PSEHB/PED Notification No. 0309-1
PSEHB/CND Notification No. 0309-1
March 9, 2018

To: Head of Prefectural Health Department (Bureau)

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

Director of the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
(official seal omitted)

Handling of Changes to Approved Product Information Pertaining to the Quality of Drugs

In light of the results of the inspection conducted according to "Implementation of Inspection on Consistency between Actual Manufacturing Practices and Drug Approval Documents" (PSEHB/ELD Notification No. 0119-1 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated January 19, 2016), it was requested for marketing authorization holders, etc. to have their staff informed of and ensure thorough verification between actual manufacturing practices and drug approval documents, establishment of appropriate implementation systems for change control, and thorough prevention of recurrence under "Strict Compliance with the Marketing Approval Documents of Drugs" (PSEHB/ELD Notification No. 0601-3 and PSEHB/CND Notification No. 0601-2 jointly issued by the Director of the Evaluation and Licensing Division and the Director of the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated June 1, 2016; hereinafter referred to as "Notification on Strict Compliance").

The following rules were recently established for the purposes of ensuring appropriate changes to approved product information associated with changes to the manufacturing process, etc. of drugs and promoting smooth changes to the manufacturing process, etc. Please inform business operators in your jurisdiction accordingly.

The terms used in this notification are defined as follows:

Act: Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960)

Order: Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Cabinet Order No. 11 of 1963)

Regulation: Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHW Ordinance No. 1 of 1961)

Approval applications: Applications for marketing approval of drugs pursuant to Article 14, Paragraph 1 or Article 19-2, Paragraph 1 of the Act

Partial change applications: Applications for approval of partial changes to the approved product information of drugs pursuant to Article 14, Paragraph 9 of the Act (including cases where it shall apply mutatis mutandis in Article 19-2, Paragraph 5 of the Act)

Drug minor change notifications: Notifications of minor changes to the approved product information of drugs pursuant to Article 14, Paragraph 10 of the Act (including cases where it shall apply mutatis mutandis in Article 19-2, Paragraph 5 of the Act)

Approved product information: Product information described in the application form for an application approved pursuant to Article 14, Paragraph 1 or Article 19-2, Paragraph 1 of the Act (including the cited registration information if registration information is cited in part, and it should be the information after the change implemented by the approval or notification if a partial change application has been approved or a drug minor change notification has been submitted)

Approved quality-related product information: Approved product information indicated under the columns "Ingredients and quantities or nature" (limited to those pertaining to specifications of ingredients [including separate specifications]), "Manufacturing process," "Storage method and shelf life," "Specification," "Manufacturing site of the item to be marketed," and "Manufacturing site of the drug substance" in the application or notification form

GMP compliance inspection: Inspection pursuant to Paragraph 6, as applied mutatis mutandis in Article 14, Paragraph 9 of the Act (including cases where it shall apply mutatis mutandis in Article 19-2, Paragraph 5 of the Act)

MF: Master File

MF registration applications: Applications for MF registration pursuant to Article 80-6, Paragraph 1 of the Act

MF change registration applications: Applications for changes to MF registration information pursuant to Article 80-8, Paragraph 1 of the Act

MF minor change notifications: Notifications of minor changes to MF registration information pursuant to Article 80-8, Paragraph 2 of the Act

Registration information: Information described in the application form for an MF-registered application pursuant to Article 80-6, Paragraph 1 of the Act (it should be the information after the change implemented by the registration or notification if an MF change registration application has been registered or an MF minor change notification has been submitted)

ICH: International Conference on Harmonization

Q2 Notification: "Text on Validation of Analytical Procedures" (PAB/PCD Notification No. 755 issued by the Director of the Pharmaceuticals and Cosmetics Division, Pharmaceutical Affairs Bureau, Ministry of Health and PMBWelfare dated July 20, 1995)

"Validation of Analytical Procedures: Methodology" (PMSB/ELD Notification No. 338 issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare dated October 28, 1997)

Q3 Notification: "Revision of the Guideline on Impurities in New Drug Substances" (PMSB/ELD Notification No. 1216001 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare dated December 16, 2002)
"Revision of the Guideline on Impurities in New Drug Products" (PMSB/ELD Notification No. 0624001 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare dated June 24, 2003)
"Guideline for Residual Solvents in Drugs" (PMSB/ELD Notification No. 307 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare dated March 30, 1998)
"Guidelines for Elemental Impurities" (PFSB/ELD Notification No. 0930-4 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated September 30, 2015)

Q6 Notification: "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (PMSB/ELD Notification No. 568 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare dated May 1, 2001)
"Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products" (PMSB/ELD Notification No. 571 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare dated May 1, 2001)

Q10 Notification: "Pharmaceutical Quality System" (PFSB/ELD Notification No. 0219-1 and PFSB/CND Notification No. 0219-1 jointly issued by the Director of Evaluation and Licensing Division and the Director of Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare dated February 19, 2010)

CTDs: Common Technical Documents based on the example shown in the "Guideline on Preparing Data Attached to Application Form for Approval Application of Manufacture or Import of a New Pharmaceutical" (PMSB/ELD Notification No. 899 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare dated June 21, 2001)

PMDA: Pharmaceuticals and Medical Devices Agency

AMED: Japan Agency for Medical Research and Development

Marketing authorization holders, etc.: Marketing authorization holders or foreign exceptional approval holders

I Trial implementation of the change system for approved product information using post-approval change management protocols

1. Purpose of the change system for approved product information using post-approval change management protocols

A post-approval change management protocol (hereinafter referred to as "PACMP") is an idea shown in "ICH Q12 Pharmaceutical Product Lifecycle Management (draft)," which is a draft guideline agreed upon at the ICH. The PACMP-based change system for approved product

information is a mechanism in which the marketing authorization holder, etc. and the PMDA agree in advance on the change to the manufacturing process, etc., evaluation method and acceptance criteria for the change, change proposal for approved quality-related product information, category of change procedure, and need for GMP compliance inspections, etc., and the marketing authorization holder, etc. then conducts an investigation according to the agreed evaluation method, and if the expected results are obtained, the approved quality-related product information can be promptly changed to the proposal.

