be stated. For medicinal products as those subject to re-examination on the ground that such medicinal products added efficacy·effectiveness which is obviously different from previously approved medicinal products, date when a change is approved due to addition of efficacy·effectiveness as well as date of original approval shall be stated.

B) For re-examination period, the re-examination period assigned to approval conditions at the time of approval for a medicinal product shall be stated(ex.: '18.12.31.~ '24.12.30, 6 years). For a medicinal product which re-examination period is remaining period of previously approved medicinal product, re-examination period specified in approval conditions shall be stated and in case where an applicant knows re-examination period of previously approved medicinal product, such period shall be stated as well.

B. Summary of post-market surveillance protocol(「Re-examination standard for new drugs etc.」 annexed paper no. 1 form**,** annexed paper form**)**

Write 「summary of Post market surveillance protocol」 by summarizing details described in 「Post market surveillance protocol」 and for summary of changed post market surveillance protocol, add a summary of changed protocol.

1) Use-result surveillance

A) General use-result surveillance

(1) Summary of surveillance

General use-result surveillance briefly describes the purpose of the surveillance, number of Target product to surveillance, method of the surveillance and scheduled surveillance period.

(2) Surveillance of special patients

Surveillance of special patients includes surveillance of children, surveillance of the aged, surveillance of pregnant women, surveillance of patients with renal disorder, surveillance of patients with hepatopathy and surveillance of patients with other

special disease .

Surveillance of these cases may be conducted in case where there are special patients in general use-result surveillance. For example, provided that approved matters (precautions) specifies 'administration to children requires caution', if there are children in a general use-result surveillance result, the children will be examined. Provided, however, that surveillance of special patients is not conducted, the reason for not conducting the surveillance shall be stated.

B) Long term use-result surveillance

In case where long term use-result surveillance is conducted separately from general use-result surveillance, whether to conduct surveillance or not, Target product to surveillance, surveillance period etc. shall be briefly described. Provided, however, that long term use-result surveillance is not conducted, the reason shall be descried.

2) Special surveillance

For special surveillance, describe whether the surveillance, types of special surveillance to be conducted, reason for implementation, Target product to surveillance, surveillance method, and surveillance period briefly. However, for Post Market Database Research, describe whether the study to be conducted, purpose for the study, outline of medical information database for surveillance, target product to surveillance period(data period), surveillance design, definition of exposure-non exposure group(patient-control group), definition of the result, analysis item and method.

3) Post-marketing clinical trials

For post-marketing clinical trials, describe whether the trial has been conducted, reason for implementation, Target product to surveillance, surveillance method and surveillance period briefly.

4) Problems of safety

Describe problems at the time of development, problem of mimetic preparations, problems considered from use experience in various countries briefly.

5) Summary of protocol change

A) In case where there occur matters that need to be changed in previously submitted surveillance protocol, write it briefly in changed protocol and a summary of special mention and attach a list and new surveillance protocol.

B) For the following minor changes, surveillance change protocol may not be submitted and a change shall be submitted at the time of periodic report.

(1) a change in investigation agency

(2) a change in investigators in business enterprise

(3) a change in order or arrangement in items in surveillance list

(4) a change in description in an item

(5) a change in surveillance list due to revision of precautions etc.

(6) addition, change or removal of items that do not influence analysis of efficacy or safety

(7) A manufacturer's name and product's name of the item that is being conducted joint post marketing surveillance, change of the surveillance relevant person (However, case where the item is added is not included)

(8) The change of 20% less on the number of surveillance subjects (only for a case where the number of surveillance subjects is increased)

3. Preparation of post-marketing surveillance protocol(「Re-examination standard for new drugs etc.」 annexed paper no. **1 form, required documents)**

A. Summary of the product subject to be re-examined

Write product name stated in a written permission of pharmaceutical subject to re-examination, re-examination period, date of approval, marketing(scheduled) etc.

B**. Information on safety**

Describe information verified through literature, academic society's data or other

ways(present supportive literature).

1) For problems at the time of development, write information which has been shown in findings of studies until approval in Republic of Korea (including clinical overseas).

2) For mimetic preparations, write information generally known in medicinal effect group of similar kinds (drugs of similar mechanism) or preparations of similar structure.

3) For problems considered from use experience in various countries, write information shown by using preparations with same ingredients in other countries.

4) Submit a foreign country that granted approval (year when approval was granted) and present condition of market (including year when sale was made) as reference.

C. **U**se-result surveillance protocol

1) Purpose of surveillance

The purpose of use-result surveillance shall be described considering the following.

(1) Serious adverse events · adverse drug reaction

In case where falling under serious adverse events prescribed in 「Regulations on Safety of Pharmaceuticals, etc.」 [annexed paper no. 77-2 form]

(2) Unexpected adverse events · adverse drug reaction which are not reflected in precautions

(3) Previously known adverse drug reaction

(4) Non-serious Adverse Drug Reaction

(5) Information on safety · efficacy

2) Subject group of surveillance

A) Patient groups subject to surveillance are those whom pharmaceutical subject to surveillance are to be administered on investigator's judgment in terms of medical science.

B) Those who did not use pharmaceutical subject to surveillance within the scope of approval shall not be included in the subject of surveillance in principle.

※ In case where data of Target product to surveillance who did not use a product within the scope of matters approved[2] have been collected, they shall be analyzed as special item.

C) Describe method of actually selecting Target product to surveillance in detail.

3) Number of surveillance subjects

A) The number of Target product to surveillance shall be calculated by product unit and at this time objective and justifiable ground which is required for the calculation of the number of Target product to surveillance shall be submitted. However, for the following number of Target product to surveillance, it may not necessary to submit the evidence.

Target Product	The number of Target Product
○ New Drug -The world's first New Drug developed in Korea -The New Drug being developed abroad(Not yet authorized) - The New Drug developed abroad and authorized in Korea and has not passed 3 years from its authorization date - The New Drug developed abroad and authorized in Korea and not used outside of the developring country	More than 3000 persons
○ Other New Drug, drug for which data has been submitted	More than 600 persons

B) An objective and rational supporting data required to calculate the number of subject product to surveillance will be filled out considering the following the items, the supporting data may be adjusted according to medicine properties.

(1) Epidemiologic properties of the indication(incident rate, prevalence rate, fatality rate, etc.) The properties shall be submitted estimating incident rate of the indication based on published literature, national health insurance claims data from National

Health Insurance Service or Health Insurance Review & Assessment Service and cancer registration and statistics program report of National Cancer Center. The domestic prevalence and fatality rate of the indication shall be estimated and the expected number of the patients during the re-review period shall be estimated and submitted, if necessary, the number of the patients may be described by year, age and gender.

(2) Usefulness and properties of the item

The usefulness of the item considering home and abroad medical guideline for the indication and current status of the existing treatment shall be submitted and dosage form properties for the scope of the item (use or availability of infants, the elderly, pregnant women, patients with kidney trouble·liver dysfunction) shall be filled out.

(3) A current market share status(only if possible) for the item prescribed based on the subject indication, a current competitive item status prescribed based on the same indication, market share rate, sale performance, prescription performance shall be filled out, the comparison among numbers of the subject product to surveillance shall be included, if the item is a subject to be re-examined.

(4) Payment of the item

medicine pricing, payment availability and payment criteria, date of start of the payment(estimate) shall be filled out.

(5) Estimated number of the patient to use the item

A scope of the estimated number of the patient to use the item shall be showed, considering epidemiologic properties of the indication, usefulness and properties of the item and current market share status.

(6) Safety information on the item

A frequency of the significant safety in the clinical trials(identified significant risk, potential significant risk, supplement information, etc), importance, risk level, safety information of analogue, adverse drug reaction and prevalence rate subject to focus on reviewing safety considered from the experience of using the item in each country. An appropriate number of the subject product to surveillance can be

estimated considering the difference among prevalence frequencies by adverse drug reaction, in this case, the appropriate number of the subject product to surveillance can be estimated utilizing 'Rule of Three', if the adverse drug reaction prevalence rate for the item shall be identified to the 95 % confidence interval.

Table. A number of subject product to surveillance to identify adverse drug reaction of the prevalence frequency to the 95 % confidence interval

Prevalence frequency of ADR	A number of subject product to surveillance
1 of 100	300
1 of 200	600
1 of 300	900
1 of 500	1,500
1 of 1000	3,000

(7) Possible number of subject product to surveillance for the item

Possible number of subject product to surveillance for the item based on the estimated number of the patient to use the item and safety information for the item shall be submitted.

C) In case where surveillance is conducted towards two or more products depending on a difference in content (including a case that there is difference in dosage form), number of Target product to surveillance may be integrated.

(Example 1) in case where dosage form is same but content is different; tablets of 5mg and 10mg

(Example 2) in case where administration route is same but dosage form has been changed; cream⇔ointment / tablet⇔capsule

(Example 3) contrast agent etc.: 300mg, 350mg, 400mg of contrast agent

※ In case where there has been a change in administration route, integration is not possible.

D) In case where injections and tablets with the same ingredient are administered to the same person, they shall be counted respectively in calculating number of Target product to use-result surveillance .

E) In case where two or more businesses are granted the same pharmaceutical or

several companies conduct surveillance jointly by joint development(joint marketing), the number of Target product to surveillance shall be the sum of each case. In such case, surveillance methods, contents and list should be same among business enterprises and details of business enterprises that conduct joint surveillance must be included in the name of manufacturer and name of products subject to re-examination.

F) In case where any business enterprise is granted remaining period of other business enterprise as re-examination period for the same product with its approval, number of Target product to surveillance may be calculated considering such remaining period.

G) For Post market clinical trials conducted out of the approval scope, a surveillance protocol may be submitted before clinical trial starts and examined by Ministry of Food and Drug Safety and them clinical trial may be included number of Target product to re-examination.

H) In case where certain pharmaceutical has been administered to a person and administration discontinued and it is administered to the same person, the person is not counted as separate subject.

(Example) For anticancer drugs with treatment cycle, each treatment cycle is not counted as separate subject.

4) Expected period of surveillance

A) Surveillance period shall be adequate to collect number of Target product to surveillance and it shall be set based on re-examination period and scheduled release date.

B) Understanding appearance condition immediately after a product is released is necessary and thus surveillance protocol shall be made before a product is released and it is recommended that surveillance should be started at the same time as releasing.

C) In case where there has been a change in dosage form or dosage of previously approved product and a business enterprise is granted a product and then another business enterprise is granted the same product, remaining period of re-examination

period stipulated in approval condition for previously approved product from the date of approval shall be written as surveillance period.

5) Expected institution of surveillance

Scheduled investigation agencies shall be selected from hospitals and clinics that relevant pharmaceutical is used and that can meet the following requirements and their names shall be stated. In case where scheduled investigation agencies have not been selected before surveillance is conducted, agency and medical departments which surveillance is primarily conducted depending on property of drug shall be written.

A) Agency with equipment, facility and work force that is able to fully achieve purpose of surveillance

B) Agency with investigators who have expertise in indicated pharmaceutical and indicated diseases and have received education · training or have hands-on experience which are needed to conduct surveillance

C) Agency that can handle personal information of a person subject to surveillance in a way that confidentiality is kept

D) Agency that helps investigators well acquainted with a notice and a surveillance protocol

6) Surveillance items and methods

A) **S**urveillance items

(1) Select proper surveillance items according to property of relevant pharmaceutic and write them. Determine the most appropriate items based on areas that relevant pharmaceutic can be applied and knowledge in mimetic drug in treatment and write them.

(2) Surveillance items can be collected by using surveillance list or electronic document. For electronic document, it should be possible to check changes in surveillance record later.

(3) The following surveillance items may be considered.

· Information on investigation agency

medical centers name, medical department name, name of physician in charge of surveillance, date when a contract is made etc.

· Basic information on Target product to surveillance

Serial number (or registration number etc.), gender, and age of Target product to surveillance

· Case history of Target product to surveillance

Complications[3], diseases accompanied[4], whether there is dyshepatia· renal disorder, whether there is history of allergy, past history of disease, whether there is pregnancy, whether there is breast breeding(if possible, write severity, date of diagnosis etc.)

· Present condition of use of relevant pharmaceutical

Administration · dosage(amount of administration, number of administration, route of administration etc.), administration time(date of starting administration, date of ending administration), purpose of administration(name of diagnosis)etc.

· Concomitant drug

Name of concomitant drug used during the period of administration of relevant pharmaceuticals, administration period(date of starting administration, date of ending administration), administration purpose(case history, treatment, disease prevention, adverse events etc.)

· Safety

Whether there is adverse event which appears during the period of administration of relevant pharmaceutical and after administration, type of adverse event, date of appearance of adverse event, date of disappearance of adverse event, severity, progress, causal relationship, investigator's opinions etc.

Provided however that there is adverse event which requires special attention from surveillance until approval and surveillance of mimetic pharmaceutical preparations or there is any matter which is problematic with regard to efficacy · safety, main surveillance points may be stipulated. In case where there is no above mentioned problem, it is all right not to stipulate main surveillance

points.

- Efficacy

  Efficacy shall be investigated by using objective or subjective indicators (classified into improved, unchanged and aggravated etc.) to judge effect of drugs.

B) Surveillance method

Surveillance method shall be described in detail so that the following can be included in matters.

(1) General information

- Surveillance shall be conducted after a contract is made in writing before starting surveillance. Making a contract with the head of investigation agency or making a contract with an investigator with consent of the head of investigation agency is recommended. In case where an investigator is changed during agreed surveillance period, measures which are needed for the continuation of surveillance shall be taken and additional contract shall be made.
- Surveillance shall be conducted in such a way that it can grasp actual appearance of adverse events.
- Surveillance shall be conducted based on an objective way that can select Target product to surveillance in a systematic way.
- Grasping the present condition of appearance of adverse events immediately after putting a product on the market is required and thus a surveillance protocol must be made before putting a product on the market and surveillance shall be commenced as early as possible.
- Collect even adverse events which deems to be no causal relationship with relevant pharmaceutical that appears during the period of administration or after administration to definitely find unexpected adverse drug reaction among adverse drug reaction that appeared.
- Examine the likelihood that using drugs jointly influences safety · efficacy.
- Surveillance shall be conducted in such a way that experiment result

examination outlier can be grasped as much as possible.

- In case where a dropout is found to show adverse event through follow-up, he/she shall be counted as a person who is available in evaluating safety. For a dropout whom follow-up was not given, write the reason for it.
- In case where surveillance methods vary depending on investigation agency or departments, surveillance process and method and data collection process for selected method shall be described.

(2) Matters for safety

(A) For pharmaceutical that needs continuous follow-up study after administration ends such as vaccine and anticancer drugs, follow-up time shall be set.

(B) Adverse events that are reported by an investigator among adverse events that appear within follow-up time even after administration ends shall be included in surveillance result.

(C) In case where follow-up study is needed, surveillance method shall be described in detail (ex. by phone, by letter etc.).

(D) Grasp whether adverse event is serious.

① Serious adverse event(Serious)

- A case that is likely to cause death or threaten life
- A case that needs hospitalization or extension of hospitalization period
- A case that causes continuous or serious disability or depression
- A case that causes congenital malformation or abnormality
- A case that needs treatment due to occurrence of important conditions in terms of medical science such as drug dependence or abuse, or blood dyscrasia

② Non-serious adverse event(Non-serious)

(E) Causal relationship shall be evaluated as follows. Cases that are difficult to be deemed to be unrelated including 'conditional/unclassified' and 'unassessable/unclassifiable' may be evaluated as related. (see 「Regulations on Safety of Pharmaceuticals, etc.」[annexed paper no. 77-2 form])

① **Certain** : A case that context for administration ·use of pharmaceutical etc.

is reasonable and that is not explained by other pharmaceutical or chemicals or disease accompanied and that shows clinically valid reaction at the time that administration of such pharmaceutical is discontinued and that at the time that such pharmaceutical is administered again as needed, it is decisive in terms of pharmacology or phenomenology

② **Probable/likely** : A case that temporal relationship with administration ·use of pharmaceutical etc. is reasonable and that does not seem to be caused by other pharmaceutical or chemicals or disease accompanied and that shows clinically valid reaction at the time that administration of such pharmaceutical etc. is discontinued(there is no information on re-administration)

③ **Possible** : A case that temporal relationship with administration ·use of pharmaceutical etc. is reasonable but can be explained by other pharmaceutical or chemicals or disease accompanied and that information on discontinuation of such pharmaceutical etc. is insufficient or indefinite

④ **Unlikely** : A case that is temporary one which is unlikely to have causal relationship with administration ·use of pharmaceutical etc. and that can be explained by other pharmaceutical or chemicals or potential diseases

⑤ **Conditional/unclassified** : A case that needs more data for proper evaluation or additional data are under examination

⑥ **Unassessable/unclassifiable** : A case that it is impossible to evaluate due to insufficient or conflicting information and that is it impossible to supplement or check

(F) The level of adverse events shall be decided referring to the following.

