Provisional Translation (as of March 2026)[*]

Administrative Notice
March 12, 2026

To: Appended Parties

Center for Product Evaluation
Pharmaceuticals and Medical Devices Agency

Considerations for Pre-specifying the Change Categories for Manufacturing Process Parameters Identified as Established Conditions for Drug Products (Chemical Products)
(Early Consideration)

We would like to express our sincere gratitude for your understanding and cooperation with the review and other operations of the Pharmaceuticals and Medical Devices Agency (PMDA).

In Japan, based on the "Guideline on Technical and Regulatory Considerations for Pharmaceutical Lifecycle Management" (PSEHB/PED Notification No. 1029-1 and PSEHB/PSD Notification No. 1029-1 dated October 29, 2021; ICH Q12 Guideline), manufacturing process parameters determined to be Established Conditions are required to be described in the manufacturing method section of the marketing application.

The Quality Group for the Chemical Products, Center for Product Evaluation at PMDA has prepared the attached document, which summarizes the basic approach to pre-specifying change categories for process parameters to be described in the application (i.e., partial change approval application or minor change notification), on the premise that Established Conditions for the manufacturing process have been identified in accordance with the concepts described in the ICH Q12 Guideline. We hereby inform you of this for your reference.

Please note that "Early Consideration" is a reference for promoting the practical application of new technologies and the development of innovative pharmaceuticals, even though scientific knowledge and information have not necessarily been sufficiently accumulated at this stage, and that it may change in the future due to newly obtained knowledge and scientific progress.

[*] This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

(Appended Parties)

The Federation of Pharmaceutical Manufacturers' Association of Japan

Japan Pharmaceutical Manufacturers Association

Pharmaceutical Research and Manufacturers of America

European Federation of Pharmaceutical Industries and Associations

Considerations for Pre-specifying the Change Categories for Manufacturing Process Parameters Identified as Established Conditions for Drug Products (Chemical Products) (Early Consideration)

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1. Introduction

In the "Guideline on Technical and Regulatory Considerations for Pharmaceutical Lifecycle Management" (PSEHB/PED Notification No. 1029-1 and PSEHB/PSD Notification No. 1029-1 dated October 29, 2021; ICH Q12 Guideline), Established Conditions for manufacturing and control (ECs) are defined as "legally binding information considered necessary to assure product quality," and any change to ECs after approval requires regulatory procedures.

In the Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters in the ICH Q12 Guideline, process parameters that are Critical Process Parameters (CPPs) and other process parameters where an impact on product quality cannot be reasonably excluded are determined to be ECs. In Japan, process parameters determined to be ECs must be described in the Manufacturing Method section of the marketing application for pharmaceuticals (hereinafter referred to as "the application").

Regarding the information described in the application, discussions are currently underway, taking international harmonization into account, including the introduction of moderate change categories and annual reporting. This document is prepared independently of those discussions and, on the premise that ECs for manufacturing processes have been identified based on the concepts presented in the ICH Q12 Guideline, focuses on drug products (limited to chemical products) and presents basic considerations for the prior designation of change categories for changes in process parameters (items requiring a partial change approval application or items subject to minor change notification). This document presents considerations focusing mainly on the relationship between the Proven Acceptable Range (PAR) and the Normal Operating Range (NOR), which is the range of normal operation/procedures specified in product standard specifications and similar documents. Even in cases where consideration has not been conducted based on the concepts presented in the ICH Q12 Guideline, the considerations focusing on the relationship between PAR and NOR described in this document may be referred to as appropriate.

Discussions on whether process parameters should be described as target value/set value in the application are outside the scope of this document. It should also be noted that cases in which the evaluation of PAR is insufficient (for example, where only a single plot under a specific condition is presented rather than an evaluation of PAR as a range) are not included within the scope of this document.

The considerations presented in this document represent one example and do not preclude other science-

and risk-based approaches. In addition, this document has been prepared and reviewed based on scientific knowledge and related information available as of March 2026, and its content may change considering newly obtained knowledge or scientific advances. It should also be noted that this document does not necessarily guarantee the acceptability of the content described in a marketing application.

2. Basic Considerations for Pre-specifying the Change Categories for Process Parameters Identified as ECs

When change categories for process parameters identified as ECs are designated in advance, it is necessary to consider the potential risk to product quality when the parameter is changed, and to determine the range or value of the process parameter described in the Manufacturing Method section of the application, as well as the change category.