We will trial this system to contribute to improved predictability and transparency pertaining to changes in approved quality-related product information after marketing approval.

2. Specific procedure for PACMP-based change system for approved product information

(1) Formulation of PACMP

When marketing authorization holders, etc. intend to use the PACMP-based change system for approved product information, they need to formulate a PACMP in advance using "Consultation on the PACMP-based change system for approved product information" (hereinafter referred to as "PACMP consultation") provided by the PMDA. If agreement cannot be reached with the PMDA, the marketing authorization holder, etc. cannot formulate a PACMP or use this system to change approved quality-related product information.

(2) Change procedure for approved product information

The change procedure for approved product information using this system is as follows:

[1] The marketing authorization holder, etc. performs tests and investigations regarding the change to the manufacturing process, etc. based on the PACMP.

[2] If the results of the tests and investigations meet the acceptance criteria described in the PACMP, the approved product information may be changed to the change proposal described in the PACMP, according to the category of change procedure described in the PACMP.

[3] Partial change applications or drug minor change notifications should be accompanied by a record prepared by the PMDA in the PACMP consultation (including the PACMP) and a written statement or testimony to the effect that the application or notification does not deviate from the PACMP. It should be stated in the comment column of the application or notification form that the application or notification is based on the PACMP-based change system for approved product information, and "19112" should be specified in the priority review column for Comment 2.

[4] If the PMDA judges, in the PACMP consultation, that the change to the approved product information sought by the PACMP is not a change listed in each item of Article 47, Paragraph 1 of the Regulation, the marketing authorization holder, etc. may implement the change via a drug minor change notification, or otherwise via a partial change application.

[5] In this system, the Ministry of Health, Labour and Welfare and the PMDA endeavor to limit the total review period from the partial change application until approval to a median of 3 months, except for changes to approved product information by a partial change application where it is necessary to change the criteria prescribed in Article 42 of

the Act (including cases where it shall apply mutatis mutandis in Article 68-19 of the Act) or when the PMDA requests the submission of additional data necessary for a review, etc.

3. Applicability

For the time being, this system applies to changes to approved product information that meet all of the following conditions:

(1) It is a change to the approved quality-related information of a prescription drug (excluding in-vitro diagnostics; hereinafter the same) (excluding the cited registration information if registration information is cited).

(2) It is a change to a drug for which the data to be attached to the approval application or partial change application immediately before the application for PACMP consultation have been submitted as a CTD.

(3) If a GMP compliance inspection is required for the change, the PMDA is the only inspector of the GMP compliance inspection for the PACMP-based change.

(4) The manufacturing site involved in the change appropriately operates the pharmaceutical quality system in accordance with Q10 Notification and performs manufacturing control and quality control of the drug related to the change. In addition, it can submit the results of confirmation for the actual practices of the pharmaceutical quality system by the marketing authorization holder, etc. to the PMDA.

(5) In the case of drugs for which a description adjustment notification has been submitted based on "Procedure after Inspection on Consistency between Actual Manufacturing Practices and Drug Approval Documents" (PSEHB/ELD Notification No. 0212-4 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated February 12, 2016; hereinafter referred to as "Notification on Procedure"), it is a change to a drug by which the underline of the approved product information pursuant to 4(2) and 5(2) of the Notification on Procedure has been deleted due to the confirmation of the said description adjustment notification by the PMDA completed according to the partial change application after submission.

(6) Information from clinical or non-clinical studies on the pharmacokinetics, pharmacodynamics, efficacy, or safety of the drug is not required to assess the impact of the change.

II Rationalization of descriptions in the specification column

1. Rationalization of descriptions in the specification column of application forms

(1) It is acceptable to rationalize descriptions, including describing specification values or acceptance criteria for tests in percentage, describing prepared solutions, etc. in final concentrations, or describing analytical procedures in a bulleted list, in the specification column (including the specification column in the separate specification if specifications of ingredients are provided as separate specifications in the ingredients and quantity or nature column; the same in II) of application forms for approval applications, partial change applications, MF registration applications, or MF change registration applications (hereinafter

referred to simply as "application forms" in II and III below) in reference to the attachment "Report on Rationalization of Descriptions in the Specification Column in Marketing Approval Application Forms" (hereinafter referred to simply as the "Report") prepared based on a report on the sub-theme "Study on quality assurance over the life cycle of drug substances" under a research project on regulatory science of pharmaceuticals and medical devices funded by AMED Research Grants in FY 2016 entitled "Study on quality control techniques in a new development and manufacturing change of pharmaceuticals."

The marketing authorization holder, etc. should thoroughly confirm that the rationalized description reflects the actual practice of quality control at the manufacturing site.

(2) The rule specified in (1) is not limited to descriptions of test methods for which examples of rationalized descriptions (hereinafter referred to simply as "description examples") are provided. However, if it is intended to rationalize descriptions of test methods for which no description examples are provided in the Report, it is necessary to receive confirmation of the appropriateness of the idea of rationalization through a procedural consultation conducted by the PMDA in advance, for the time being.