① Mild

A case that there is subjective or objective symptom but it does not cause relevant person trouble in everyday life. A case that continuous treatment is possible without changing dose of relevant pharmaceutical

② Moderate

A symptom which a person feels trouble in everyday life. A level that needs treatment or reduced dose due to adverse events

③ Severe

A symptom which a person is unable to live a everyday life as he/she wishes. A case that administration of relevant pharmaceutical needs to be discontinued due to severe adverse event

(3) Matters for efficacy

(A) It is desirable that efficacy should be evaluated by using objective evaluation standard which are presented concretely to prevent evaluation · decision standard for each item from being changed depending on investigation agency(investigator) and physician should conduct an evaluation on his/her judgement by referring to above mentioned matter. In case where objective evaluation standard are used, they must be specified in a surveillance protocol.

(B) In case where stages of improved, unchanged and aggravated are applied instead of objective efficacy evaluation, stages shall be defined properly referring to the following.

① Improved : A case that symptom is deemed to be improved or maintained

② Unchanged : A case that symptom does not show improvemen compared with a case before administration and neither seems to be maintenance effect

③ Aggravated : A case that symptom gets worse than before administration

※ Maintenance effect : A case that symptom is more likely to get worse if administration is discontinued or a case that effect which is equal to existing drugs is maintained in case where replaced with existing drugs

(C) For a person subject to surveillance who was already treated or is being treated, in case where pharmaceutical subject to re-examination shows continuation of effect or maintenance effect, though there is no improvement after administration in terms of figure, it may be evaluated as improvement on physician's judgement.

(D) For cases that are difficult to be evaluated under ordinary medical treatment such as vaccine and anticancer drugs, efficacy evaluation may be omitted.

(E) In case where evaluation lays physical or economic burden on Target product to

surveillance, efficacy evaluation may be omitted and in such cases, justifiable ground shall be described and Minister of Ministry of Food and Drug Safety shall examine it.

(4) Matters for the selection of Target product to surveillance

(A) Methods of selecting Target product to surveillance shall be described in an objective and concrete manner to prevent prejudice.

(B) A person who has obtained marketing approval shall describe a method of conducting surveillance concretely in principle and may select continuous surveillance method · total surveillance method etc. and select a method which is suitable for use-result surveillance and describe it.

① Continuous surveillance method

A method that a physician in charge of surveillance writes the number of Target product to surveillance whom relevant pharmaceutical is administered first after surveillance starts continuously in a questionnaire

② Total surveillance method

A method that a physician in charge of surveillance writes all Target product to surveillance whom relevant pharmaceutical is administered first during the period of requested specific surveillance after surveillance starts thoroughly in a questionnaire

③ Central registration method

A method that a physician who makes a contract with a business enterprise after surveillance starts registers patients in the business enterprise or a center that business enterprise designated in advance at the time that administration of relevant pharmaceutical starts and writes registered all patients in a questionnaire

(Ex. : a physician in charge of surveillance working at a hospital that made a contract before administration starts sends information on Target product to surveillance to a business enterprise or a center that business enterprise designated in advance by fax or electronic mail and has them registered and then investigates registered Target product to surveillance thoroughly)

(C) For surveillance of special patients, criteria for selecting Target product to

surveillance shall be set.

< Criteria for examining age >

Name	Chinese character · English	Age
Newborn infants	Term newborn infants	Date of birth NOTE[1] ~ less than 28 days
Infants and toddlers	Infants and toddlers	28days ~ less than 24 month NOTE[2]
Children	Children	24 months NOTE[3] ~ less than 12 years
Adolescent	Adolescent	12 ages ~less than 19 years
The aged(Geriatrics)	Geriatrics	65 years or more

NOTE[1] 'Date of birth' means 0 day under ICH Guideline.(ex.: born on January 1, 2002)

NOTE[2] 'Less than 24 months' means 23 months and fewer than 1 month.(ex.: December 31, 2002)

NOTE[3] '24 months or more' means 24 months inclusive of the first day of 24 months.(ex.: January 1, 2003)

- ○ Infants : 24 month or more ~ less than 6 years
- ○ Children(pediatric population) : This term is a common designation for newborn infants, Infants and toddlers, children and adolescent and may be used as a meaning which is distinguished from an adult.

7) Evaluation items, methods and analysis methods

A) Evaluation items

(1) Organization of Target product to surveillance

Present criteria for calculation such as collection of a questionnaire, number of Target product to surveillance, the number of Target product to surveillance of safety evaluation, the number of Target product to surveillance of efficacy evaluation, the number of Target product to surveillance disqualified and reason for disqualification.

※ Target product to surveillance of safety evaluation : persons who have experience of relevant pharmaceutical having been administered at least once and have undergone follow-up

※ Target product to surveillance of efficacy evaluation : persons whom efficacy evaluation is recorded as instructed in a surveillance protocol among Target

product to surveillance of safety evaluation

(2) Provisions for safety

(A) The present condition of adverse events

(B) Factors which are deemed to influence safety

(3) Provisions for efficacy

(4) Provisions for special patients (children, the aged, pregnant women, patients with renal disorder, patients with dyshepatia, patients with other special disease): It is necessary to set criteria for analyzing special patients. Provided, however, that there is a definition of special patients (criteria for age etc.) in matters for approval, the definition shall apply.

B) Evaluation methods and analysis methods

(1) A periodic report shall submit aggregate of investigated data(a periodic report shall present adverse event appearance ratio for cases coming under relevant period and include 95% confidence interval).

(2) Proper statistical analysis method according to characteristics of evaluation items shall be stated in a final report(a written re-examination application). Proper statistical analysis method may include chi-square test, z-test, nonparametric statistical test, survival analysis and multivariate analysis.

(3) Analysis method shall describe judgement in terms of medicine and pharmacy based on a result from surveillance.

8) Other requirements

A) Examine the need for changing a surveillance protocol based on new knowledge acquired through use-result surveillance and change a surveillance protocol if needed. In case where partial change in administration · dosage or efficacy · effectiveness is permitted during the period of re-examination of relevant medicinal products, examine the need for changing a surveillance protocol and change the protocol if needed as well.

B) In case where contents in a surveillance protocol, other than slight case, a protocol on change shall be submitted to Minister of Ministry of Food and Drug Safety in

advance.

C) For a thing entrusting·a contract product with different product name based on a permit, evaluation items and methods in a surveillance protocol shall be described in the same way and an integrated analysis protocol shall be described so that information on safety of a contract product can be evaluated in a comprehensive manner.

D. Special surveillance(conditions at the time of approval, pharmacoepidemiology study, Post Market Database Research etc.) protocol

1) Purpose of surveillance

Special surveillance includes evaluation of information gained from surveillance (or test) conducted based on conditions given at the time of approval in matters to be checked or verified after putting a product on the market, use result surveillance, and voluntary report on adverse events and surveillance (further study after approval, pharmacoepidemiology study, Post Market database research) conducted to obtain additional information in case where analysis finds any problem.

2) General precautions

Purposes and methods of special surveillance vary and thus it is difficult to present specific methods but referring to pharmacovigilance method* stated in ICH Guideline (ICH Pharmacovigilance protocolning, E2E) is recommended and in such case, prior consultation with Ministry of Food and Drug Safety is required. In case where Ministry of Food and Drug Safety directs special surveillance as a condition at the time of approval, a protocol shall be submitted and a surveillance shall be conducted.

* pharmacovigilance method : active surveillance(using local hospitals, patient registration program, monitoring according to cases), comparative observational research(cohort study, case control study, cross sectional study), descriptive study(observing progress of disease, studying present condition of use of pharmaceutical), database study etc.

※ Study Protocol for Post Market Database

A) **Purpose of surveillance**

For the purpose of the post market database research, items PICOT shall be stated. If the purpose of the surveillance is multiple, the surveillance protocol shall be stated for each purpose.

- Patient: target population to surveillance
- Intervention/Exposure: target exposure to surveillance(target product, etc.)
- Comparison: comparison intervention(comparative drug)
- Outcome: consideration to safety or efficacy for the target group
- Timing: follow-up period

B) Summary of the target medical information database to surveillance

- The type, feature and follow-up period of the target medical information database to surveillance shall be stated, why the use and period set up of the database is appropriate based on the purpose of the surveillance shall be explained. The evidence that the database and follow-up period is appropriate to the surveillance purpose shall be provided by considering epidemiologic information including estimated number of patient for the medical product or comparative drug, the number of the patient with the indication for the drug throughout the country.
- For the stepwise interpretation, estimated interpretation timing for each interpretation, follow-up period and data lock points shall be stated.
- For the Summary of the target medical information database to surveillance, the following information shall be included. In this time, not only the database to surveillance but also obtainable or available whole database shall be explained.

· The Name of Medical Information Database Holder

· The purpose of use data

· The scale of medical information database : the whole scale of obtainable or available database (approximate number of persons that can be included) shall be explained.

- Reliability of medical information database: Summary of reliability(quality control, quality assurance) of obtainable or available database and its validity shall be explained.
- Period of medical information database : the period of obtainable or available database shall be stated.
- Interaction of medical information database : if the multiple databases interacts with each other, how to interact shall be stated.
- Possibility to followed up for each case: the availability to follow medical information database on each case shall be explained.
- Feature of the group included in medical information database : if there is anything of note, it shall be stated.
- Feature of the exposure information included in medical information database: if there is anything of note, it shall be stated.
- Feature of the covariate information included in medical information database : if there is anything of note, it shall be stated.
- Name of data item : all obtainable or available names of data items shall be listed by the tables included in the database. The disease code (e,g. disease code (KCD-7 code) shall be written and, there will be no problem even if the data item is written in appendix.
- Feature of medical information database that may lead to the limitation of surveillance
- Protection of personal information: if it is necessary to note anything to utilize database, it shall be stated.
- Ethics : if it is necessary to note anything to utilize database, it shall be stated.

c) The number of target person

- The sample size to surveillance or detecting capability of medical information database to be utilized shall be stated as much as possible.
- The sample size and how to calculate detecting capability shall be stated.

e,g.) Set estimated sample size and multiple values of effect indicator to be detected,

list the detecting capability for each value.

d) Surveillance item

- The name of data item among all available data items to be used in this surveillance shall be stated, if necessary, it shall be written in appendix.

e) Surveillance method

- The method shall be stated by including the period, protocol(e,g. cohort, patient group-control group in cohort, etc.), scope of target person, analysis item and method, validation, etc.

E. Post market clinical trials

Post market clinical trials mean a test conducted to investigate adverse events and to observe clinical effect of matters approved pursuant to Article 31 or Paragraph 5, Article 42 of「Pharmaceutical Affairs Act」and Subparagraph 1, Paragraph 8, Article 24 of 「Regulations on Safety of Pharmaceuticals, etc.」 to verify estimation gained from examination of clinical trial or use result surveillance and to collect information on quality, efficacy and safety that cannot be obtained from medical treatment.

In case where Post market clinical trials for re-examination are conducted, a protocol for Post market clinical trial shall be submitted to Ministry of Food and Drug Safety for examination and Post market clinical trials shall be conducted pursuant to Article 30 of 「Regulations on Safety of Pharmaceuticals, etc.」and [attached table 4] of Good Clinical Practice.

Chapter 4 Preparation of periodic report on post-marketing surveillance

1. General information

A. A periodic report on Post market surveillance (hereinafter referred to as “periodic report”) shall be prepared in accordance with a surveillance protocol reported in advance.

B. A periodic report shall be submitted every six months for first two years from date of approval and thereafter every year with results of post market surveillance conducted during relevant period attached to Minister of Ministry of Food and Drug Safety within two months of expiration of such surveillance period and the final periodic report may be replaced with re-examination application. In case where use result surveillance is not conducted, a periodic report in a form of [enclosure no.1] shall be submitted with reason for not conducting use result surveillance stated.

C. It is desirable for a pharmaceutical of which re-examination period is remaining period of previously approved pharmaceutical to be reported in accordance with periodic report period of previously approved pharmaceutical.

D. In case where two or more businesses receive medicinal products with the same primary ingredient or several companies conduct surveillance jointly by joint development(joint marketing), it is desirable for a report to be made jointly at the same time.

E. In case where use result surveillance ends because total number of Target product to surveillance needed for re-examination is more than necessary stated in previous periodic report, data in addition to use result surveillance shall be collected during remaining re-examination period and reported to Minister of Ministry of Food and Drug Safety in accordance with the same form and procedure.

F. For slight changes which modified surveillance protocol is not submitted, contents of such changes shall be stated in a periodic report at the time of relevant periodic report.

G. In case where separate post market surveillance protocol has not been submitted because previously submitted risk management protocol complied with relevant provisions and a result of evaluating the execution of risk management protocol is submitted in the same schedule stated in Paragraph 1, Article 7 of 「Re-examination standard for new drugs etc.」 with data coming under a periodic report suitable for Paragraph 2, Article 7, separate periodic report on post market surveillance may not be submitted.

2. Summary of data to be submitted in a periodic report on post market surveillance (Example**)**

A. 「Re-examination standard for new drugs etc.」 [annexed paper no. 2 form] a periodic report on post market surveillance

B. Post-market surveillance protocol(the final version)

C. Post Market Surveillance Result
- General information, number of target agency, number of target person, surveillance method, etc.
- Summary of surveillance result: Summary of surveillance, purpose, demographic raw data, case history of Target person to surveillance, present condition of administration of relevant pharmaceutical, drugs used jointly etc.
- Post Market Surveillance result: safety analysis result, efficacy evaluation result
- Review of surveillance result and countermeasures

D. Result report of test (limited to post market clinical trial)]

E. Safety data at home and abroad in addition to post market surveillance

- Domestic adverse event and current status in Korea in addition to post market surveillance
- Overseas adverse event and current status abroad
- Other safety information at home and abroad

F. Data on current market status at home and abroad and overseas approval status

- Domestic production or import performance(release performance, etc.) per year
- Data on overseas market and current approval status (data on current status of overseas pharmaceutical pharmacopoeia)
- Overseas measure regarding safety and efficacy

G. Attachment: Enclosure No.1 ~No. 4

3. Preparation of periodic report on post market surveillance

A periodic report shall be prepared as follows in accordance with 「Re-examination standard for new drugs etc.」 [enclosure no. 2 form].

A. Applicant(reporter)

1) In case where pharmaceutical subject to re-examination comes under manufactured articles, business license number shall be stated. In case where pharmaceutical subject to re-examination comes under imported goods, the importing business notification number shall be stated and in case where there is no importing business notification number, it may not be stated.
2) For name and location of production facility(business office), name and location approved by Minister of Ministry of Food and Drug Safety, name and date of birth of representative shall be stated.

B. Manufacturer

1) In case of manufactured medicinal products, name and location of production facility approved by Minister of Ministry of Food and Drug Safety shall be stated. In case of a branch factory, name and location of branch factory shall be stated as approved(ex. : Seoul Factory of ○○ Pharmaceutical. Ltd.).
2) In case of imported medicinal products, name and location of production facility and country of origin recorded on written permission shall be stated.

C. Information on pharmaceutical subject to re-examination(product name, re-examination period, approval number and date of approval)

1) Name of pharmaceutical subject to re-examination, re-examination period, approval number and date of approval shall be stated. For pharmaceutical designated as pharmaceutical subject to re-examination on the ground that such pharmaceutical added efficacy·effect which is obviously different from previously approved pharmaceutical, date when a change is approved due to addition of efficacy·effect as well as date of original approval shall be stated.
2) For re-examination period, the re-examination period assigned to approval conditions at the time of approval for a pharmaceutical shall be stated(ex.: '18.12.31.～'24.12.30, 6 years). For a pharmaceutical which re-examination period is remaining period of previously approved pharmaceutical, re-examination period specified in approval conditions shall be stated and in case where an applicant knows re-examination period of previously approved pharmaceutical, such period shall be stated as well.

D. Post-marketing surveillance result

1) Use result surveillance and special surveillance results
(1) Surveillance period and number of Target product to surveillance
Use result surveillance period for relevant report shall be specified. For number of

Target product to surveillance, number of Target product to surveillance from whom questionnaires are collected, number of Target product to safety evaluation and number of Target product to efficacy evaluation shall be described.