(3) Modules 2 and 3 of the CTD attached to the application form need to provide descriptions in sufficient detail necessary to determine the appropriateness of the specification, including an outline of the test procedure.

2. Rationalization of descriptions of approved product information

If it is intended to rationalize descriptions in the specification column of the approved product information by referring to the rule specified in 1, it is necessary to undergo a partial change or MF change registration application.

3. Applicability

This rule applies to approved prescription drugs of a marketing authorization holder, etc., with sufficient understanding of the specification, that meet all of the following conditions:

(1) It is a drug for which analytical procedures used in the specification have been verified according to Q2 Notification with an appropriate standard operating procedure maintained.

(2) It is a drug whose specification has been established according to Q6 Notification.

(3) It is a drug for which acceptance criteria have been established according to Q3 Notification with an appropriate standard operating procedure maintained, even when a limit test directly comparing the peak areas of the standard solution and the sample solution in the Purity is changed to a specification value or acceptance criterion expressed in percentage.

(4) It is a drug for which the data to be attached to approval applications, partial change applications, MF registration applications, or MF change registration applications can be submitted as a CTD.

4. Points to consider when changing specifications after rationalizing descriptions in the specification column

When changing the specification after rationalizing descriptions in the specification column, the change procedure for approved product information may sometimes become unnecessary for

changes to the extent that would have required the change procedure before rationalization, but it is necessary to continue appropriate change control as before.

III Post-inspection procedure for consistency between approved product information and actual manufacturing practices

The consistency between the approved product information and actual manufacturing practices requires periodic confirmation, rather than a temporary inspection. The following procedures should be followed in the future when discrepancies between the approved product information and actual manufacturing practices or other similar deficiencies (hereinafter referred to simply as "deficiency") are discovered for prescription drugs during inspections, etc. based on the Notification on Strict Compliance.

1. Procedure for those that are unlikely to affect the quality, efficacy, or safety of the product

(1) In the case of deficiencies for which periodic verifications between the approved product information and actual manufacturing practices and an appropriate implementation system for change control are maintained and there is no risk of affecting the quality, efficacy, or safety of the product as deemed by the marketing authorization holder, etc., such as those caused by a clerical error of the application form, the marketing authorization holder, etc. should submit a drug minor change notification or MF minor change notification promptly after it receives confirmation for no risk of affecting the quality, efficacy, or safety, as well as no interference with the implementation system for change control as determined from the background of occurrence, in a simple consultation before change notification for drugs or simple consultation before change notification for generic drugs provided by the PMDA.
When submitting the notification, the applicant should attach the response received from the PMDA, and describe in the comment column of the notification form that the applicant has received confirmation through a simple consultation before change notification for drugs or simple consultation before change notification for generic drugs.

(2) In the case of a drug minor change notification, "19113" should be specified in the priority review column for Comment 2 in the minor change notification form.

(3) In the case of an MF minor change notification, the person who submitted the MF minor change notification should notify the marketing authorization holder, etc. of the cited drug.

(4) If it is determined in the consultation with the PMDA that the deficiency is not subject to the above, the procedure specified in 2 should be conducted promptly.

2. Procedure for those other than 1

(1) If it is determined that the discovered deficiency is not subject to 1 above, a document summarizing the background leading to the report, details of the deficiency, and possible impacts on quality, efficacy, or safety, as well as proposed measures taking these into account should be prepared and reported to the Pharmaceutical Evaluation Division immediately.

(2) At the same time, necessary actions, such as recall, provision of information to medical institutions, etc., and other necessary measures, should be taken immediately.

IV Descriptions in flexible disk applications

The rules for descriptions in flexible disk applications are specified in "Handling of Flexible Disk Applications" (PFSB/ELD Notification No. 1027-3 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated October 27, 2014; hereinafter referred to as "FD Notification"). The following items may be omitted in the FD Notification Attachment to eliminate the need for duplicate descriptions:

41 Drugs/quasi-drugs, application form for foreign manufacturer accreditation
(2) c Furigana (limited to cases where b. name is written in hiragana or katakana)
63. Drugs/quasi-drugs/cosmetics, application form for marketing approval
(4) e Separate specifications
81 Drugs/quasi-drugs/cosmetics, notification form for marketing approval succession
(1) f Manufacturing site

V Approved product information that may be changed when changes are implemented for other reasons

For changes in the following approved product information, information described in the notification form submitted pursuant to Article 14-9, Paragraph 1 of the Act (information after the change implemented by the notification if a notification pursuant to Article 14-9, Paragraph 2 of the Act has been submitted), or information described in the notification form submitted pursuant to Article 74, Paragraph 1 of the Order (information after the change implemented by the notification if a notification pursuant to Article 265, Paragraph 3 of the Regulation has been submitted), it is acceptable to implement the change when there is an opportunity to implement a change for other reasons, because the information is already held by an administrative organ or there is no change to the actual practices of the manufacturing process, etc.

Question 2 and its answer in the attachment to "Q&As on Master Files (Part 4)" (Administrative Notice from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated October 29, 2013) will be deleted.

(1) When the name or address of the manufacturing site is changed (limited to cases where there is no change to the manufacturing business license number or foreign manufacturer accreditation number)
(2) When the name or address of the testing organization specified in Article 12, Paragraph 1 of the Regulation is changed (limited to cases where there is no change to the corporate number)
(3) When the date of MF change registration is changed (limited to cases where registration information is cited and it is associated with a change in the cited MF to the uncited registration information only)
(4) When it is referred to as a Japanese Pharmacopoeia specification without changing the actual manufacturing process, specification, etc.
(5) When the name of a reagent, reference standard, ingredient, test method, etc. to which the Japanese Pharmacopoeia applies is changed due to the revision of the Japanese Pharmacopoeia to the name in the revised Japanese Pharmacopoeia

(6) When the description of approved product information is adjusted to match the latest description of approved product information for the drug using the same drug substance, drug substance intermediate, or drug product intermediate without changing the actual manufacturing process, specification, etc. (limited to standardization of descriptions between drugs from the same marketing authorization holder, etc.)

(7) When the notation is changed in the same system of units

VI Procedure to extend the shelf life of biologicals

As specified in II-2.(9) of the "Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law" (PFSB/ELD Notification No. 0210001 issued by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated February 10, 2005), the shelf life of drugs, etc., excluding biologicals, may be extended by a drug minor change notification based on the results of stability studies continued after approval according to the commitment submitted at the time of approval review. In light of recent development in genetic recombination technology, cell culture technology, and other scientific technologies as well as accumulated knowledge on the quality, safety, and efficacy of biologicals, biologicals will be handled in the same manner as other drugs.

VII Effective date

This notification will be effective from April 1, 2018.

Attachment

Report on Rationalization of Descriptions in the Specification Column in Marketing Approval Application Forms

Contents

1. Introduction

A method to rationalize descriptions in the specification column (hereinafter, all including separate specifications) in marketing approval application forms (hereinafter referred to as "approval application forms")/marketing approval documents (hereinafter referred to as "approval documents") was examined among persons from the industry, the National Institute of Health Sciences, and the Pharmaceuticals and Medical Devices Agency (PMDA), from the viewpoint of reducing the burden of regulatory procedures while ensuring the quality of test methods.

According to Section 2.1.(1) of "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (PMSB/ELD Notification No. 568 dated May 1, 2001; ICH Q6A), the specification column in approval application forms should be "described by following General Notices, General Rules for Preparations, General Tests, Reference Standards, Reagents and Test Solutions, etc. of the Japanese Pharmacopoeia in principle, but adoption of test methods other than those in the Japanese Pharmacopoeia is acceptable if they are listed in the United States Pharmacopeia, European Pharmacopoeia, etc." For drugs other than new drugs, "the description method should be adjusted in accordance with the description method in the Japanese Pharmacopoeia, etc." according to Part II, Chapter 4, Section 2. (2) 8) d) of the Pharmaceutical Marketing Guidance 2016[Note 1]. Based on these descriptions, it has been practically required in Japan that descriptions are adjusted by following the description method in the Japanese Pharmacopoeia for both new drugs and non-new drugs.

On the other hand, ICH Q12 "Guideline on Pharmaceutical Product Lifecycle Management (tentative title)," a new ICH topic, examines Established Conditions for specifications, and which post-approval changes require post-approval regulatory procedures is being discussed. In order to facilitate this discussion, a method to rationalize descriptions in the specification column in Japan beyond the description method following the Japanese Pharmacopoeia was examined. Part of this examination was presented and discussed at the 19th Pharmaceutical Quality Forum (Tokyo, February 2017)[Note 2].

The results of examination on the rationalization of descriptions in approval application forms/approval documents according to the descriptions for "Analysis by liquid chromatography," etc. in the Japanese Pharmacopoeia are presented below as an example. A proposal to rationalize descriptions in approval application forms to be submitted at the time of application for approval of new drugs is presented in Appendix-1, and points to consider when changing approval documents for approved products according to this approach are presented in Appendix-2. This report is not intended to create a new concept for approved product information.

However, it assumes that the test method is described in sufficient detail necessary for reviewers to determine the appropriateness of the test method, including an outline of the test procedure, in Modules 2 and 3 of the Common Technical Document (CTD).

This report does not refer to items subject to partial change applications or minor change notifications. It does not intend either to discuss descriptions of monographs in the Japanese Pharmacopoeia or harmonization among the Japanese Pharmacopoeia, the European Pharmacopoeia (Ph. Eur.), and the United States Pharmacopeia (USP) with respect to the description method of pharmaceutical test methods.

2. Points to consider when rationalizing descriptions in the specification column in approval application forms/approval documents

2.-1 Current status of descriptions in the specification column

In Japan, it has been recommended to describe test methods by following the description in the Japanese Pharmacopoeia, when describing test methods in the specification column in approval application forms. The reason for this is that the intention of the author of the specification can be conveyed accurately by following the Japanese Pharmacopoeia, and this appears to help people, especially those who have knowledge of pharmaceutical sciences at least, perform a test promptly as intended by the author of the specification and judge the acceptance or rejection easier.

The descriptions of the specification (analysis by liquid chromatography) in the Japanese Pharmacopoeia are characterized by:

- Concrete description of the preparation methods of reagents, test solutions, and mobile phases, including the amounts taken
- Direct comparison of the peak areas of the standard solution and the sample solution in the limit test, with the limit determined
- Expression in sentences using the terms "accurate" and "exact" defined in the General Notices of the JP, rather than in bulleted lists or tables
- Consideration of the feasibility of performing the test in Japan (availability of pipettes and volumetric flasks, etc.)

As a result, there are advantages that a person having knowledge equivalent to the undergraduate degree of chemistry can reproduce a precision- and accuracy-guaranteed test method in Japan if the pharmaceutical procedure is clearly defined, and the acceptance criteria are clear.