(2) Summary of use result surveillance result and analysis result

The result of use result surveillance collected during the period of relevant surveillance shall be stated briefly centering around present condition of appearance of adverse events.

Types of adverse events, appearance ratio of adverse events, serious adverse events · adverse drug reactions and unexpected adverse drug reactions shall be described.

(3) Review of surveillance result and future countermeasure

The result of surveillance of safety · efficacy collected during the period of relevant surveillance shall be described briefly and comparison with previous report shall be stated as well. In addition, countermeasures by a business enterprise in accordance with surveillance result by relevant report period shall be stated.

2) Post-marketing clinical trial result

In case where post-marketing clinical trial is under way, it may be replaced with a report on progress. In case where post-marketing clinical trial ends during the period of relevant report, a report on the result of post-marketing clinical trial shall be submitted. In case where information on safety · efficacy which deserves making special mention is gained, even though post-marketing clinical trial is under way, it shall be stated in a periodic report.

E. Safety data at home and abroad in addition to post market surveillance

1) Analysis · evaluation data on adverse event collected from domestic clinical trials and voluntary report and current status
2) Analysis · evaluation data on the reports on adverse drug reactions of relevant pharmaceutical collecctd from in foreign countries during the period of re-examination
3) Data on existence and nonexistence of adverse drug reactions of relevant pharmaceutical, adverse drug reaction cases and occurrence by types collected from information on safety at home and abroad and information from literature and

academic society

※ In case where periodic report result pursuant to Item A, Subparagraph 8 of Standard for Safety Control of Pharmaceutical after Marketing as stated in [schedule 4-3] of 「Regulations on Safety of Pharmaceuticals, etc.」, separate data on safety at home and abroad may not be submitted.

4) For death (brain death, cardiac arrest, sudden death, fetal death, etc.) or serious adverse event led to death and unexpected serious adverse event among domestic safety data, whether the approvals are applied, causal relationship with drugs, comments from pharmaceutical companies and counter measures (if necessary) shall be stated. However, if regular implementation · evaluation result of the risk management plan(RMP) shall be submitted according to Article 47 (1) subparagarph 5 of the 「Regulation on Safety of Pharmaceuticals, etc.」 and Article 7-2(6) of the 「Regulation for Pharmaceutical Approvals, Notifications and Reviews」, relevant data including surveillance result of medicines may not submitted. In this case, the reference information shall be provided to enable the identification of the relevant data in the implementation · evaluation result report.

F. Data on current market status at home and abroad and overseas approval status

1) Domestic market performance or release performance for reporting year shall be stated. In the absence of market performance or release performance, production or import performance shall be stated.
2) In case where medicinal products with different content or dosage form are investigated by the same surveillance protocol, results shall be stated according to content · dosage form · product.
3) In case where joint surveillance is conducted, overall results from joint surveillance shall be stated and results shall be recorded according to products so that result of relevant product can be identified.
4) Overseas current market and approval status and pharmacopoeia status shall be stated

to help judging the safety · efficacy of the pharmaceutical.

5) The latest information including overseas couter measures related to other safety ·efficacy

6) However, if regular report shall be submitted according to Appendix 4-3 of the 「Regulation on Safety of Pharmaceuticals, etc.」 and sub paragraph 8 a of the 「Standards on Post Market Safety Control, relevant data may not submitted. In this case, the reference information shall be provided to enable the identification of the relevant data in the implementation · evaluation result report.

4. Preparation of required documents for periodic report on post market surveillance

Required documents prescribed in「Re-examination standard for new drugs etc.」[annexed paper no. 2 form] shall be prepared referring to a guide to preparation by forms [enclosure no. 1] ~ [enclosure no. 5] in accordance with surveillance result in a relevant year.

- · [Enclosure no. 1] summary of implementation of post market surveillance
- · [Enclosure no. 2] list of organization of Target product to post market surveillance
- · [Enclosure no. 3-1] list of appearance of adverse drug reaction in post market surveillance
- · [Enclosure no. 3-2] list of appearance of serious adverse events · adverse drug reaction in post market surveillance
- · [Enclosure no. 4] list of appearance of adverse events
- · [Enclosure no. 5] data on domestic and abroad marketing and license status

※ However, if regular report shall be submitted according to Annex 4-3 of the「Regulation on Safety of Pharmaceuticals, etc.」and sub paragraph 8 a of the「Post-marketing Safety Control Standards for Medicinal Products, etc., relevant data such as「appendix 4」may not submitted. In this case, the reference information shall be provided to enable the identification of the relevant data in the implementation · evaluation result report.

A. [Enclosure no. **1]** summary of implementation of post market surveillance

- · Implementation conditions(number of investigation agency, number of Target product to surveillance etc.), scheduled implementation, countermeasures for surveillance or reason for which surveillance was not conducted shall be stated. In case where surveillance is completed, state “surveillance is completed”.
- · Fill out [enclosure no. 1] in accordance with contents of previously submitted surveillance protocol. Provided, however, that separate implementation of long term use result surveillance is specified in a protocol, write implementation conditions of long term use result surveillance in accordance with [enclosure no. 1].
- · In case where post-marketing clinical trials and special surveillance(patient group

study, case -control study etc.) are scheduled to be conducted in a surveillance protocol, write summary of each implementation condition, surveillance implementation condition (number of investigation agency, number of Target product to surveillance, surveillance methods etc.) in relevant year according to surveillance and countermeasures for future surveillance.

- In case where there are special patients while conducting general use result surveillance in accordance with contents of previously submitted surveillance protocol, write number of special patients subject to surveillance, adverse event appearance ratio and effective ratio briefly according to special patient group.

B. [enclosure no. **2]** list of organization of surveillance subjects to post market surveillance

- Write use result surveillance.
- Write number of Target product to surveillance from whom a surveillance list is collected, number of Target product to safety evaluation, number of Target product to efficacy evaluation, Target product to surveillance who are excluded from safety evaluation and efficacy evaluation and reasons for exclusion.

C. [enclosure no. **3]** list of appearance of adverse events · adverse drug reaction

- The appearance of adverse events · adverse drug reaction stipulated on the post market surveillance and voluntary reportn shall be provided(enclosure No.3)
  For voluntary report on adverse events based on 「Regulations on Safety of Pharmaceuticals, etc.」 [Annex 4-3] Post-marketing Safety Control Standards for Medicinal Products, etc., it is not possible to find out appearance ratio and thus write only number of appearance of adverse events and number of cases.

D. Report on adverse events

Submit all adverse events collected in an Excel file reported to Korea Institute of Drug Safety & Risk Management in accordance with Paragraph 4, Article 5 and Paragraph

1, Article 7 of「Re-examination standard for new drugs etc.」. Write ‘whether collected adverse events are reflected in matters approved’ and report it. Write faithfully in accordance with「Re-examination standard for new drugs etc.」and guideline so that report items needed at the time of examination are not left out.

E. [enclosure no. 4] Data on domestic and abroad marketing and license status

Write the following information in all countries that sale is approved in accordance with [enclosure no. 5].

- Renewal after sale
- Date of sale
- Product name
- Information on safety related to sale approval such as restriction on indication
- Indication specified in sale approval and target person group
- Details that a company withdrew submission of approval application associated with safety or efficacy

Chapter 5 Filling out pharmaceuticals re-examination application form

1. General

A. A person who wishes to have pharmaceutical re-examined (hereinafter referred to as "applicant") pursuant to Article 33 and Paragraph 5, Article 42 of Pharmaceutical Affairs Act shall submit data on periodic report result by products in accordance with Paragraph 1, Article 23 of 「Regulations on Safety of Pharmaceuticals, etc.」 and [annexed paper no. 21 form], [attached table4-3] of the same regulation and Item A, Subparagraph 8 of Standard for Safety Management of Pharmaceutical after Marketing.

B. Re-examination application shall be submitted to Minister of Ministry of Food and Drug Safety by deadline specified in approval conditions for relevant product(within three months of day when re-examination period assigned at the time of approval expires).

C. In case where two or more businesses receive medicinal products with the same active pharmaceutical ingredient or several companies conduct surveillance jointly by joint development(joint marketing), it is desirable for a report to be made jointly at the same time for a contract product with different product name based on a permit. In such case, re-examination application form shall be filled out according to applicants and products and submitted and integrated analysis result shall be submitted so that information on can be evaluated comprehensively.

D. In case where post market surveillance ends early because total number of Target product to surveillance needed for re-examination is more than necessary, all Target product to surveillance investigated during the period of re-examination shall be reported. In case where post market surveillance ends early, re-examination application shall be submitted by the deadline of re-examination application prescribed in approval conditions.

E. Additional required documents at the time of applying for re-examination shall be submitted with them attached with [enclosure no. 1]～[enclosure no. 9] and surveillance protocol(the final version).

2. Summary of data to be submitted for re-examination application (Example**)**

A. Pharmaceutical re-examination application prescribed in「Regulations on Safety of Pharmaceuticals, etc.」[annexed paper no. 21 form]

B. Post market surveillance protocol (the final version)

C. General conditions concerning implementation of surveillance[enclosure no. 1]
- number of investigation agencies, number of Target product to surveillance, surveillance methods etc.

D. Result of analysis and evaluation of use result surveillance
- Summary of surveillance, purpose of surveillance, demographic raw data, present condition of adverse event appearance, safety·efficacy evaluation result, review of surveillance result and countermeasures etc.

1) Matters for organization of Target product to surveillance[enclosure no. 2]
2) Appearance according to types of adverse events[enclosure no. 3] ~ [enclosure no. 4]
3) Adverse drug reaction appearance according to factors
4) Unexpected adverse drug reaction, serious adverse events · adverse drug reaction
5) Evaluation of efficacy
6) Analysis of special patients
7) Review of final evaluation result

E. Voluntary report on adverse event at home and abroad
- For a case which RMP should be submitted, data on periodic report result pursuant to Item A, Subparagraph 8 Standard for Safety Control of Pharmaceutical after

Marketing as stated in [schedule 4-3] to 「Regulations on Safety of Pharmaceuticals, etc.」.

F. Table of contents of report of research [enclosure no. 7] and report of research[enclosure no. 8]

G. Data that can be compared with use result surveillance result among phase 3 clinical trial conducted in foreign countries

H. Data on present condition of sale at home and abroad

I. present condition of sale around the world [enclosure no. 5] and a result of measures taken by health authorities at home and abroad[enclosure no.9]

J. Comparative table of matters approved at home and abroad(country that developed a product or country of origin)

K. required documents : [enclosure no. 1] ~ [enclosure no. 9]

3. Filling out re-examination application

A. Fill out re-examination application as follows in accordance with 「Regulations on Safety of Pharmaceuticals, etc.」 [annexed paper no. 21 form].

1) Applicant(reporter)

A) In case where pharmaceutical subject to re-examination comes under manufactured articles, business license number shall be stated. In case where pharmaceutical subject to re-examination comes under imported goods, the importing business notification number shall be stated and in case where there is no importing business notification number, it may not be stated.

B) For name and location of production facility(business office), name and location approved by Minister of Ministry of Food and Drug Safety, name and date of birth of representative shall be stated.

2) Manufacturer

A) For manufactured articles, name and location of production facility approved by Minister of Ministry of Food and Drug Safety shall be stated. For a branch factory, name and location of branch factory shall be stated as approved(ex. : Seoul Factory of ○○ Pharmaceutical. Ltd.).

B) For imported goods, name and location of production facility and country of origin recorded on written permission shall be stated.

3) Information on pharmaceutical subject to re-examination(product name, re-examination period, approval number and date of approval)

A) Name of medicinal product subject to re-examination, re-examination period, approval number and date of approval shall be stated. For medicinal product designated as pharmaceutical subject to re-examination on the ground that such medicinal product added efficacy·effect which is obviously different from previously approved medicinal product, date when a change is approved due to addition of efficacy·effect as well as date of original approval shall be stated.

B) For re-examination period, the re-examination period assigned to approval conditions at the time of approval for a pharmaceutical shall be stated(ex.: '09. 12.31.～'15.12.30, 6 years). For a pharmaceutical which re-examination period is remaining period of previously approved pharmaceutical, re-examination period specified in approval conditions shall be stated and in case where an applicant knows re-examination period of previously approved pharmaceutical, such period shall be stated as well.

4) Surveillance result

A) Surveillance period and the number of Target product to surveillance

(1) For surveillance period, actual period which is spent in investigating use result shall be stated.

(2) For the number of Target product to surveillance, the number of Target product

to surveillance in accordance with Post market surveillance protocol shall be stated and the number of Target product to surveillance according to Post market surveillance types shall be stated. For use result surveillance, the number of Target product to surveillance from whom questionnaires are collected, number of Target product to safety evaluation and number of Target product to efficacy evaluation shall be described.

B) Summary of surveillance result and analysis result

(1) Statistical analysis aims at adverse drug reaction in principle but it also aims at adverse events as it is difficult to judge causal relationship.

(2) For summary of surveillance result, write use result surveillance and special surveillance etc. collected during the period of surveillance briefly but state types of adverse events associated with safety, serious adverse events · adverse drug reaction collected and unexpected adverse drug reaction and a result of degree of effect (efficacy evaluation etc.) for items specified to be investigated related to efficacy briefly.

(3) Write reports on safety of adverse events at home and abroad collected during the period of re-examination and reports on safety from literature and academic society at home and abroad with them classified according to sources briefly.

(4) For analysis result, write a result gained through use result surveillance considering data obtained through clinical trials conducted at home and abroad and literature review. Analysis result shall be stated placing emphasis on serious adverse events · adverse drug reaction and unexpected adverse drug reaction. For matters that need to be reflected in precautions and matters that other measures are needed based on surveillance result, present ground such as adverse event appearance ratio.

5) Production performance(release performance)

They shall be stated in the same way as guideline for preparing a periodic report.

6) Others

A) For a person in charge, write names of safety control manager and a person in charge of surveillance of relevant product.

B) For phone number, write phone numbers of safety control manager or a person in charge of surveillance.

7) Required documents

A) For submission of re-examination application, submit a result of periodic report in accordance with Item A, Subparagraph 8 of Standard for Safety Control of Pharmaceutical after Marketing as stated in [schedule 4-3] of 「Regulations on Safety of Pharmaceuticals, etc.」 with [enclosure no. 1]~[enclosure no. 9] in a guideline and a surveillance protocol(the final version) attached.

· [Enclosure no. 1] ~ [enclosure no. 5] same as periodic report form (including adverse event report table which was reported to Korea Institute of Drug Safety & Risk Management)
· [Enclosure no. 6] a table of appearance cases of serious adverse events · adverse drug reactions and unexpected adverse drug reactions
· [Enclosure no. 7] a table of contents of a report of research
· [Enclosure no. 8] a report on investigation of a report of research
· [Enclosure no. 9] a report on investigation of measures such as suspension, recall and disposal of manufacturing in foreign countries

B) For required documents, each document shall be attached in such a way that it can be identified(using sign is possible). In case where there are lots of data, a table of contents of required documents shall be attached on the reverse of an application.

C) For foreign country's data, submit a summary in Korean(extract main points) and original text. A translation shall be submitted if it is requested .

D) Comprehensive review of previously reported periodic reports shall be described.

8) Review of safety data

A) Re-examination application shall be submitted after reviewing safety data whether submitted data ([enclosure no. 3] list of adverse event appearance and report table of cases of adverse events in Korea) accord with data *reported to and Korea Institute of Drug Safety & Risk Management.

* <Searching reporting details at medicine adverse event report system

(https://kaers.drugsafe.or.kr)>

Reporting Output Details or data reported relating to Subject Product to re-review output from the screen of Electronic Civil Petition/Reporting>Adverse Drug Event>Reporting Details Output at medicine Integrated Information System(https://nedrug.mfds.go.kr)

B) Submit the following data to Korea Institute of Drug Safety & Risk Management(e-mail : kids_qna@drugsafe.or.kr), compare with the list of adverse event·adverse drug reaction provided by KIDS and turn in a document that certifies review of completeness to Ministry of Food and Drug Safety.

* Data to be submitted :

- name of relevant product and re-examination period, product standard code coded at the time of report, component code, corporate registration number and department in charge from MFDS
- [enclosure no. 3] list of domestic adverse event appearance condition and report table of cases of adverse events

B. Prepare a report along with re-examination application including the following.

1) Summary of surveillance implementation condition

Enter surveillance implementation condition such as number of investigation agencies, number of Target product to surveillance and surveillance methods in accordance with previously submitted surveillance protocol in [enclosure no. 1]. In case where implementation of long term use result surveillance is specified in a surveillance protocol, implementation condition of long term use result surveillance shall be included.