On the other hand, current approval documents adopting the description method following the Japanese Pharmacopoeia also have similar advantages, but the following differences can be found from an international perspective:

- In foreign countries, reagents, test solutions, mobile phases, and diluents are often expressed in concentration, in accordance with the USP.
- The specification values/acceptance criteria for Purity are often expressed in %.
- In foreign countries, the content described in Module 3 of the CTD is understood as the regulatory commitment (approved product information).

As a result, the following difficulties exist in the post-marketing management and operation of current approval application forms: That is,

- In the regulatory system in Japan, changes to the preparation method of reagents, etc. are regarded as changes to the approved product information, causing an enormous amount of regulatory procedures.
- Clerical work due to differences in document formats arises for business operators doing business in foreign countries.
- Especially for studies conducted at foreign manufacturing sites, some changes that do not require regulatory procedures in foreign countries require regulatory procedures in Japan, causing delays in the information transmission from foreign manufacturing sites to Japanese marketing authorization holders.

- Foreign manufacturing sites are not familiar with the General Notices of the Japanese Pharmacopoeia, causing the lack of understanding of the intent of test methods by working-level persons.

2.-2 Elements to consider for rationalization of descriptions in the specification column

In view of the current situation of descriptions in approval application forms explained above, introduction of the expression of specification values/acceptance criteria for Purity in %, expression of prepared solutions, etc. (e.g., standard solution and sample solution, etc.) in concentration, and use of bulleted lists or tables to the specification column for the purpose of rationalizing descriptions to reduce administrative and operational procedures for approval documents was examined as follows.

- Analyses used in release tests are currently evaluated in accordance with the Guidelines for Validation of Analytical Procedures (ICH Q2 (R1)) during development. If an appropriate standard operating procedure (hereinafter referred to as "SOP") is maintained and an appropriate technology transfer procedure is followed, the accuracy, precision, and specificity of the analysis at the manufacturing site are considered guaranteeable, without describing the preparation method of reagents, etc. in detail in the approval document.
- With regard to the expression of specification values/acceptance criteria for Purity in % (ICH Q3A (R2)), all other unspecified impurities are usually controlled in terms of %, with 0.10% or a daily intake of 1.0 mg (whichever is lower) used for drugs with the maximum daily dose of being 2 g or less.
- The clarity of acceptance criteria is considered securable by using significant figures appropriately and, if necessary, by describing calculation formulas or calculation methods as adequate.
- With regard to the expression of prepared solutions, etc. in concentration and use of bulleted lists, it targets a limited number of experimenters unlike the test methods applied to JP-listed drugs that target a broad range of relevant persons, suggesting that rationalized descriptions such as those using bulleted lists will not give rise to the confusion given that an SOP is appropriately maintained based on the development data and training and technology transfer are performed.

3. Conclusion

Based on the above examination, it has been concluded that there is no substantial problem in ensuring the quality of test methods if the description method in the specification column in approval application forms/approval documents is changed as follows:

- Expression of specification values/acceptance criteria for Purity using liquid chromatography (HPLC), etc. in %
- Expression of prepared solutions, etc. in the Purity and Assay using HPLC, etc. in concentration
- Use of bulleted lists for analytical procedures in the Purity and Assay using HPLC, etc.

However, local public health institutes and the National Institute of Health Sciences conduct sampling tests as part of quality assurance of drugs as official medicines control laboratories (hereinafter referred to as "OMCL"). Therefore, it should be noted that marketing authorization

holders of relevant drugs need to maintain an appropriate SOP at the testing site and provide the SOP, etc. to the OMCL promptly upon request for sampling tests.

Appendix-1　Description examples

Idea in creating description examples

Regarding rationalized descriptions in approval application forms/approval documents, the description method was examined according to the above policy for the elements described in tests by HPLC, etc. for drugs listed the monographs of the Japanese Pharmacopoeia, and description examples were created. The description examples were examined assuming drugs subject to ICH Q6A and Q6B, but they are also considered applicable to drugs not covered by these guidelines as appropriate.

The description examples were created considering the following points:

- Contributing to the reduction of regulatory procedures for change control
  - Allowing the expression of prepared solutions, etc. in concentration
  - Being concise and avoiding misleading language
- Being error-free in terms of analytical chemistry
  - Describing accurate and exact operation as necessary under "Precautions" if the analytical operation involves an accurate or exact weighing or pipetting procedure
- Being able to make release decisions unambiguously
- Not materially changing the current acceptance criteria
- Not creating new regulations
- Using descriptions following the General Notices, General Rules for Preparations, and General Tests of the Japanese Pharmacopoeia as appropriate
- Not forcing large variations in the review or inspection resources and schemes
- Clarifying the description elements of the specification

In addition,

- Being internationally consistent
- Being applicable to approval application forms for not only new drugs but also generic drugs

In the description examples, the following headings are set with the terms used in ICH Q6A and Q6B and the Japanese Pharmacopoeia as much as possible to clarify the description elements of the specification:

- Test method
- Specification value/acceptance criterion
- Analytical procedure
- Operating conditions
- System suitability
- Precautions

Sampling and pretreatment should be described according to the type of the test and the characteristics of the analyte. In the case of quantitative testing of tablets, it is necessary to describe the number of samples and pretreatment (whether it is weighed or dissolved after being powdered).

In the preparation of a solution, there may be two cases: a case where a solution is prepared by adding a certain amount of water (or solvent), and a case where a solution is prepared by fill-up so that the total volume becomes constant (fill-up method). When the concentration is expressed in XX

g/L (mol/L), it usually implies that the solution is prepared by the fill-up method, but it is allowed not to distinguish between the two cases in the descriptions in approval documents. The specific preparation method of the solution should be described in the SOP. If the difference in the preparation method of the solution affects the analysis results, it is also necessary to provide an appropriate description in the approval application form so that the operating method is identifiable.

Description methods different from those in the Japanese Pharmacopoeia are included in the notes to description examples.

The description examples herein do not cover all cases, but the idea shown in these examples can be applied to other cases, including those in the reagent and test solution column. In the preparation of approval application forms/approval documents, it goes without saying that scientific judgment is required on a case-by-case basis to ensure the quality of the test method.

1) Description example of Purity for a chemically synthesized drug substance (when the sample solution is diluted and used as the standard solution)

A description example created using ofloxacin as a model compound is presented below.

Example of rationalized description

(2) Related substances
Test method: Liquid chromatography, ultraviolet absorption photometer, peak area
Specification value/acceptance criterion: Not more than 0.20% for individual related substances, not more than 0.50% for total related substances

Individual related substances (%)
= 0.5 × individual related substances from the sample solution/ofloxacin from the standard solution

Total related substances (%) = 0.5 × total related substances from the sample solution/ofloxacin from the standard solution

Analytical procedure

Sample solution: Dissolve ofloxacin in the diluent (0.2 mg/mL).
Standard solution: Dilute the sample solution 200 times with the diluent.
Diluent: A mixture of water and acetonitrile (6:1).
Injection volume: 10 μL.
Operating conditions
Wavelength: 294 nm.
Column: Octadecylsilanized silica gel (5 μm), 4.6 mm in inside diameter, 25 cm in length.
Column temperature: About 45°C.
Mobile phase: A mixture of a solution of sodium perchlorate monohydrate (5.4 g/L) and ammonium acetate (3.1 g/L) adjusted to pH2.2 with phosphoric acid and acetonitrile (65:12).
Flow rate: The retention time of ofloxacin is about 20 minutes.
Time span of measurement: About 1.8 times as long as the retention time of ofloxacin beginning after the solvent peak.

System suitability

Test for required detectability: Ofloxacin from the standard solution diluted 20 times with the diluent is 4 to 6% of that from the standard solution.

System performance: Ofloxacin demethyl substance and ofloxacin are eluted in this order from the solution of ofloxacin (1 μg/mL) and ofloxacin demethyl substance (0.5 μg/mL) in the diluent, with the resolution being not less than 2.5.

System repeatability: The relative standard deviation of ofloxacin from the standard solution (6 replicates) is not more than 2.0%.

Precautions: Conduct this procedure without exposure to light and, if necessary, operate accurately and exactly.

Notes

- Specification values/acceptance criteria should be described so that the calculation method can be understood.
- If "peak area" is indicated in the test method, the description may be omitted in other places where indication of peak area is obvious.
- The concentration of the sample solution is expressed as the median value. If the concentration range of the solution to be prepared is particularly important, the concentration range of the solution to be prepared should be specified under "Precautions."
- There are two cases for preparing "a mixture of a solution of sodium perchlorate monohydrate (5.4 g/L) and ammonium acetate (3.1 g/L) adjusted to pH 2.2 with phosphoric acid and acetonitrile (65:12)": a case of "preparation by adding a certain amount of water to the salt, and mixing the total amount of the pH-adjusted solution with the solvent (A)" and a case of "preparation by mixing a solution prepared by fill-up finally with the solvent (B)," but this is accepted as a rationalized description that encompasses the two cases because the differences in the actual concentration, pH, and mixing ratio are presumed to be within the range of rounding. However, the details of which method is used for preparation should be described in the SOP. In addition, if detailed operation or exact concentration, pH, and mixing ratio are required to ensure assay performance, the description in the approval application form should be kept as before (A or B below).

  A: Dissolve 7.0 g of sodium perchlorate monohydrate and 4.0 g of ammonium acetate in 1300 mL of water, adjust the pH to 2.2 with phosphoric acid, and add 240 mL of acetonitrile. (Ofloxacin JP)

  B: Dissolve 7.0 g of sodium perchlorate monohydrate and 4.0 g of ammonium acetate in XX mL of water, adjust the pH to 2.2 with phosphoric acid, add water to make 1300 mL, and add 240 mL of acetonitrile.
- "Ofloxacin from the standard solution diluted 20 times with the diluent is 4 to 6% of that from the standard solution" in the test for required detectability is an example of rationalized description for the operation "Pipet 1 mL of the standard solution, add the diluent to make exactly 20 mL. Confirm that the peak area of ofloxacin obtained with this solution is equivalent to 4 to 6% of that with the standard solution."

Reference: Description example in the JP (extracted from Purity for Ofloxacin, JP)

(2) Related substances Conduct this procedure without exposure to light. Dissolve 10 mg of Ofloxacin in 50 mL of a mixture of water and acetonitrile (6:1), and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add a mixture of water and acetonitrile (6:1) to make exactly 20 mL. Pipet 1 mL of this solution, add a mixture of water and acetonitrile (6:1) to make exactly 10 mL, and use this solution as the standard solution. Perform the test with exactly 10 µL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine each peak area by the automatic integration method: the area of the peak other than ofloxacin obtained from the sample solution is not larger than 2/5 times the peak area of ofloxacin from the standard solution, and the total area of the peaks is not larger than the peak area from the standard solution.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 294 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 µm in particle diameter).

Column temperature: A constant temperature of about 45°C.

Mobile phase: Dissolve 7.0 g of sodium perchlorate monohydrate and 4.0 g of ammonium acetate in 1300 mL of water, adjust the pH to 2.2 with phosphoric acid, and add 240 mL of acetonitrile.

Flow rate: Adjust so that the retention time of ofloxacin is about 20 minutes.