2) A result of analysis · evaluation of use result surveillance

A) Matters for organization of Target product to surveillance

Write the number of Target product to surveillance from whom a surveillance list is collected and number of Target product to surveillance who are included in safety and efficacy evaluations in accordance with [enclosure no. 2], table of organization

of Target product to surveillance according to types of surveillance conducted. For number of Target product to surveillance who are excluded from safety and efficacy evaluations, write a reason for exclusion. For long term use result surveillance, other special surveillance, and post-marketing clinical trials, present criteria for selecting Target product to surveillance.

B) Appearance condition according to adverse event types

Serious adverse events · adverse drug reaction found through use result surveillance·special surveillance·post-market clinical trials shall be presented in [enclosure no. 3]. For a list of adverse event appearance condition in accordance with Standard for Safety Control of Pharmaceutical after Marketing as stated in [schedule 4-3] to 「Regulations on Safety of Pharmaceuticals, etc.」, write only number of adverse event appearance and number of cases of adverse events as appearance ratio is not available.

C) Appearance condition of adverse drug reaction according to factors

In order to study factors which are deemed to influence safety, analyze appearance condition according to the following background factors as needed and present it in a tabular form. At the time of analysis, present adverse event appearance ratio according to background factors and its 95% confidence interval.

- Comparative table of adverse event according to organs of the body
- Table of adverse event appearance condition according to gender
- Table of adverse event appearance condition according to age
- Table of adverse event appearance condition depending on whether there is complication or disease accompanied
- Table of adverse event appearance condition depending on whether there is past medical history of disease
- Table of adverse event appearance condition depending on whether there is drug used jointly (therapy used jointly)
- Table of severity according to adverse event types
- Table of adverse event appearance condition according to severity before administration
- Table of adverse event appearance condition according to duration of administration

- Table of adverse event appearance condition according to daily average dose
- Table of adverse event appearance condition according to total dose
- Table of adverse event appearance condition according to purpose of administration(name of diseases)

For items which whether there is difference in adverse event appearance ratio according to patient's background factor can be analyzed by χ^2-test etc. and which are statistically significant, describe them in terms of medicine and pharmacy.

D) Unexpected adverse drug reaction and serious adverse events · adverse drug reaction

Describe a result of analyzing unexpected adverse drug reaction, serious adverse events · adverse drug reaction found through use result surveillance, appearance ratio and causal relationship. Describe adverse event and adverse drug reaction in [enclosure no. 3]. For information on serious adverse events · adverse drug reaction and unexpected adverse drug reaction, write details of each patient in accordance with a table of appearance of serious adverse events · adverse drug reaction and unexpected adverse drug reaction as shown in [enclosure no. 5].

E) Evaluation of efficacy

Describe the level of effect of items (investigator's evaluation of efficacy etc.) which are specified to be investigated for efficacy in a surveillance protocol briefly according to types of surveillance(improved ○○%, unchanged ○○%, aggravated ○○% etc.). A result of evaluation of efficacy and analysis according to patient's demographic characteristics(age, gender etc.) and therapeutic factors(reason for which relevant pharmaceutical is used, expiry date, dose, types of drugs used jointly, whether there is complication etc.) may be added. Whether there is a difference according to background factors of Target product to surveillance can be analyzed through X^2 test. Multivariate analysis etc. can be conducted to estimate factors which are deemed to influence efficacy result. In case where efficacy related variables(blood pressure, blood cholesterol concentration etc.)have been measured, a change in performance before and after relevant pharmaceutical is administered can be presented and in such case, whether a change is significant can be tested by using paired t-test and whether a change according to background factors is significant can be tested by

using multivariate analysis etc. In case where you intend to use post-marketing clinical trials result conducted with the approval of Minister of Ministry of Food and Drug Safety after a product is approved as use result surveillance data, describe clinical trials design and efficacy evaluation result briefly.

F) Analysis of special patient

In case where special patients have been analyzed, describe appearance of adverse events according to Target product to surveillance and efficacy analysis result.

G) Discussion about the final evaluation

Describe causal relationship with safety of adverse drug reaction etc. results of surveillance of relevant factors, countermeasures and opinions from business based on evaluation of safety · efficacy and statistical analysis result.

3) Voluntary report on domestic adverse event

A) Describe adverse event appearance condition collected from domestic voluntary report on adverse event briefly and make a list in [enclosure no. 3].

B) Describe serious adverse event · adverse drug reaction or unexpected adverse drug reaction briefly and make a list.

C) When making a list, you can use a data form submitted to Korea Institute of Drug Safety & Risk Management.

D) For death (brain death, cardiac arrest, sudden death, fetal death, etc.) or serious adverse event led to death and unexpected serious adverse event among domestic safety data, whether the approvals are applied, causal relationship with drugs, comments from pharmaceutical companies and counter measures (if necessary) shall be stated.

4) Voluntary report on foreign adverse event

A) Make a list or line-listing of serious adverse drug reactions reported in foreign countries during the period of re-examination.

B) When making a list, use a form designated in this guideline or a form provided by foreign countries.

5) Prepare a report of research which is deemed to influence safety and efficacy of relevant pharmaceutical collected after approval. Write table of contents of report of

research in accordance with [enclosure no. 7] and a report of surveillance of report of research in accordance with [enclosure no. 8] and attach a copy of relevant original text.

6) In case where there is clinical trial result that can be compared with use result surveillance result among phase 3 clinical trial conducted in foreign countries, make a table of adverse event appearance condition according to organs of the body and diseases.

7) For data on sale at home and abroad, present sale(release)performance at home and abroad during the period of re-examination as market volume (releases) in order of year and total market volume (releases). In case where sale(release)performance cannot be presented concretely, present production(import)performance which can replace them.

8) Write a result of measures taken by health authorities at home and abroad and present condition of sale around the world in accordance with [enclosure no. 5]. Specific information shall be compiled in accordance with [enclosure no. 9] but it shall include date of approving manufactured medicinal products · imported medicinal products(including date of original approval from a country that developed a product) and date of marketing, approved efficacy · effectiveness, administration · dosage and precautions and restrictions or conditions relating to sale such as restriction on indication due to problem of safety.

9) Make a comparative table of matters approved (efficacy · effectiveness, administratio n · dosage, precautions in use etc.) in Republic of Korea and matters approved in foreign countries(a country that developed a product or country of origin).

Chapter 6 Time and procedure for application for adjusting the number of surveillance subjects

1. General information

A. A changed surveillance protocol in accordance with 「re-review standard for new drugs etc.」[annexed paper no. 1 form] shall be submitted in advance, in case where it is necessary to change total number of subject product to surveillance in surveillance protocol falling under any of the following cases.

1) In case where domestic prevalence of indication subject to re-review is remarkably low such as a case which the number of patients of indication subject to re-review is equal to the number prescribed in Subparagraph 1, Article 2 of 「Regulation on Designation of Orphan Drug」
2) In case where reasons for adjustment or integration are reasonable such as submission of objective and valid basis for calculation of number of Subject Product to surveillance.

B. **In case where total number of persons are subject to re-examination is adjusted according to products or integrated between products, data falling any one of the following shall be attached to a changed protocol.**

C. **A** total number of subject product needed to re-examine may be adjusted by item or filed an application to integrate among items , in case where falling under any of the following cases.

1) In case where domestic prevalence of indication subject to re-examination is remarkably low such as a case which the number of patients of indication subject to re-examination is equal to the number prescribed in Subparagraph 1, Article 2 of 「 Regulation on Designation of Orphan Drug」
2) In case where reasons for adjustment or integration in terms of properties of

preparations · dosage form are reasonable

3) In case where reasons for adjustment or integration are reasonable such as submission of objective and valid basis for calculation of number of Target product to surveillance

C. **When submitting a periodic report, turn in present condition of collection of surveillance list about number of surveillance subjects and its progress.**

D. Minister of Ministry of Food and Drug Safety reviews a changed protocol and a periodic report submitted and if needed, may demand correction or supplementation**.**

2. Time and procedure for application for adjusting the number of surveillance subjects

A. Time for application for adjusting the number of surveillance subjects

1) Application for adjustment of number of Target product to surveillance is allowed only after at least a half of the period ranging from the date of product approval to the date of expiration of period of re-examination elapses.

A) For a product which re-examination period is six years, application for adjustment of number of Target product to surveillance is allowed three years after the date of product approval elapses.

B) For a product which re-examination period is four years, application for adjustment of number of Target product to surveillance is allowed two years after the date of product approval elapses.

2) Application for adjustment of number of Target product to surveillance is allowed from the date of product approval to at least one year before the date of expiration of period of re-examination.

3) In case where application for adjustment is needed when time for adjustment elapsed or when time for adjustment is not reached, application for adjustment is allowed after discussing it with Ministry of Food and Drug Safety.

A) In case where time for adjustment of Target product to surveillance is not reached, if it is deemed to be necessary to adjust number of Target product to surveillance for objective reason such as prevalence, apply for adjustment after discussing it with Ministry of Food and Drug Safety.

B) In case where time for adjustment of Target product to surveillance elapsed, apply for adjustment with its reason and ground presented after discussing it with Ministry of Food and Drug Safety.

B. Procedures for applying for adjustment

1) Application method

A) In case where total number of Target product to surveillance needs to be changed in a surveillance protocol, a changed surveillance protocol shall be submitted to Minister of Ministry of Food and Drug Safety in advance in accordance with 「Re-examination standard for new drugs etc.」 [annexed paper no. 1 form].

B) Submit a changed protocol with reason for adjustment of number of Target product to surveillance according to products and ground data.

2) Procedures for handling

A) Check a changed protocol submitted for whether reason for adjustment or integration of number of Target product to surveillance is reasonable.

(1) Whether reason for adjustment or integration of number of Target product to surveillance is reasonable in accordance with Paragraph 3 to 4, Article 6 of 「Re-examination standard for new drugs etc.」

(2) Whether collection of surveillance list was conducted faithfully

(3) Whether the period of collecting surveillance list is right

(4) Whether it is possible to collect in various ways during remaining period

B) Minister of Ministry of Food and Drug Safety may consult Central Pharmaceutical Affairs Council or outside experts about adjustment of number of Target product to surveillance needed for re-examination and such period shall be excluded from handling deadline.

C) In case where seeking advice, Minister of Ministry of Food and Drug Safety may extend handling period with the period needed for advice specified and shall notify it to a company.

D) Minister of Ministry of Food and Drug Safety shall review a changed protocol submitted and notify a result of its adjustment. If needed, may demand correction or supplementation and if he/she deems reason for adjustment unreasonable, he/she may demand correction of content of a changed protocol and if needed, he/she may demand method of collecting report on a case of a disease and a protocol during remaining period.

E) Additional data to be submitted when turning in a periodic report

(1) When submitting a periodic report one year after the date of product approval, submit present condition of surveillance list collection and progress concerning the number of Target product to surveillance.

(2) Minister of Ministry of Food and Drug Safety shall examine a periodic report submitted and may request correction or supplementation if needed.

(3) If Minister of Ministry of Food and Drug Safety deems that there is no collection or collection has not been conducted faithfully as protocolned, he/she may demand that the persons concerned should do their best in collecting questionnaires or if needed, demand surveillance list collection method and protocol considering the number of Target product to surveillance and remaining period.

Attached 1.

「Re-examination standard for new drugs etc.」 **[annexed paper no. 1 form]**

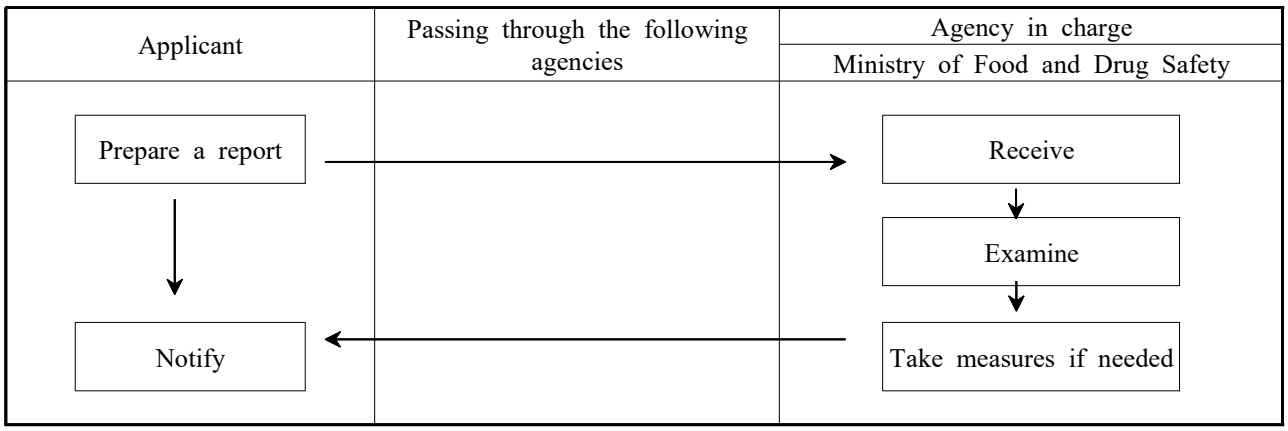
(obverse side)

<table>
<tr><td colspan="5">Post market surveillance (change) protocol</td></tr>
<tr><td rowspan="5">Reporter</td><td>Business license(importer identification)number</td><td colspan="3"></td></tr>
<tr><td>Name of production facility (business office)</td><td colspan="3"></td></tr>
<tr><td>Location of production facility (place of business)</td><td colspan="3"></td></tr>
<tr><td>Name</td><td></td><td>Date of birth</td><td></td></tr>
<tr><td rowspan="2">Manufacturer</td><td>Name of manufacturer</td><td></td><td>Country of origin</td><td></td></tr>
<tr><td>Location</td><td colspan="3"></td></tr>
<tr><td colspan="2">Name of products subject to re-examination</td><td></td><td>Re-examination period</td><td></td></tr>
<tr><td colspan="2">Approval number</td><td></td><td>Date of approval</td><td></td></tr>
<tr><td colspan="5">I submit surveillance (change) protocol with annexed paper in accordance with Article 6 of Reexamination Standard for New Drug etc.

Applicant (signature or seal)
Safety control manager
Person in charge
Phone number
To Minister of Ministry of Food and Drug Safety</td></tr>
<tr><td colspan="5">Required documents
1. Summary of products subject to re-examination
2. Information on safety
3. Use result surveillance and special surveillance protocol
4. Post-marketing clinical trials protocol(limited to a case of implementation)
5. A copy of comparative table of surveillance protocol(limited to a case of change).</td></tr>
</table>

[210㎜×297㎜[plain paper 60g/㎡(recycled paper)]

This application is handled as follows. (reverse side)



(annexed paper form)

<table>
<tr><th colspan="4">Summary of post market surveillance protocol</th></tr>
<tr><td rowspan="9">Use result surveillance</td><td colspan="2">summary of surveillance</td><td></td></tr>
<tr><td>General use result surveillance</td><td></td><td></td></tr>
<tr><td colspan="2">Summary of surveillance</td><td></td></tr>
<tr><td rowspan="6">Surveillance of special patients</td><td>Surveillance of children</td><td></td></tr>
<tr><td>Surveillance of the aged</td><td></td></tr>
<tr><td>Surveillance of pregnant women</td><td></td></tr>
<tr><td>Surveillance of patients with renal disorder</td><td></td></tr>
<tr><td>Surveillance of patients with hepatopathy</td><td></td></tr>
<tr><td>Surveillance of patients with other special disorders</td><td></td></tr>
<tr><td>Special surveillance</td><td colspan="2"></td><td></td></tr>
<tr><td>Post-marketing clinical trials</td><td colspan="2"></td><td></td></tr>
<tr><td colspan="4">Problems of safety</td></tr>
<tr><td colspan="3">Problems at the time of development</td><td></td></tr>
<tr><td colspan="3">Problem of mimetic preparations</td><td></td></tr>
<tr><td colspan="3">Problems considered from use experience in each country</td><td></td></tr>
<tr><td colspan="4">Summary of a change in a protocol</td></tr>
<tr><td colspan="4"></td></tr>
</table>

Attached 2.