Time span of measurement: About 1.8 times as long as the retention time of ofloxacin, beginning after the solvent peak.

System suitability

Test for required detectability: Pipet 1 mL of the standard solution, and add a mixture of water and acetonitrile (6:1) to make exactly 20 mL. Confirm that the peak area of ofloxacin obtained with 10 µL of this solution is equivalent to 4 to 6% of that with the standard solution.

System performance: To 0.5 mL of the sample solution add 1 mL of a solution of ofloxacin demethyl substance in a mixture of water and acetonitrile (6:1) (1 in 20,000) and a mixture of water and acetonitrile (6:1) to make 100 mL. When the procedure is run with 10 µL of this solution under the above operating conditions, ofloxacin demethyl substance and ofloxacin are eluted in this order with the resolution between these peaks being not less than 2.5.

System repeatability: When the test is repeated 6 times with 10 µL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of ofloxacin is not more than 2.0%.

2) Description example of Purity for a chemically synthesized drug substance (when the standard solution is prepared from the reference material of a related substance)

A description example created using amphotericin B as a model compound is presented below.

Example of rationalized description

Purity Amphotericin A
Test method: Ultraviolet-visible spectrophotometry, absorbance
Specification value/acceptance criterion: Not more than 5% (for injections) for amphotericin A, not more than 15% (not for injections) for amphotericin A (%)
$= [M_S \times \{(A_{Sa1} \times A_{T2}) - (A_{Sa2} \times A_{T1})\} \times 25] / [M_T \times \{(A_{Sa1} \times A_{Sb2}) - (A_{Sa2} \times A_{Sb1})\}]$
M_S: Amount (mg) of Nystatin RS taken
M_T: Amount (mg) of Amphotericin A taken
A_{Sa1}: Standard solution (1), 282 nm A_{Sb1}: Standard solution (2), 282 nm A_{Sa2}: Standard solution (1), 304 nm
A_{Sb2}: Standard solution (2), 304 nm A_{T1}: Sample solution, 282 nm A_{T2}: Sample solution, 304 nm
Analytical procedure
Sample solution: Dissolve Amphotericin B in dimethylsulfoxide (about 5 mg/mL), and dilute with methanol (about 80 μg/mL).
Standard solution (1): Dissolve Amphotericin B RS in dimethylsulfoxide (about 5 mg/mL), and dilute with methanol (about 80 μg/mL).
Standard solution (2): Dissolve Nystatin RS in dimethylsulfoxide of a volume 4 times as much as that used to prepare the sample solution (about 0.5 mg/mL), and dilute with methanol (about 8 μg/mL).
Blank solution: Proceed in the same manner as the sample solution.
Operating conditions
Wavelength: 282 nm, 304 nm. Control: Blank solution.
Precautions: Operate accurately and exactly as necessary.

Notes

- If the molecular and structural formulae of the related substance are described, they should be described at the end of the test method.
- Again for "Dissolve Amphotericin B RS in dimethylsulfoxide (about 5 mg/mL)," there are cases of "adding a certain amount of dimethylsulfoxide to Amphotericin B RS to dissolve (A)" and "adding dimethylsulfoxide to Amphotericin B RS to dissolve, and filling up to a certain volume (B)," but these two cases are not distinguished. The specific preparation method of the solution should be described in the SOP. If the difference in the preparation method of the solution affects the analysis results, it is necessary to provide an appropriate description so that the operation method is identifiable.
- The calculation formula has not been changed from Purity for Amphotericin B, JP. However, the calculation formula may be changed as shown below because the sample solution and standard solution are now expressed in concentration. In this case, the volume of dimethylsulfoxide used to dissolve Nystatin RS in the standard solution (2) does not need to be 4 times as much as that used to prepare the sample solution.
  Amphotericin A (%)
  $= \{(A_{Sa1} \times A_{T2}) - (A_{Sa2} \times A_{T1})\} / \{(A_{Sa1} \times A_{Sb2}) - (A_{Sa2} \times A_{Sb1})\} \times C_S / C_T \times 100$
  A_{Sa1}: Standard solution (1), 282 nm A_{Sb1}: Standard solution (2), 282 nm A_{Sa2}: Standard solution (1), 304 nm A_{Sb2}: Standard solution (2), 304 nm A_{T1}: Sample solution, 282 nm A_{T2}:

Sample solution, 304 nm C_S: Nystatin concentration (μg/mL) in the standard solution (2) C_T: Amphotericin B concentration (μg/mL) in the sample solution

Reference: Description example in the JP (extracted from Purity for Amphotericin B, JP)

Purity Amphotericin A — Weigh accurately about 50 mg each of Amphotericin B and Amphotericin B RS, add exactly 10 mL each of dimethylsulfoxide to dissolve, and add methanol to make exactly 50 mL. Pipet 4 mL each of these solutions, add methanol to make exactly 50 mL, and use these solutions as the sample solution and standard solution (1), respectively. Separately, weigh accurately about 20 mg of Nystatin RS, add exactly 40 mL of dimethylsulfoxide to dissolve, then add methanol to make exactly 200 mL. Pipet 4 mL of this solution, add methanol to make exactly 50 mL, and use this solution as the standard solution (2). Perform the test with these solutions as directed under Ultraviolet-visible Spectrophotometry <*2.24*> using a solution obtained in the same manner as the sample solution as the blank, and determine the absorbances at 282 nm and at 304 nm. Calculate the amount of amphotericin A by the following equation: not more than 5% for Amphotericin B used for injections, and not more than 15% for Amphotericin B not used for injections.