「Re-examination standard for new drugs etc.」 **[annexed paper no. 2 form]**

(obverse side)

<table>
<tr><th colspan="6">periodic report on post market surveillance(Number of times)</th></tr>
<tr><td rowspan="5">Reporter</td><td>Business license(importer identification)number</td><td colspan="4"></td></tr>
<tr><td>Name of production facility (place of business)</td><td colspan="4"></td></tr>
<tr><td>Location of production facility (place of business)</td><td colspan="4"></td></tr>
<tr><td>Name</td><td></td><td>Date of birth</td><td colspan="2"></td></tr>
<tr><td rowspan="2">Manufacturer</td><td>Name of manufacturer</td><td></td><td>Country of origin</td><td colspan="2"></td></tr>
<tr><td>Location</td><td colspan="4"></td></tr>
<tr><td colspan="2">Name of product subject to re-examination</td><td></td><td>Re-examination period</td><td colspan="2"></td></tr>
<tr><td colspan="2">Approval number</td><td></td><td>Date of approval</td><td colspan="2"></td></tr>
<tr><td rowspan="2">Surveillance result</td><td>Surveillance period and number of Target product to surveillance</td><td colspan="4"></td></tr>
<tr><td>Summary of surveillance result and analysis result</td><td colspan="4"></td></tr>
<tr><td colspan="2">Production performance(release performance)</td><td colspan="4"></td></tr>
<tr><td colspan="6">I submit periodic report on post market surveillance as above in accordance with Paragraph 1, Article 7 of Re-examination standard for Re-examination of New Drug etc.

Reporter (signature or seal)
Safety control manager :
Person in charge :
Phone number :
To Minister of Ministry of Food and Drug Safety</td></tr>
<tr><td colspan="6">Required documents
1. Result of post market surveillance
2. Report on result according to surveillance(limited to post-marketing clinical trials)
3. Data on safety at home and abroad other than subparagraph 1 above</td></tr>
</table>

210㎜×297㎜[plain paper 60g/㎡(recycled paper)]

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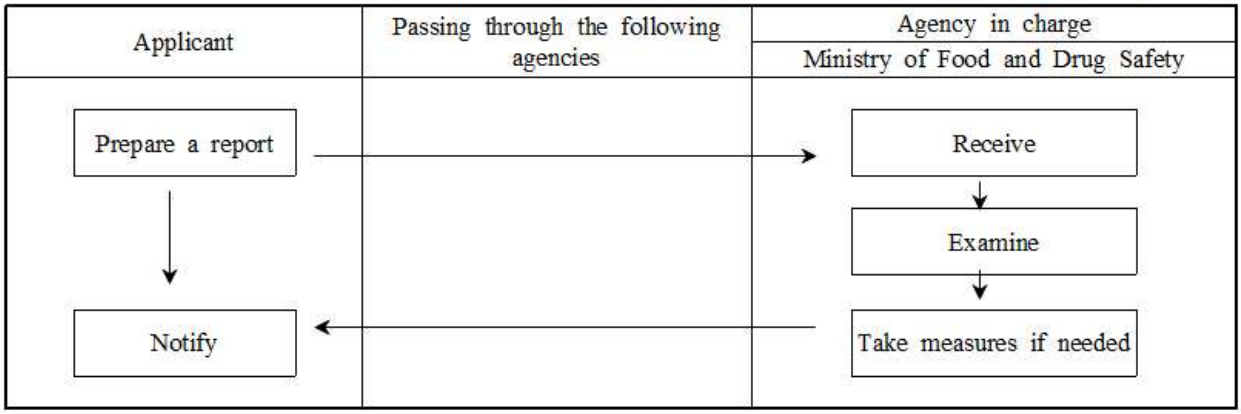

Attached 3.

「Regulations on Safety of Pharmaceuticals, etc.」[annexed paper no. 21 form]

Application form of re-examination of pharmaceuticals

Receipt number	Date of receipt	Date of issuance	Handling period 150days

Applicant	Business license(business notification)number	
	Name of production facility(place of business)	
	Location of production facility (place of business)	
	Representative	Date of birth

Manufacturer	Name of manufacturer	Country of origin
	Location	

Name of product subject to re-examination	Re-examination period

Approval number	Date of approval

Surveillance result	Surveillance period and number of cases in surveillance
	Summary of surveillance result and analysis result

Production(import)performance (release performance)

I apply for re-examination of pharmaceutical as above in accordance with Article 32 of「 Pharmaceutical Affairs Act」and Paragraph 1, Article 23 of「Regulations on Safety of Pharmaceuticals, etc.」.

Applicant (signature or seal)

Name of a person in charge

Phone number of a person in charge

To Minister of Ministry of Food and Drug Safety

Accompanying documents	1. Results of periodic report in accordance with Item A, Subparagraph 8 of Standard for Post market Safety Control of Pharmaceutical etc. stated in attached table of 「Regulations on Safety of Pharmaceuticals, etc.」 2. Data obtained by analyzing and evaluating results stated in subparagraph 1 above comprehensively	Service charge Sum of money notified by Minister of Ministry of

		Food and Drug Safety

Procedures for handling application

210mm×297mm[woodfree paper(80g/㎡) or school book paper(80g/㎡)]

Attached 4.

「Regulations on Safety of Pharmaceuticals, etc.」 [annexed paper no. 22 form]

No.

A notice of pharmaceutical re-examination result

Client	Name		Date of birth
	Name of production facility (place of business)		
	Location of production facility(place of business)		
Manufacturer	Name of manufacturer		Country of origin
	Location		
Name of product subject to re-examination			
Approval number		Date of approval	
Drug substance and its quantity			
Whether it is adequate			
Corrections			

I notify pharmaceutical re-examination result as above in accordance with Paragraph 3, Article 23 of 「Regulations on Safety of Pharmaceuticals, etc.」

Minister of the Ministry of Food and Drug Safety

Official seal

210mm×297mm[plain paper 60g/㎡]

Attached 5. [enclosure no. 1] ~ [enclosure no. 9] forms

[Enclosure no. 1] Summary of implementation of post market surveillance

<table>
<tr><th colspan="3">Types of post market surveillance</th><th>Number of Target product to surveillance</th><th>Implementation and future countermeasures</th></tr>
<tr><td rowspan="9">use result surveillance</td><td colspan="2">General use result surveillance</td><td></td><td>Implementation(number of investigation agencies, number of Target product to surveillance etc.) and countermeasures for future surveillance or reason for which surveillance has not been conducted</td></tr>
<tr><td rowspan="8">Surveillance of special patients</td><td>Surveillance of children</td><td></td><td></td></tr>
<tr><td>Surveillance of the aged</td><td></td><td></td></tr>
<tr><td>Surveillance of pregnant women</td><td></td><td></td></tr>
<tr><td>Surveillance of patients with renal disorder</td><td></td><td></td></tr>
<tr><td>Surveillance of patients with hepatopathy</td><td></td><td></td></tr>
<tr><td>Surveillance of long term use</td><td></td><td></td></tr>
<tr><td>Surveillance of other special patients</td><td></td><td></td></tr>
<tr><td>special surveillance</td><td colspan="2"></td><td></td><td>Content and condition of protocol or implementation(number of investigation agencies, number of Target product to surveillance etc.), surveillance schedule etc.</td></tr>
<tr><td>post-marketing clinical trials</td><td colspan="2"></td><td></td><td>Content and condition of protocol or implementation(number of investigation agencies, number of Target product to surveillance etc.), surveillance schedule etc.</td></tr>
</table>

Types of post market surveillance			Number of Target product to surveillance	Implementation and future countermeasures
use result surveillance	General use result surveillance			Implementation(number of investigation agencies, number of Target product to surveillance etc.) and countermeasures for future surveillance or reason for which surveillance has not been conducted
	Surveillance of special patients	Surveillance of children		
		Surveillance of the aged		
		Surveillance of pregnant women		
		Surveillance of patients with renal disorder		
		Surveillance of patients with hepatopathy		
		Surveillance of long term use		
		Surveillance of other special patients		
special surveillance				Content and condition of protocol or implementation(number of investigation agencies, number of Target product to surveillance etc.), surveillance schedule etc.
post-marketing clinical trials				Content and condition of protocol or implementation(number of investigation agencies, number of Target product to surveillance etc.), surveillance schedule etc.

[Enclosure no. 2] Table of organization of surveillance subjects to post market surveillance

Collect questionnaires
Number of Target product to post market surveillance : OOOO

Number of Target product to surveillance excluded from safety evaluation : OO person

Reasons	Number of Target product to surveillance
Cases which pharmaceutical is administered before a contract for surveillance is made	OO
Failed follow-up	OO
Efficacy · effect other than matters approved	OO
Pharmaceutical subject to surveillance has not been taken	OO

Number of Target product to safety evaluation : OOOO

Number of Target product to surveillance excluded from efficacy evaluation : OO

Reasons	Number of Target product to surveillance
Efficacy evaluation has been left out	OO
Target product to have not been visited	OO

Number of Target product to efficacy evaluation : OOOO

[Enclosure no. 3] List[1] of Domestic adverse drug reaction appearance in post market research

Period / Items	Condition until approval[4] –	Use result surveillance						aggregate
		first year (~)	second year (~)	third year (~)	fourth year (~)	fifth year (~)	sixth year (~)	
Number of investigation agencies								
Number of Target product to safety evaluation								
Number of Target product to adverse drug reaction appearance surveillance								
Number of adverse drug reaction appearance[2]								
Adverse drug reaction appearance ratio[3]								

Types of adverse events[5,6]	Serious								No Serious									
	first year (~)		second year (~)		third year (~)		aggregate		first year (~)		second year (~)		third year (~)		aggregate	reflection of approval	note[7]
	CAE (%)	CADR(%)	CAE(%)	CADR(%)	CAE(%)	CADR(%)	CAE(%)	CADR(%)	CAE (%)		CAE (%)		CAE (%)		CAE (%)		
SOC																	
PT 1																	
PT 2																	
PT 3																	
aggregate																	

CAE: Case of Adverse Event

CADR: Case of Adverse Drug Reaction

Note 1. Type of adverse drug reaction shall be stated by Body System-organ and unexpected adverse drug reaction shall be stated separately and marked so that it can be identified. (ex. : write unexpected adverse drug reaction first and then write expected adverse drug reaction and prefix * to unexpected adverse drug reaction)

Note 2. In case where the same person shows several types of adverse drug reactions, identify them according to each adverse drug reaction. In case where several cases occur in each adverse drug reaction, cases that occur shall be counted respectively.

Note 3. Adverse drug reaction appearance ratio = (number of Target product to surveillance of adverse drug reaction appearance ÷ number of Target product to surveillance of safety evaluation)×100

Note 4. Enter adverse drug reaction appearance based on data collected from clinical trials conducted until approval in a column of “condition until approval”.(limited to a case which is available)

Note 5. In case where the same person shows several types of adverse events, adverse drug reactions, each case shall be counted.

Note 6. For adverse events and adverse drug reaction related terms, optimum terms from MedDRA may be used. When using MedDRA, identify ground.

Note 7. In case where the adverse events data are entered based on the combined collection resource, ‘Combined collection resource’ shall be stated in ‘Note’.

※ The adverse event cases can be written in Excel format, to show the adverse events data in effective manner, some forms can be modified.

Note) The Risk Management Plan(RMP) change shall be considered according to adverse drug reaction appearance status, in this context, comments(including RMP changes, etc.) from pharmaceutical companies shall be submitted to periodically report.

[Enclosure no. 4] Data on domestic and abroad marketing and license status*(Example)*

Country	**Date of approval(date of taking actions)**	**Date of issue**	**Product name**	**Remarks**
Sweden	*A-7/90* *AR-10/95*	*12/90* -	*Bacteroff* -	- -
Brazil	*A-10/91* *A-1/93*	*2/92* *3/93*	*Bactoff* *Bactoff-IV*	- *IV administration volume*
UK	*AQ-3/92* *A-4/94*	*6/92* *7/94*	*Bacgone* *Bacgone-C (skin infs)*	*excluding the aged(>65)(PK) cream for a part*
Japan	*LA-12/92*	-	-	*it should be supplemented*
France	*V-9/92*	-	-	*irrelevant to safety*
Nigeria	*A-5/93* *A-9/93*	*7/93* *1/94*	*Bactoff* *Bactoff*	- *new indication*
Republic of Korea				

*acronym : A=Authorized, AQ= Authorized with qualifications, LA=Lack of approval, V=Voluntary marketing application withdrawal by company, AR=Authorization renewal

[Enclosure no. 5] List of appearance of serious adverse events · adverse drug reaction and unexpected adverse drug reaction

<table>
<tr><th colspan="14">Table of serious adverse event · adverse drug reaction and unexpected adverse drug reaction appearance cases[주1]</th></tr>
<tr><td rowspan="2">name of a person subject to surveillance (enter name in acronym or initial)</td><td rowspan="2">male · female</td><td rowspan="2">(age)</td><td rowspan="2">Weight</td><td colspan="3">hospitalized outpatient hospitalized/outpatient</td><td colspan="2">pregnancy: no · yes (gestational age) · unclear</td><td colspan="3" rowspan="2">Adverse event · adverse drug reaction past history no · unclear · yes( )</td><td colspan="2" rowspan="2">past history of disease, patient's constitution etc. no · unclear · yes ( )</td><td rowspan="2">identification number of a person subject to surveillance[주5] ( )</td></tr>
<tr><td colspan="3">medical center and its location :</td><td colspan="2">Occupation:</td></tr>
<tr><td rowspan="2">product name (business enterprise name)</td><td rowspan="2">General name</td><td rowspan="2">S[주2] · O</td><td colspan="4">Use method</td><td rowspan="2">underline reason for use and underlying disease and put complication in parenthesis</td><td rowspan="2">Adverse event · name of adverse drug reactions[주3]</td><td colspan="5" rowspan="2"></td></tr>
<tr><td>route</td><td>daily dose</td><td>start</td><td>end</td></tr>
<tr><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td>[주4]</td><td colspan="3">Adverse event · adverse drug reaction appearance, symptom and treatment etc.</td><td colspan="2">precautions, reflection etc.</td></tr>
<tr><td></td><td colspan="3"></td><td colspan="2"></td></tr>
<tr><td colspan="6">Other treatments : nonexistence · existence(radiation therapy, blood transfusion, surgery, anesthesia, others( )) · unclear</td><td colspan="4">re-administration : existence · non-existence(recurred · not recurred)</td><td colspan="2">result( )</td><td></td></tr>
<tr><td>Opinion from a physician in charge</td><td colspan="3"></td><td>Opinion from business enterprise that reports</td><td colspan="3"></td><td>measures and future countermeasure</td><td colspan="3"></td></tr>
</table>

[Enclosure no. 5] Table of serious adverse event · adverse drug reaction and unexpected adverse drug reaction appearance cases

Note 1. Write Target product to serious adverse event · adverse drug reaction and unexpected adverse drug reaction surveillance collected in a relevant year.

Note 2. Enter S(suspected) in a column of S · O for pharmaceutical which is suspected of adverse drug reaction and O a column of others.

Note 3. Enter all adverse events · adverse drug reaction that occurred among Target product to surveillance in a column of adverse event · adverse drug reaction and underline serious or unexpected adverse drug reaction.

Note 4. Underline date when adverse events · adverse drug reaction appears among things entered in a column of date.

Note 5. Enter identification number of Target product to serious adverse event · adverse drug reaction and unexpected adverse drug reaction appearance case surveillance in a column of number in [enclosure no. 5].

※ Some forms can be modified to show the adverse events data in effective manner.

[Enclosure no. 6] Table of research report

Number [주1]	Types [주2]	Heading	Name of researcher	Name of literature [주3]

[Enclosure no. 6] Table of research report

Note 1. Enter a report of research by types and for a report of research of the same category, enter in the order of date when literature is published.

Note 2. Enter efficacy and safety according to content of relevant report of research in a column of ‘type’.

Note 3. Enter name of literature (or name of academic society) in which relevant report of research is published, volume, page, publication year in a column of ‘name of literature’. In case where a report of research has not been published, enter such fact and relevant year

* In case where there is relevant information in PSUR, you can extract and summarize it.

[Enclosure no. 7] Report on surveillance

<table>
<tr><td>Control number · number of report</td><td></td><td></td><td>Date of report</td><td>Date of the first acquisition</td><td colspan="2">Classification of new drugs</td><td>Handling (leave this column blank)</td></tr>
<tr><td>General names</td><td></td><td></td><td rowspan="2">Official announcement of a report of research</td><td colspan="2" rowspan="2"></td><td rowspan="2">Country making official announcement</td><td rowspan="2"></td></tr>
<tr><td>Name of sale(company name)</td><td></td><td></td></tr>
<tr><td>Summary of a report of research</td><td colspan="5"></td><td>“Precautions” statement · notes etc.</td></tr>
<tr><td colspan="4">Opinion from business enterprise that reports</td><td colspan="3">Future countermeasure</td><td rowspan="2"></td></tr>
<tr><td colspan="4"></td><td colspan="3"></td></tr>
</table>

* In case where there is relevant information in PSUR, you can extract and summarize it.