Amount (%) of amphotericin A

$= [M_S \times \{(A_{Sa1} \times A_{T2}) - (A_{Sa2} \times A_{T1})\} \times 25] / [M_T \times \{(A_{Sa1} \times A_{Sb2}) - (A_{Sa2} \times A_{Sb1})\}]$

M_S: Amount (mg) of Nystatin RS taken

M_T: Amount (mg) of Amphotericin B taken

A_{Sa1}: Absorbance at 282 nm of the standard solution (1)

A_{Sa1}: Absorbance at 282 nm of the standard solution (2)

A_{Sa2}: Absorbance at 304 nm of the standard solution (1)

A_{Sb2}: Absorbance at 304 nm of the standard solution (2)

A_{T1}: Absorbance at 282 nm of the sample solution

A_{T2}: Absorbance at 304 nm of the sample solution

3) Description example of Assay for a chemically synthesized drug product

A description example created using estriol tablets as a model compound is presented below.

Example of rationalized description

Assay

Test method: Liquid chromatography, ultraviolet absorption photometer, peak area

Estriol (mg) = $M_S \times Q_T / Q_S \times 1/25$

M_S: Amount (mg) of Estriol RS taken

Q_T: Ratio of estriol from the sample solution to the internal standard

Q_S: Ratio of estriol from the standard solution to the internal standard

Analytical procedure

Sample solution: Powder not less than 20 tablets. Disperse the powder with water (about 0.2 mg/mL as the theoretical concentration of estriol), perform 3 solid-liquid separations using 5 volumes of methanol, and collect the supernatant liquid. Add the internal standard solution and dilute with methanol (about 10 μg/mL of estriol).

Standard solution: Dissolve Estriol RS in methanol, add the internal standard solution, and dilute with methanol to make 25 times as much as the sample solution (about 10 μg/mL of estriol).

Add the internal standard solution so that it is the same as the amount of the internal standard relative to the theoretical amount of estriol in the sample solution.

Internal standard solution: Dissolve methyl benzoate for estriol test in methanol (0.2 mg/mL).

Injection volume: 20 μL.

Operating conditions: Proceed as directed in the Assay under Estriol.

System suitability: Proceed as directed in the Assay under Estriol.

Precautions

Operate accurately and exactly as necessary.

Estriol RS: Dry at 105°C for 3 hours.

Notes

- If assessment is made after conversion in the specification value/acceptance criterion, it should be described as "X.X to X.X% (on the anhydrous basis)," "not less than X.X (on the dried basis)," etc.
- "Drying conditions for reference materials" should be described under "Precautions."
- "Make 25 times as much as ..." for the standard solution is a description including preparation of a 25-times volume as calculated, in a dilution procedure such as "Pipet 4 mL of this solution, ... add methanol to make 100 mL, and use this solution as the standard solution" in the Assay for Estriol Tablets, JP.
- The calculation formula has not been changed from the Assay for Estriol Tablets, JP. However, the calculation formula may be changed as shown below because the sample solution and standard solution are now expressed in concentration. In this case, the volume of the standard solution does not need to be 25 times the volume of the sample solution. Content (%) of estriol with respect to the labeled amount

  $= Q_T / Q_S \times C_S / C_T \times 100$

  Q_T: Ratio of estriol from the sample solution to the internal standard

  Q_S: Ratio of estriol from the standard solution to the internal standard

  C_T: Theoretical concentration (μg/mL) of estriol in the sample solution

  C_S: Concentration (μg/mL) of estriol in the standard solution

Reference: Description example in the JP (extracted from Assay for Estriol Tablets, JP)

Assay Weigh accurately and powder not less than 20 Estriol Tablets. Weigh accurately a portion of the powder, equivalent to about 1 mg of estriol ($C_{18}H_{24}O_3$), add exactly 5 mL of water, disperse the fine particles by sonicating, shake with 25 mL of methanol for 10 minutes, centrifuge, and take the supernatant liquid. Add 25 mL of methanol, repeat the above procedure twice, combine the supernatant liquid, add exactly 5 mL of the internal standard solution, then add methanol to make 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 25 mg of Estriol RS, previously dried at 105°C for 3 hours, and dissolve in methanol to make exactly 100 mL. Pipet 4 mL of this solution, add exactly 5 mL of the internal standard solution, then add methanol to make 100 mL, and use this solution as the standard solution. Proceed with 20 μL each of the sample solution and standard solution as directed in the Assay under Estriol.

Amount (mg) of estriol ($C_{18}H_{24}O_3$) = $M_S \times Q_T / Q_S \times 1/25$

MS: Amount (mg) of Estriol RS taken

Internal standard solution — A solution of methyl benzoate for estriol test in methanol (1 in 5000).

Appendix-2 Points to consider when changing the content of the current approval document

- A similar description to the description examples presented in Appendix-1 is also considered possible when changing the description in the current approval document to a reasonable description through regulatory procedures. However, in the case of the limit test for Purity (if evaluated only with the validation characteristics required for the limit test in the validation of analytical procedures), it is not considered appropriate to change the specification value/acceptance criterion to % expression (description example in the case of limit test "Individual related substances: not more than 2/5, individual related substances in the sample solution/ofloxacin in the standard solution").

Notes:

Note 1 Pharmaceutical Marketing Guidance 2016. Supervised by the Society for Regulatory Science of Medical Products. Jiho. October 2016.

Note 2 Nagai Y. Rationalization of specifications (2) from the viewpoint of chemical products (This reference contains contents on pages 1-15 of this report as well as contents of pages 16-25 related to life cycle management currently discussed in ICH Q12).