[Enclosure no. 8] A report on surveillance of measures such as suspension of manufacturing, recall and disposal of manufacturing in foreign countries

<table>
<tr><td>Identification number · number of report</td><td colspan="2"></td><td>Report date</td><td>Date of the first acquisition</td><td colspan="2">Classification of new drugs</td><td>Handling (leave this column blank)</td></tr>
<tr><td>General name</td><td colspan="2"></td><td rowspan="2">Official announcement of measures in foreign countries</td><td colspan="2" rowspan="2"></td><td>Country making official announcement</td><td rowspan="2"></td></tr>
<tr><td>Name of sale(company name)</td><td colspan="2"></td><td></td></tr>
<tr><td>Summary of measures in foreign countries</td><td colspan="5"></td><td>“Precautions” statement · notes etc.</td></tr>
<tr><td colspan="4">Opinion from business enterprise that reports</td><td colspan="3">Future countermeasure</td><td rowspan="2"></td></tr>
<tr><td colspan="4"></td><td colspan="3"></td></tr>
</table>

Ⅱ. Q&A

1. Post-market surveillance protocol

1.1. (Conducting surveillance as protocolned) Is it possible to conduct post-market surveillance immediately after a post-market surveillance protocol is submitted to Ministry of Food and Drug Safety?

☞ A person who has gained an approval for post-market surveillance shall submit a post-market surveillance protocol to Ministry of Food and Drug Safety after putting on the market pursuant to annexed paper no. 1 form and receive a result of examination of the protocol to conduct surveillance.

1.2. (Post-market surveillance method) Is it possible to use post market surveillance as Post market clinical trial without use result **surveillance or special surveillance?**

☞ There are use result surveillance, special surveillance, and Post market clinical trial as post market surveillance. You should have post market surveillance protocol on Post market clinical trial reviewed.

1.3. (Surveillance table) In case where evaluation methods vary depending on indication, should I compile a separate surveillance table?

☞ Investigation business should decide it considering convenience of surveillance.

1.4. (Charge) Is there any standard for charge per case?

☞ It is recommended that a charge for post market surveillance should be decided voluntarily through discussion between investigation business and physician in charge of surveillance and investigation agency depending on property and indication of drugs. You are advised to refer to the permissible range of economic gain stated in Paragraph 4, Article 44 of 「Enforcement Regulations of the Pharmaceutical Affairs Act」 and [schedule 2] .

1.5. (Administrative measures) If I fail to submit a protocol by deadline, is there any measure?

☞ Post-market surveillance protocol must be submitted one month before putting on the market or else you will undergo administrative measure of one month suspension of sale. In case where you fail to correct violation, you may undergo another administrative measure; second administrative measure(3 month suspension of sale), third administrative measure(6 month suspension of sale) and fourth administrative measure(revocation of approval).

* Ground : Articles 32, 42 「Pharmaceutical Affairs Act」 and Article 23 「**Regulations on Safety of Pharmaceuticals, etc.**」

1.6. (The number of Target product to surveillance) In case where separate re-examination is assigned according to dosage form as dosage forms with different administration route have been permitted at the same time, is it possible to integrate the number of Target product to post market surveillance?

☞ For dosage form with different administration route, integrating the number of Target product to surveillance is not allowed in principle. Provided, however, that integration is reasonable considering property of pharmaceuticals ·dosage form, the number of Target product to post market surveillance may be integrated between products.

* Ground : Paragraph 3, Article 6 「Re-examination standard for new drugs etc.」

1.7. (The number of Target product to surveillance) In case where long term use surveillance is conducted separately, what is criteria for calculating the number of Target product to surveillance?

☞ For drugs used in chronic diseases such as hypertension, hyperuricemia and diabetes, mellitus, it is desirable to conduct long term use surveillance. You may discuss and adjust the number of Target product to the surveillance with Ministry of Food and Drug Safety by presenting reasonable basis for calculation according to property of drug. If the number of Target product to surveillance is three thousand, the number of Target product to long term use surveillance is set to hundreds of people.

1.8. (Addition of efficacy · effectiveness) In case where separate re-examination period has not been assigned during the period of a product which use result **surveillance has already been conducted and if there is a change such as addition of efficacy · effectiveness, what I should do?**

☞ 1) For a product subject to re-examination, reflect content of added efficacy · effectiveness in a use result surveillance protocol.

2) For a product subject to RMP and re-examination, change RMP protocol including use result surveillance change protocol at the time of changing approval for addition of efficacy· effectiveness.

1.9. (Addition of efficacy · effectiveness) In case where additional efficacy · effectiveness is approved without re-examination period assigned after existing post market surveillance is completed, should I conduct additional surveillance of it ?

☞ No. You need not conduct additional surveillance because active pharmaceutical ingredient and administration route are same as previously approved medicinal products but distinctly different efficacy·effectiveness have not been added.

* Ground : Item A, Subparagraph 2, Paragraph 1, Article 22 of 「**Regulations on Safety of Pharmaceuticals, etc.**」

1.10. (Addition of efficacy · effectiveness) In case where administration route and efficacy · effectiveness are added during the period of re-examination, how should I make use result **surveillance protocol?**

☞ 1) In case where new re-examination period is designated for addition of dosage forms with different efficacy·effectiveness or administration route, you are advised to make a Post market surveillance protocol separately from an existing surveillance protocol for dosage forms and efficacy·effectiveness. In such case, it is desirable to submit separate basic protocol in "previously approved dosage forms · effectiveness '○○' with Ministry of Food and Drug Safety stating " approved on (day, Month, year)".

2) In case where Post market surveillance of addition of dosage forms with the

same efficacy·effectiveness or administration route is conducted during remaining period,

- if an existing surveillance protocol is changed, you should submit a changed protocol,
- if a new surveillance protocol is added, you should make an additional protocol and submit it.

1.11. (Addition of efficacy · effectiveness) In case where new re-examination period is assigned due to addition of efficacy·effectiveness of the same active pharmaceutical ingredients after an existing efficacy·effectiveness re-examination period ends, how should I draw up a use result **surveillance protocol?**

☞ In case where additional re-examination period is assigned to new efficacy·effectiveness, you are advised to draw up a new surveillance protocol separately from an existing surveillance protocol. In such case, it is desirable to state "re-examination period in previously approved dosage forms · efficacy '○○' is (day, Month, year) and re-examination period ends" for submission.

1.12. (Transfer and receipt) In case where it is impossible to import · complete target number of Target product to surveillance during remaining period because number of Target product to surveillance collected by previous company is too small after a contract of transfer or receipt, is it possible to adjust number of Target product to surveillance?

☞ A contract of transfer or receipt succeeds to all obligations of an assignor and thus adjusting number of Target product to surveillance is not right on the ground of transfer or receipt only.

1.13. (Transfer and receipt) After making a contract of transfer or receipt, should I submit original surveillance protocol or a changed protocol?

☞ You should submit a changed protocol on post market surveillance as report business has been changed.

1.14. (Generic) Is it possible for generic products to be approved during the period of re-examination of orphan drug subject to re-examination?

☞ When approving same pharmaceutical during the period of re-examination of previously approved orphan drug, you should submit data other than data submitted at the original approval of previously approved product and data which are equivalent or higher in accordance with Subparagraph 8, Paragraph 2, Article 25 and Paragraph 8, Article 27 of 「Regulation on pharmaceuticals approval notification & review」. In such case, 'data which are equivalent or higher' mean above the range of data submitted when pharmaceutical designated as subject of re-examination is approved and in case where using data is permitted by original licenser or developer or pharmaceutical falling under Subparagraph 8, Paragraph 2, Article 25 is applied for approval after re-examination period ends, above mentioned data may not be submitted.

1.15. (Others) If each company conducts surveillance of entrusting ·entrusted products (same pharmaceuticals with only names different) approved based on a written permission separately, may each company submit its own analysis result only?

☞ For **entrusting · entrusted products with only names different permitted based on a written permission, describe evaluation items and methods in a surveillance protocol in the same way and an integrated analysis protocol so that information on safety between entrusting · entrusted products** can be evaluated comprehensively. Thereafter, when submitting re-examination application, you are advised to submit an integrated analysis result by integrating the number of Target product to surveillance between products so that information on safety can be evaluated comprehensively.

2. periodic report

2.1. (No implementation of surveillance) In case where there are no Target product to surveillance collected in reporting year due to no release or no contract for use result **surveillance after release, should annual report be submitted?**

☞ You should submit periodic report on post market surveillance for a product you intend to conduct post market surveillance with reasons for which post market surveillance has not been conducted and relevant data attached.

* Ground : Article 7 Paragraph 1 of 「Re-examination standard for new drugs etc.」

2.2. (Surveillance at the time that number of persons is completed) In case where target number of Target product to surveillance is collected and completed during the period of re-examination, should surveillance continue to proceed during remaining re-examination period?

☞ Even if use result surveillance was completed in previous periodic report because total number of Target product to surveillance needed for re-examination was exceeded, during remaining re-examination period, you should collect data other than use result surveillance(voluntary report on adverse events at home and abroad, report on safety from literature and academic society at home and abroad, data on sale at home and abroad and approval in foreign countries) and report them to Minister of Ministry of Food and Drug Safety in accordance with the same form and procedure.

* Ground :Article 7 of 「Re-examination standard for new drugs etc.」

2.3. (Matters other than approval) In case where the number of Target product to surveillance of efficacy·effect which has not been approved, can such persons be included in efficacy · safety evaluation?

☞ A person who has been investigated for efficacy·effect which has not been approved is not allowed to be included in efficacy · safety evaluation in principle. You are advised to submit such data by analyzing it as separate item.

2.4. (Questionnaire) In case where surveillance listhas not been prepared properly, what measures should be taken?

☞ In case where safety control manager in charge of post market surveillance finds surveillance is unsatisfactory or needs verification, you should request re-surveillance from investigator(physician, dentist and oriental medical doctor responsible for

conducting post market surveillance in investigation agency). You are advised to write relevant matters in a standard to prevent omission.

2.5. (Questionnaire) Is it possible to conduct post market surveillance using electronic document form questionnaire(e-CRF)?

☞ Yes. You should manage and operate in accordance with Subparagraph 6, Paragraph 7, Article 5 and Article 9 of 「Re-examination standard for new drugs etc.」 and make it possible to check a change in surveillance record later.

2.6. (Surveillance period) Should surveillance period in annual report be stated as actual surveillance period or relevant annual period?

☞ You should write surveillance period in annual report as relevant annual period.

2.7. (Addition of efficacy· effectiveness) In case where separate re-examination has not assigned even though efficacy· effectiveness which are not similar are added during the period of re-examination, should I proceed with re-examination with only indication before addition?

☞ You are advised to make a changed protocol for added efficacy·effectiveness and submit it and proceed with re-examination with additional efficacy·effectiveness added.

2.8. (The number of Target product to surveillance) In case where it is not possible to conduct use result **surveillance any more due to poor sale resulting from a change in insurance benefit standard, is it possible to adjust number of Target product to surveillance?**

☞ It is not possible to adjust number of Target product to surveillance for reason of poor sale only.

2.9. (The number of Target product to surveillance) What data should be submitted when applying for adjusting number of Target product to surveillance?

☞ The following data should be included to calculate number of Target product to

surveillance and additional data may be needed depending on property of a product.

① Efficacy of relevant drug

② Mechanical property of relevant indication(disease incidence, prevalence and mortality at home and abroad. Stratification according to age, gender and ethnic group race if needed)

- Comparison with domestic present condition and ground data(total number of patients using relevant pharmaceutical around the world)
- Number of Target product to clinical trials, number of patients using pharmaceutical after putting it on the market

③ market·import performance(or prescription) and expected number of patients

- In case where there are patients prescribed who were not approved, relevant ratio and ground data

④ Progress of post market surveillance

- Contracting agency, investigator, cases of contract(including a date when a contract is made or a date when surveillance starts), cases of registration, cases of collection
- Cases of report
- A series of progress such as date when a product is put on the market, application for insurance, approval for protocol(change)

⑤ Reasons for which collecting number of Target product to surveillance is poor and ground data

- Present condition of market share of drugs prescribed as the same indication(in case where a person is subject to re-examination, include comparison of number of Target product to surveillance)
- Present condition of domestic clinical trials and dynamics study etc.(period, number of cases, summary of a study when relevant study ends)

⑥ Business enterprise’s effort to collect number of Target product to surveillance and ground data

⑦ Future protocol and adjustment(protocol) of number of Target product to surveillance

- Check information on expected specific safety and calculate number of Target product to surveillance

· Investigated risk needed for additional evaluation and ground data

Ex.) Investigated risk : ▲ Fully check in clinical trial result ▲ Adverse events with significant difference with control group ▲ Side effects and adverse events which are recognized as having causal relationship with relevant pharmaceutical

· Calculation of the number of Target product to surveillance to check relevant risk and ground data

⑧ Other ground data needed for calculation of the number of Target product to surveillance

- Data for present condition of use in foreign countries(PSUR, re-examination data in Japan etc.)

※ Some data(③~⑥) are necessary in case that adjusting the number of Target product to surveillance is needed after conducting post market surveillance

2.10. (Periodic Report) In case where falling under products subject to risk management protocol and re-examination, should a report on implementation·evaluation in accordance with Subparagraph 6, Article 7-2 of 「Regulation on pharmaceuticals approval notification & review」 and a periodic report in accordance with Paragraph 1, Article 7 of 「Re-examination standard for new drugs etc.」 be submitted?

☞ If you submit a periodic report on implementation· evaluation for risk management protocol, you need not submit a periodic report on re-examination.

* Ground : Article 7, Paragraph 3 of 「Re-examination standard for new drugs etc.」

3. The final report(re-examination application)

3.1. (The number of Target product to surveillance) In case where number of Target product to surveillance of efficacy evaluation in the final report is not sufficient(for example, above mentioned number is less than 50% of total number of Target product to surveillance), how it is handled?

☞ In case where target number of Target product to surveillance of efficacy evaluation

has been specified in a protocol, when number of Target product to surveillance of efficacy evaluation is insufficient, you may demand supplementation.

3.2. (The number of Target product to surveillance) In case where target number of Target product to surveillance has not been reached as lots of persons have been excluded during examination after re-examination application, should additional use result surveillance be conducted?

☞ Additional use result surveillance should be conducted to meet number of Target product to surveillance needed.

3.3. (Vaccine) In the event that adverse event occurs, should vaccine be evaluated based on the number of inoculation or number of Target product to surveillance?

☞ Vaccine should be evaluated based on number of Target product to surveillance.

3.4. (Anticancer drug) In the event that adverse event occurs, should anticancer drug be evaluated based on treatment cycle or number of Target product to surveillance??

☞ Anticancer should be evaluated based on number of Target product to surveillance.

3.5. (Things to be reported) Should even serious adverse events · adverse drug reaction that do not have causal relationship be reported?

☞ Yes, You should report them with periodic report result in accordance with Item A, Subparagraph 8 of Standard for Safety Control of Pharmaceutical after Marketing as stated in [schedule 4-3] of 「Regulations on Safety of Pharmaceuticals, etc.」 「Regulations on Safety of Pharmaceuticals, etc.」. In such case, adverse events which are irrelevant to causal relationship should also be included for a report.

* Ground : Subparagraph 8 of 「Regulations on Safety of Pharmaceuticals, etc.」 [schedule 4-3] and Paragraph 1, Article 7 of 「Re-examination standard for new drugs et c.」

3.6. (Handling process) Is it possible to know how re-examination application is handled?

☞ After reviewing an application, if needed, we notify the final result on advice of Central Pharmaceutical Affairs Council and research on the actual condition.

3.7. In case where there is a difference after conducting factor analysis, what I should do?

☞ You should analyze and present its medical · pharmaceutical meaning.

3.8. (Change in adverse event) If unknown adverse event changes before change to previously known adverse event after change because precautions are changed during the period of re-examination, how should it be handled in the final report?

☞ It should be handled as previously known adverse event and at this time, adverse event name is based on optimum terms(in general, Preferred Term (PT) but you are advised to use terms lower than optimum terms as needed.

3.9. (The number of Target product to surveillance) In case where number of some Target product to surveillance has not been collected even though supplementary surveillance has been conducted, because target number of Target product to surveillance was not collected when applying for re-examination, is there any punishment?

☞ Administrative measure will be imposed in accordance with II. Individual Standard Item B Subparagraph 8 in [schedule 8] of 「**Regulations on Safety of Pharmaceuticals, etc.**」.

3.10. (Indicated diseases) When applying for re-examination, data on efficacy according to indicated diseases or patients should be attached and for indicated diseases, indication which is granted to addition of efficacy · effect during the period of re-examination is also included or originally approved indication is only included?

☞ All indications are included.

3.11. (Reflecting a result) How is unexpected adverse drug reaction reflected in

precautions?

☞ Whether unexpected adverse drug reaction will be reflected in precautions is decided after reviewing opinion of whether there is causal relationship with drug from investigators and business enterprise.

3.12. (Integrated Analysis) For entrusting·entrusted products with the same active substances, if the post market surveillance is conducted to each product, is the integrated analysis required to file an re-examination application?

☞ In such a case, to file an re-examination application, the integrated analysis data on each product with the same active substance shall be submitted. It is also desirable to include the data from when post market surveillance protocol is established.

4. Others

4.1. (Date re-examination is completed) Article 9 of 「Re-examination standard for new drugs etc.」 **provides that a person who** has obtained marketing approval**, investigation agency and investigator shall retain documents related to post market surveillance prepared during the period of re-examination for three years after re-examination is completed and when is date re-examination is completed?**

☞ Civil petitions undergo application, receipt and notice of result pursuant to Civil Petitions Treatment Act and thus it is reasonable to consider date re-examination is completed as point of time that notice of result is completed.

4.2. (Data protection) For pharmaceutical subject to submission to RMP, during active surveillance/comparative observational study, must post market surveillance be included unconditionally? If another study method is also allowed, are its data protected in the same way?

☞ You should select optimum pharmaceutical surveillance method considering property of pharmaceutical and pharmaceutical subject to submission to risk management protocol must either active surveillance or comparative observational study. Data

protection is one thing and risk management protocol is another and active surveillance does not necessarily include Post market surveillance.

4.3 (Terminology) What terminology should I use to periodically report the adverse event?

☞ It is desirable to use MedDRA PT(Preferred Term) like the term reflected on the points to consider to obtain authorization. However, if it is not possible to use PT, it is recommended to use LLT(Lowest Level Term) to report the event to KIDS.

Ⅲ. Example of Circulation on Number of the Subject Product to Surveillance

'Number of the subject Product to surveillance' shall be calculated and determined based on the reasonable supporting data by item, when the post marketing surveillance protocol is filled out. In this context, to help understanding for calculation number of the subject product to surveillance and filling out supporting data, the following is provided for your information, selecting some parts of the submitted cases in the meantime and reorganizing them by the supporting data item to understand easily.

1. Epidemiological properties of the indication

A. Example 1

(1) Prevalence and fatality rate of 'Example 1 indication'

(A) one of 10 persons older than 50 years old is suffering from the disease, three of 10 persons older than 65 years old is suffering from it.

(B) A timing of the treatment for the indication may be missed as most 'Example 1 indication' is discovered after the disease has progressed to some extent rather than high fatality.

(2) A use subject of medicine containing A component and narrow therapeutic window of the indication due to the disease and drug properties

(A) The item has a indication which can use to a 20~30% patient with a serious case of 'Example 1 indication', unlike normal drug of 'Example 1 indication'.

(3) Small number of new patient

(A) A new patient with more serious case of 'Example 1 indication' is small number and repeat prescription accounts for more than 3 times.

☞ Most patients already experienced the symptoms in the past, as one patient experiences one symptom for several times in his/her life.

B. Example 2

(1) Limitation on the patient who can be administered

(1) Limitation on the number of the patient

(A) 'According to the published data, 'A indication' is the disease with the lower prevalence rate, which 334 patients and 413 patients respectively have been diagnosed for the last 2 years, has the small number of target patientss, according to annual report of national 000, the increase rate of annual prevalence rate for

‘B indication’ has decreased respectively annually.

(B) A medicine containing component ‘B’ can be administered to the limited patient as it was approved as 2nd or 3rd therapy depending on each indication

(C) A medicine containing component ‘B’ has not applied to the insurance benefit for the ‘A indication’ for a long time in Korea, the access of the patient is lower due to the limited application of insurance.

(D) An administration of medicine containing component ‘B’ for the patients with the indication was limited before 0000 as the ‘B indication’ became the insurance benefit subject in 0000.

(2) A prevalence rate and expected number of the patient based on its rate

(A) ‘A indication’

· According to national 000 annual report, about 30,000 patients have developed ‘A indication and the increase rate of prevalence rate for the disease has decreased for 3 years. The number of patients with ’A indication’ accounts for 14% of overall ‘A indication’.

The patient diagnosed new metastatic ‘A indication’ accounts for about 4 % of the above indication

☞ The number of the target patientss for this medicine is estimated at approximately 550 persons considering IMS data

(B) ‘B indication

· A national 000 annual report says that the incidence rate of ‘B indication’ has gradually decreased and the width of the decrease has been greater.

· A claim data from Health Insurance Review and Assessment Service demonstrate that about 3,000 patients have been administered medicine containing other components, only the patient who failed to be cured with other medicine containing other components can be administered medicine containing B

C. Example 3

(1) A study report on 00 indication for Korean in 0000 shows that the prevalence rate of the indication for the adults over 30 years old in Korea in 00 is △%

(2) The number of the target patients who can apply to the item is small

(A) The number of the target patients considered the approved indication, health insurance criteria among patients with the disease is about 60,000 persons, the number of the target patients considered IMS data of 60,000 persons is about 600~35,00 persons

(B) The expected number of the patient based on IMS data is about 4,000 persons

(C) The number of the patient whose records were completed in the standard case report is about 1,000 persons

(3) A drug registration rate and prescription rate in hospital level medical institution

(A) 30% of the institutions which prescribed the medication of hospital level medical institutions registered in the prescribed medicine list

2. Properties and usefulness of the item

A. Example 2

(1) Clinical usefulness

(A) A medicine containing A component is the only medicine which conducted RCT(randomized, controlled trial) for the ‘A indication’ target patients in Korea

(B) Safety and efficacy in the exact target patient was identified in the 3 phase clinical trial unlike the other medicine used empirically for the ‘A indication’ currently.

(C) A medicine is empirically proven by the clinician with this drug base in the ‘B indication’ treatment guideline.

B. Example 2

(1) Clinical usefulness

(A) ‘A indication’

· A medicine containing ‘B’ is the only 3rd line treatment which can be administered to ‘A indication’ patient in Korea, and recommended standard treatment as 3rd line treatment from international guideline

(B) B Indication

· A medicine containing ‘B’ is the reference treatment recommended in international guideline to be administered as 2nd line treatment to the patient with ‘B Indication’ who have failed treatment.

· A medicine containing ‘B’ is the 2nd line treatment only existing covered by insurance pay with ‘B Indication’.

☞ If the above data were comprehensively evaluated, a medicine containing ‘B’ has a similar safety and efficacy to the clinical trial data. But, there was no new safety related information which impacts on the change of overall benefit-risk to use in the approved indication.

Example 3

(1) XX chemical which does not have immunogenicity side effect

(A) This item is the only XX chemical of targeted treatments to the indication, which is expected to have continuous effectiveness and safety as it does not have immunogenicity side effects unlike biological products. Therefore, it is useful treatment option to minimize drug switch.

(B) An effective treatment option as monotherapy

· Useful treatment alternative for patients as single administration is capable of clinical improvement similar to the combination therapy unlike the existing biological products

* As a result of comparing monotherapy and combination therapy of this item, monotherapy showed as significant clinical improvement as combination therapy, showing that effective treatment alone is possible. In fact, as a result of market research in the U.S, which was first marketed, it was observed that about half of the patients receiving this product were being treated with monotherapy.

** For existing biologics, most patients use combination therapy

(C) The only targeted therapy that can be taken orally

· It is the only drug that can be taken orally among target indication drugs

* As all biologics are injections, not only is the convenience of administration low, but also the limitations of administration-related side effects occurs

· Positive effect on patient acceptance, medication compliance, and treatment continuity by improving oral intake, storage at room temperature and convenience(improvement of inconvenience such as additional medical institution visits or special disposal for drug administration) regardless of meals.

3. Marketing authorization and sales status of items prescribed for target indication

A. Example 1

(1) Prescribing patterns of clinicians

(A) Since patients with severe symptoms have already experienced symptoms several times in the past, and there many high-risk patients such as old age, comorbidities, and hospitalization, clinicians should focus on drugs that patients have used. There is a strong tendency to prescribe drugs that are prescribed or that the clinician has had several prescription experiences.

(B) In fact, when clinicians use other drugs for chronic diseases, they prescribe drugs that have been successfully treated in the past for reasons such as tolerance, and show a pattern of continuting if there are no serious sides effects.

(C) Due to the characteristics of patients with ‘indication A’, clinicians cannot help but consider hospitalization if severe symptoms occur, and when hospitalized, they first consider injections that are easy to administer. Unlike other drugs, this product does not contain injections, so it may not be considered.

(D) Patients with ‘A indication’ often have ●● diseases as an underlying disease. In this case, unlike other competitor products, it is often difficult for clinicians to choose first because there is not indication for A drug.

(2) Existence of other competing products

(A) In the treatment guideline for ‘A indication’, if 4 or more severe, especially if additional drugs are required, clinicians consider using other drugs.

☞ 00-series medicines are used only in severity level 4 or higher of ‘A indication’. An average of 15% of patients with ‘indication A’ 4 severity or higher used 00 series drugs.

☞ For severely ill patients with ‘A’ indication 4 or higher, 00 series drugs account for about 10% of actual UBIST market data.

☞ Currently, domestic clinicians prescribe medicines of other series first, and then, when treatment is not successful, they usually prescribe medicines of the 00 series as a second line.

☞ Since more than 80% of patients are usually treated with the first (initial) treatment, only about 10% of patients are transferred to 00 series drugs.

☞ Among the 00 series oral medicines, when considering the main prescription recommended as a prescription drug for severely ill patients with 'Indication A' 4 or higher, while having approval for severity of 'Indication A' 4 or higher, the

relevant item (a drug) is 1 % occupied.

B. Example 2

(1) Small market share due to various competing products

(A) Currently, various products with the same indications as this product, including biological agents and biosimilars, are released

(2) Status of re-review of products with similar efficacy

(A) Reduction of new patients registered for PMS due to recent approval of drugs with the same mechanism of action

Product Name	Period of Re-review	Name of Inspector	Indication
○○○			○○/△△/□□
×××			○○/△□/□□
○▲○			○○/△△/□□
○▲△			△△
▲▲▲			△△

C. Example 3

(1) Changes in marketability due to competing items

(A) Decreased market share of this product due to the strength of competing products and generic products, and the listing of 3rd generation AA drugs in health insurance benefits.

(B) According to the rate of change in prescription dispensing amount in the first half of 2018 compared to the first half of 2017, this item showed a sluggish trend of about -40% in prescription dispensing amount compared to the same period last year, despite our steady efforts to maintain and sell the item.

(C) According to the IMS DDD data, which can confirm the supply trend of medicines by institution according to wholesale shipment performance, 7 million tablets of Z enzyme inhibitor were shipped to the top 72 institutions with the largest use of Z enzyme inhibitor, and the total amount of this product used in those institutions. There are 200,000 tablets, and C component drugs are used at a rate of about 30% of all Z enzyme inhibitors.

(D) Even through the data of the top 72 wholesale drug supply organizations (IMS DDD), the share of y component drugs and AA drugs reached 55%, more than half of the entire Z enzyme inhibitor market.

4. Relevant item salary information, etc.

A. Example 1

(1) This item can be covered by insurance only for the second treatment

(A) This item has an indication of severity of 4 or higher in ‘A indication’, but caution is requested as it cannot be used as a first-line drug under the current reimbursement standard.

☞ In connection with insurance standards, hospitals cannot actively prescribe for the first time without treatment records for existing 00 series drugs for reasons such as reduction.

B. Example 2

(1) Restriction of access to medicines due to benefit restrictions

(A) Delay in release after marketing authorization, delay in drug review schedule at each hospital → Prescribing possible after a certain period of time

(B) Patients who do not respond appropriately or are intolerant to one or more biologics covered by the initial limited insurance benefit → Used in the tertiary treatment stage, so there were virtually no prescription opportunities

(C) Expansion of benefit: Health insurance benefit standard for secondary treatment is expanded

C. Example 3

(1) Restrictions based on insurance coverage standards

(A) The insurance coverage criteria is for patients who are unable to adequately control blood sugar levels with concomitant administration of ○○ drugs out of all patients with the applicable indication ▲ and are obese patients with a BMI≥30kg/m2 who are unable to undergo therapy and the scope of insurance coverage is narrow.

5. Expected number of patients using the product

A. Example 1

(1) Sales performance

(A) Estimation of number of patients compared to sales volume

· ‘A indication’ is a chronic disease, and symptoms with a severity of 4 or higher may occur several times in one patient. In addition, considering that the number of

patients with that code is only about 30% of the number of prescriptions for that disease code in HIRA data9), it is difficult to see the number of prescriptions for the same item as the number of patients who received prescriptions.

(B) Number of patients eligible to participate in PMS among target patients

· Patients subject to PMS of this product are only patients in general hospitals and tertiary general hospitals (60% of all patients exist)

※ The reason why the item can be prescribed only in tertiary general hospitals and general hospitals

▲ being used only in a limited range of patients of patients with moderate or higher indications 'A' (15% of patients with moderate or higher severity)

▲ This item has limited indications so that it can be used only for patients with moderate or higher indication A, and in particular, it is limited so that it can be used in patients without other treatment methods.

· In addition, the number of patients that can be recruited is expected to be much smaller considering that among them, PMS registration is possible only where the PMS site has been opened and the patient's consent to participate.

B. Example 2

(1) Sales performance

☞ Estimated 1,000 new patients based on cumulative sales data (approximately 1,000 new patients after the first PMS patient registration)

*A total of 300 cases of collection targets by 2018 (PMS participation: about 30%)

(2) Target number of patients

(A) Domestic adult patients with applicable indications

* Decreased by 1.34% per year

(B) Expected adult patients with applicable indications: 300,000 in 2019

(3) Number of patients treated at medical institutions prescribing biologics

(A) Most (>96%) of patients with indication E who are taking drugs with similar ingredients are receiving treatment at general hospitals and tertiary general hospitals (health insurance claim data).

(B) As a result of the investigation by the Ministry of Health and Welfare, the ratio of general hospital-level medical institutions among medical institutions that treat indication E is about 27% → Since only some general hospital-level medical institutions will prescribe biological drugs → The ratio of medical institutions that prescribe biological drugs out of all medical institutions that treat indication E is assumed about 20 %

(C) Based on this, the number of E indication patients receiving treatment at medical institutions prescribing biological products is calculated.

(4) Number of patients prescribed for biologics

(A) Calculate the number of patients prescribed for biologicals in the year based on the prescription rate of biologicals among all treatments for the corresponding indication

(B) Number of new patients prescribed for first-line biologics

· The target patient group for the indication of this item is new patients who are prescribed biologics for the first time (biologics naive)

· According to domestic market research data, about 10% of patients with indication E who are prescribed biologics are new patients who are first prescribed biologics. Therefore, by applying this ratio, the number of new patients receiving a first prescription of a biologics of patients with indication E in Korea is calculated.

C. Example 3

(1) Estimated number of patients depending on prevalence rate

(A) About 70,000 patients, considering 00% of patients according to insurance acceptance criteria for D-component drugs, and about 25% of patients with a BMI of 30kg/m or more among the applicable indications

(B) In the IMS data, the number of patients considering the market share of ▲drug and ◯drug is 600~3,500 persons

(2) Estimated number of patients based on sales performance

(A) (IMS data) Sales performance from Q0 of 2000 to Q0 of 2000 was approximately KRW 000

· Assuming an average of 6 months of treatment per patient, the expected number of patients is 4,000

6. Safety information of the item

A. Example 1

(1) Domestic safety data

(A) Safety data in use result investigations, investigation studies, and voluntary reports

· A total of 1,000 adverse events were reported from 2013 to 2018. ▽▽ Adverse reactions were the most frequently reported with 60 cases, followed by △ (50 cases), ▲ (45 cases), ● (35 cases), and ●● (25 cases). There were no additional adverse events found other than the identified adverse events.

(2) Safety data in re-review conducted in Japan

(A) As a result of comparing the safety data of the re-review of B component drug for

indication A conducted in Japan from 2011 to 2014 with the safety data of ○, a phase 3 clinical trial of B component drug, a similar trend was found.

(3) Overseas safety data

(A) PSUR

· According to the latest version of the PSUR, it is estimated that about 120,000 patients have been administered B-component drugs so far. Also, to date, there has been no new information that would change the overall assessment of benefit-risk when using a B-component drug for an approved indication.

(B) Other foreign literature data

· According to foreign literature data of 9 cases published as indication A and 3 cases published as indication D, there were no additional adverse events found in patients who received component B drugs other than those found so far.

B. Example 2

(1) Domestic use result survey collection status

(A) 4th year periodic report

· 24 adverse events (41 cases): Nausea (nausea), Oedema Peripheral (peripheral edema), Dizziness (dizziness), Herpes Zoster (herpes zoster) 3 cases each, etc.

·12 cases of adverse drug reactions (15 cases) in which a causal relationship cannot be ruled out: Dizziness in 3 cases, Nausea in 2 cases, and Herpes Zoster in 2 cases each.

·3 serious adverse events (3 cases): Appendicitis, Fracture, Pneumonia

·10 unexpected adverse events (11 cases): Dizziness was the most common in 3 cases, with Fracture (fracture), Myalgia (muscle pain), Rhinitis (rhinitis), and Mouth dry (dry mouth), 1 case each

·3 cases of adverse drug reaction (3 cases): Dizzines

(2) Status of foreign safety collection

(A) Lack of effect was observed in the interim analysis value presented at the European △△ Society last year. The most common AEs were infections such as herpes zoster virus and liver abnormalities, and SAEs were pneumonia.

(B) Currently, AEs with a similar pattern are being collected in the Korean PMS interim data and PSUR, and are similar to the profile of other products already published and the results of existing clinical trials. In the case of self-report, lack of effect was reported as the most common side effect, and in the remaining AEs, the number of cases was smaller than that of PMS registration, so it was not possible to find a specific pattern, but in terms of types, adverse events of the kind overlapped with those reported in PSUR were reported. .

C. Example 3

(1) DD clinical research

(A) Randomized, open-label, parallel-group, multicenter, phase III study to compare the effects and safety of D-component drug and X-component drug in patients with progressive indication A who had no prior treatment experience

☞ Conclusion: When used as a first-line treatment for patients with advanced indication A, drug component D provides a significantly higher therapeutic effect than drug component X.

(2) Domestic researcher-led clinical trial data

(A) A total of 8 cases of clinical and epidemiological research data by domestic researchers presented at conferences, etc.

(B) Among them, 1 study was conducted on patients with the approved indication of 'D-component drug' (indication B)

(C) Among the adverse events found through the studies, there were no significant findings compared to the contents reflected in the existing phase 3 clinical studies and product descriptions.

7. The number of people who can be subject to surveillance for the relevant item

A. Example 1

(1) Calculation of the number of subjects required to verify specific safety information

(A) All adverse events (AE/SAE) collected from various fields to select specific adverse events of interest (all clinical trials including approved clinical trials, post-market surveillance, voluntary collections, registries, and abnormalities collected abroad) case, etc.)were reviewed, and '○○ abnormal case' was selected as the most meaningful abnormal case.

(B) Adverse cases of interest: ○○ adverse cases

* Due to the difficulty in diagnosing ○○ adverse events clinically, based on the product description, the symptoms of △△ reactions and ◇◇ reactions, which can be seen as ○○ adverse events, are regarded as ○○ adverse events

(2) As a result of reviewing all adverse events (AE/SAE) from pre-authorization clinical trials and post-marketing planned and voluntary collection sources,

☞ The prevalence of adverse events related to ○○ adverse events, which are the adverse events of interest, is 0.2%. The minimum number of surveillance target to detect the selected risk by the Rule of three is about 14,00 persons.

<Formula for Calculating the Number of Targets to Surveillance>

$$\sum_{x=0}^{\alpha-1} \frac{(N\lambda)^x e^{-N\lambda}}{x!} = \beta$$

However, in the case of £=1 (one case of adverse event), the following simplified formula can be used.

$$N = \frac{-\log \beta}{\lambda}$$

α : Number of adverse events of major interes
λ: Expected adverse event incidence rate
β: Probability not finding an adverse event of major interest (=0.05)
N: Number of surveillance subjects required

B. Example 2

(1) Number of cases calculated as major observed adverse events

(A) Among the EU RMP adverse events, it is the O adverse event, which is the adverse event that is of most interest in this use result survey.

(B) Adverse reactions are common in Asians, and may affect the patient's prognosis. According to the production instruction, if the O adverse reaction is Grade 3 or higher, the administration of this product is to be discontinued. Accordingly, the number of cases was calculated using the above calculation formula using the incidence rate of Grade 3 or higher adverse events among O adverse reactions.

(2) 'A indication'

(A) When the expression rate is substituted into the above formula, an adverse event of major interest can be found when about 90 subjects are investigated (reliability of 95% or higher)

(3) ‘B indication’

(A) When the expression rate is substituted into the above formula, when a total of about 300 subjects are surveyed, adverse events of major interest can be found (reliability of 95% or higher).

C. Example 3

(1) Grounds for case adjustment following reexamination in Japan

(A) Re-review of C-component drugs in Japan monitors adverse events 000 and 00000 specified in RMP’s ‘Key Investigation Items’ (target number: 1,500 cases)

(B) As a result of clinical trials in and outside of Japan, the expression rate of 00000,

which cannot rule out a causal relationship, was 0.3% and 1.6% in Japan

* The number of cases required to detect with a 99% probability for an adverse reaction with an incidence rate of 0.3% or higher = 1,500 cases

** Number of cases required to detect with a 95% probability for an adverse event with an incidence rate of 0.3% or higher = 1,000 cases

☞ 1,500 cases is the number of cases that can be sufficiently collected for 00, another key investigation item with a higher frequency of occurrence than 00000.

* Note: Sales in Japan are about 5 times that of Korea

(2) Case number adjustment plan

(A) Calculated as 000 cases by considering the occurrence rate of '00000' among the review items of the Japanese RMP according to domestic and international safety information

♣ Actual writing example

* This data is arbitrarily edited from the previous data and is used for reference only.

1. Epidemiological characteristics of indications

A. Domestic 0000 incidence and survival rates

(1) Early detection of 0000 is not easy, recurrences occur frequently, and in fact, 80% of patients have already progressed the disease at the time of initial diagnosis.

* Out of 0000 new cases in Korea, 00 cases accounted for 11%, and the gender ratio was 2.2 (male) : 1 (female).

☞ Estimated incidence in 0000 people in 2016

(2) The 5-year survival rate of 00 patients is gradually increasing

B. Overseas 00 incidence and survival rates

(1) 00 is a leading cause of related death worldwide, with 1 million new diagnoses each year, and 00 causes 10,000 deaths each year

(2) Clinical management using complex therapies is being conducted for the initial treatment of 00, but the prognosis has not substantially improved if the disease has already progressed.

(3) The 5-year survival rate is 10%, and the treatment of the disease remains a medical challenge

2. Usefulness and features of the item

A. Characteristics of pharmaceutical ingredients

(1) C component drug, which is the active ingredient of this item, is an irreversible type A blocker

(2) Similar to the non-clinical results, the clinical trial results showed that the C component drug was effective in 00. In clinical practice, the safety characteristics of C-component drugs are related to their mechanism of action, and characteristic adverse events such as flare-ups

B. Clinical utility: improved b receptor inhibitors

(1) According to the statistics project data, the survival rate of 0000 is low at 30%, but the survival rate continues to rise, which is considered to be a large contribution of this drug

(2) Unlike existing treatments, it has the advantage of having fewer side effects by directly inhibiting b receptors that affect cell growth.

(3) According to the presentation data of the European 00 Society, the risk of treatment failure was reduced in the case of C-component drugs, which are treatments that irreversibly inhibit all of the a receptors, compared to treatments that block only the b receptors.

(4) Health Insurance Review and Assessment Service added C-component drug ingredients to questions and answers related to cross-administration. In response to the question of insurance coverage for cross-administration of other b-receptor inhibitors due to side effects

after administration of drugs, the answer was that it is recognized on a case-by-case basis because there is evidence of clinical benefit.

☞ C-component drugs have a low risk of disease progression and treatment failure, and insurance benefits are recognized when cross-administration due to side effects of other drugs, providing patients with higher quality treatment with less burden

C. Other materials

(1) In the XXX clinical results first treatment, the C component drug showed a statistically significantly superior effect to the Y component drug, and the results of the YY Real wold retrospective study showed consistent results with the above XX clinical trial

3. Marketing authorization and sales status of items prescribed for target indications

A. Changes in marketability due to competitive products

(1) Declining market share of this product due to the strength of competing products and generic products, and the listing of AA drugs in health insurance benefits

(2) According to the data on the growth rate of prescription dispensing amount, despite our steady efforts to maintain and sell this item, the prescription dispensing amount of this item was sluggish by about -50% compared to the same period last year.

(3) According to the drug supply trend data by institution according to wholesale shipment performance, 700,000 inhibitors were shipped to the top 72 institutions with the highest usage, and the total usage of this item in those institutions was 150,000 tablets, C-component drugs among the total inhibitors have been used at a rate of about 20%.

(4) Other ingredient drugs and AA drugs account for more than half of the total inhibitor market

4. Relevant item salary information, etc.

A. Restricted Access to Medicines Due to Restrictions on Benefits

(1) Delay in release after marketing authorization, delay in drug review schedule at each hospital → allow prescription after a certain period of time

(2) Initial limited insurance coverage: Patients who do not respond adequately to one or more treatments or are intolerant → Used in the tertiary treatment stage, so there were virtually no prescription opportunities.

5. Expected number of patients using the product

A. Expected future sales

(1) The prescription rate of newly diagnosed patients with C-component drugs is estimated to be about 45%, which is prescribed to about 1,000 new patients annually.

(2) About 20% of the total number of cases used for new patients per year are included in post-marketing surveillance due to reasons such as the

inability of organizations that account for a large portion of the total prescription volume to participate in post-marketing surveillance.

B. The registration rate of use result survey compared to the actual/expected number of prescribed patients is as follows

<Number of registrations by period and cumulative>

	YEAR	YEAR	YEAR	YEAR	YEAR
Number of prescription per year					
Number of annual registration					
Cumulative number of registration					
Registration rate against the number of prescribing patients(%)					

6. Safety information of the item

A. Domestic use result survey collection status

(1) During the use result surveillance period, the number of cumulative investigation agencies was 30, and the number of cumulative safety evaluation targets collected from those agencies was 200.

(2) 180 adverse events occurred in 178 out of 200 subjects for safety evaluation

B. Collection status other than domestic use result survey

<Collection status of abnormal cases in Korea other than use result investigation>

	Abnormal Cases Collected Other than Use Result Investigation
1-1st	000
1-2st	0000
2-1st	00
2-2st	00

C. PBRER Summary

Content Delected

☞ No action taken by the agency for safety reasons

D. Status of re-examination in Japan

(1) Post-marketing surveillance period: 3 years, 1,500 people from 700 institutions collected

* Japan's sales performance is about twice that of Korea, and Korea's patient pool is half that of Japan.

<Domestic use result surveillance - Comparison of post-marketing surveillance plans in Japan>

	Korea	Japan
Period	0	0
Number of patients	0	0
Number of sites	0	0

(2) Results of post-marketing surveillance in Japan

☞ As a result of the re-review of C-component drugs in Japan, no changes were found in the existing approvals related to safety and efficacy.

7. Number of potential targets for surveillance for the item (statistical calculation based on abnormal cases)

A. Grounds for case adjustment following re-review in Japan

(1) Re-review of C-component drugs in Japan monitors 0000 adverse cases specified in RMP's 'key investigation items' (target number: 1,500 cases)

(2) As a result of clinical trials in Japan and abroad, the expression rate of 0000, which cannot rule out a causal relationship, was 0.3% and 1.6% in Japan

* The number of cases required to detect with a 99% probability for an adverse reaction with an incidence rate of 0.3% or higher = 1,500 cases

** Number of cases required to detect with a 95% probability for an adverse event with an incidence rate of 0.3% or higher = 1,000 cases

(3) In the case of domestic approval matters, in the case of 0000, which is an important investigation item in the RMP, it is stated that adverse reactions

were reported in 0.**%

☞ The number of cases required to detect with a 95% probability for an adverse event with an incidence rate of 0.**% = *** cases (Rule of 3)

<Formula for Calculating the Number of Targets to Surveillance>

$$\sum_{x=0}^{\alpha-1}\frac{(N\lambda)^x e^{-N\lambda}}{x!}=\beta$$

However, in the case of £=1 (one case of adverse event), the following simplified formula can be used.

$$N=\frac{-\log\beta}{\lambda}$$

α: Number of adverse events of major interes
λ: Expected adverse event incidence rate
β: Probability not finding an adverse event of major interest (=0.05)
N: Number of surveillance subjects required

(4) In order to detect 0.**% of abnormal cases with a 95% probability according to the Rule of Three, *** cases must be collected, and this is the number of cases that can collect all abnormal cases of the priority investigation items.

B. case count adjustment

(1) Calculated as *** case considering the 0000 expression rate (domestic 0.**%, Japanese PMS *.**%) among the review items of the Japanese RMP according to domestic and international safety information

(2) Considering circumstances such as reasons for non-participation in post-marketing surveillance, early termination of agencies with difficulty in conducting surveillance, and sluggish registration rate compared to contract cases, **% of surveillance targets are expected to be registered.

< Annual and cumulative registration (expected) number of cases >

	YEAR	YEAR	YEAR	YEAR	YEAR	YEAR (Estimated)
Number of patients who prescribed-C component drugs						
Number of annual survey registration						
Number of registered cases/number of patients prescribed(%)						
Cumulative number of survey registrations						

☞ Therefore, during the re-review period, it is expected that cumulative **** people can be registered, and about *** cases can be collected considering the dropout rate.

* This is the number of cases that can detect an adverse event with a 0.**% incidence rate with a 95% probability.

8. Final number of Target product to surveillance

A. Cases applied for case adjustment are the number of cases in which an adverse event with an incidence rate of 0.**% can be detected with a 95% probability,

B. We intend to collect as many cases as possible during the domestic re-review period in order to collect as many adverse cases as possible in addition to the key investigation items in the RMP.

[Appendix 1] Standard for administrative measures related to re-examination

Measures related to re-examination pursuant to standard for administrative measures (related to Article 95) prescribed in 「Regulations on Safety of Pharmaceuticals, etc.」 [schedule 8] are as follows.

Ⅱ. Individual criterion

Violation	Ground provisions	Administrative measures			
		first	second	third	fourth
8. In case where manufacturer or importer of pharmaceutical falls under any one of the following with regard to re-examination of new drugs	Articles 32 and 42 of the Act(Article 23 of the Regulation)				
A. in case where use result surveillance protocol for re-examination of new drugs etc. has not been reported or progress of use result surveillance by years has not been reported		1 month of suspension of sale of relevant product	3 months of suspension of sale of relevant product	6 months of suspension of sale of relevant product	revocation of permission for relevant product
B. in case where a part of data needed for re-examination of new drugs etc. has not been submitted(including a case which number of Target product to surveillance is		3 months of suspension of sale of relevant product	6 months of suspension of sale of relevant product	revocation of permission for relevant product	

insufficient)					
C. in case where re-examination application has not been submitted by deadline for application (within three months after re-examination period ends) or not all data needed for re-examination have not been submitted		6 months of suspension of sale of relevant product	revocation of permission for relevant product		
D. in case where data needed for re-examination of new drugs etc. have been reported or submitted falsely		3 months of suspension of sale of relevant product	6 months of suspension of sale of relevant product	9 months of suspension of sale of relevant product	revocation of permission for relevant product
E. in case where re-examination standard prescribed by Minister of Ministry of Food and Drug Safety has been violated		1 month of suspension of sale of relevant product	3 months of suspension of sale of relevant product	6 months of suspension of sale of relevant product	revocation of permission for relevant product

[Appendix 2] Standard for Re-examination of New Drugs, etc.

Ministry of Food and Drug Safety Notice No. 2020-122, 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.

(1) 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.

(2) 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).

1. 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.

2. 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.

1. 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.

1. Matters regarding the education and training of people who are engaged in the PMS

2. 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.

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

(2) 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.

(3) 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.

(4) 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.

(1) 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.

(1) 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.

1. 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.

1. 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.

(1) 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

(1) 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.

(2) 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.

(3) 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.

(1) 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.

(1) 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.

(2) 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.

(3) 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. 2020-122, Dec. 14, 2020>

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.

“-Post-Marketing Safety Control of Drugs etc.-
Guideline on re-examination affair of new drug etc. (A guide for civil petitioner)”

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