In the above risk assessment, the following factors may be considered: the risk associated with the manufacturing process itself (comprehensively evaluated in terms of the degree of process understanding and robustness, characteristics of manufacturing equipment, difficulty of control, etc.), PAR, NOR, and the edge of failure (the boundary beyond which relevant quality attributes can no longer meet the acceptable criteria).

Whether a process parameter is a CPP and its relationship with the edge of failure can generally be summarized as follows.

- When the parameter is a CPP: Since variation of the process parameter affects the Critical Quality Attribute (CQA), it is reasonable to consider that the edge of failure exists at the limits of the PAR or relatively close to them (see Sections 2(1) and (2)).
- When the parameter is not a CPP: Although the possibility that variation of the process parameter may affect product quality cannot be excluded, the impact is limited, and the edge of failure is considered to be sufficiently distant from the PAR or practically nonexistent (see Section 2(3)).

The determination of change categories is fundamentally based on potential risk assessment (severity of harm × probability of occurrence of harm) in accordance with the ICH Q9 Guideline[1)]. Therefore, even when the NOR is set sufficiently within the PAR, if the severity of harm resulting from a failure in the process is extremely high (for example, process parameters affecting CQAs related to sterility or viral inactivation), it is appropriate to conservatively designate such changes as items requiring a partial change approval application.

(1) When the Edge of Failure for a Process Parameter Is the Limit of the PAR

PAR is generally identified, for a single process parameter, as the range within which acceptable quality meeting the relevant specifications can be obtained when operated within that range while other parameters are kept constant[2)], and in some cases the edge of failure corresponds to the limits of the PAR. In such cases, deviation from the PAR is not acceptable. Accordingly, with respect to the description of the process parameter in the Manufacturing Method section of the application, the following approaches may be

considered depending on its relationship with the PAR. Whether PAR itself or a range or value within PAR (hereinafter referred to as "range (value)") should be described should be determined on a case-by-case basis, taking actual manufacturing control into account.

Where significant interactions exist among multiple process parameters, determining PAR independently for each parameter may not necessarily be appropriate from the perspective of quality assurance. In such cases, the following approaches should be considered.

- Explain, based on multivariate analysis such as Design of Experiments (DoE), that the PAR setting is appropriate even within the allowable variation of other process parameters.
- If the impact of interactions is significant and it is difficult to determine PAR based on the range of a single parameter, consider describing control by multivariate approaches (a model or design space).

Where process parameters are described in the application as a model or design space, the appropriateness of the change category will be determined on a case-by-case basis according to the level of risk associated with changes to the model, while applying the basic concepts presented in this document. In examining the level of risk associated with changes to the model, Section 5.1 of the "ICH Quality Implementation Working Group Points to Consider (R2): ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation" (Document date December 6, 2011) may also be referenced.

1) PAR described as an item requiring a partial change approval application

- When PAR is described in the application, it must be designated as an item requiring a partial change approval application (Figure 1). At the time of application, it is necessary to explain in CTD Modules 2.3 and 3 that deviation from PAR will not occur during normal operation, taking NOR and the following points into account.
  - The impact of variation in the process parameter considering the performance and operation of the equipment used.
  - The impact of variation in other process parameters that may affect the CQAs of the drug substance and drug product.

2) A range (value) within and close to the PAR described as an item requiring a partial change approval application

- Even when a range (value) within PAR is described in the application, if sufficient margin from the PAR limits cannot be secured based on the above points (i.e., the range is close to the PAR limits), it must be designated as an item requiring a partial change approval application (Figure 1).

3) A range (value) sufficiently within the PAR described as an item subject to minor change notification

- When a range (value) within PAR is described in the application, and sufficient margin from the PAR

limits can be secured even considering the performance and operational variability of the equipment to be used as described in 1) above, the range (value) may be designated as an item subject to minor change notification (Figure 1). However, at the time of application, the appropriateness of designating the item as subject to minor change notification must be described and justified in CTD Modules 2.3 and 3, or CTD Module 1.13, based on the results of the studies related to PAR, the range (value) of the process parameter described in the application, and the performance and operational variability of the equipment used.

- When explaining the appropriateness of designating the item as subject to minor change notification, it is desirable not to rely solely on qualitative statements such as "sufficiently controllable by the equipment used," but to present objective evidence demonstrating scientific validity. Such objective evidence may include the results of process validation, process capability indices (Cp/Cpk) based on manufacturing experience using the actual equipment, and the range of variability derived from equipment calibration and validation results. These data may be used to explain that actual variation in the process parameter remains sufficiently within the limits of the PAR.

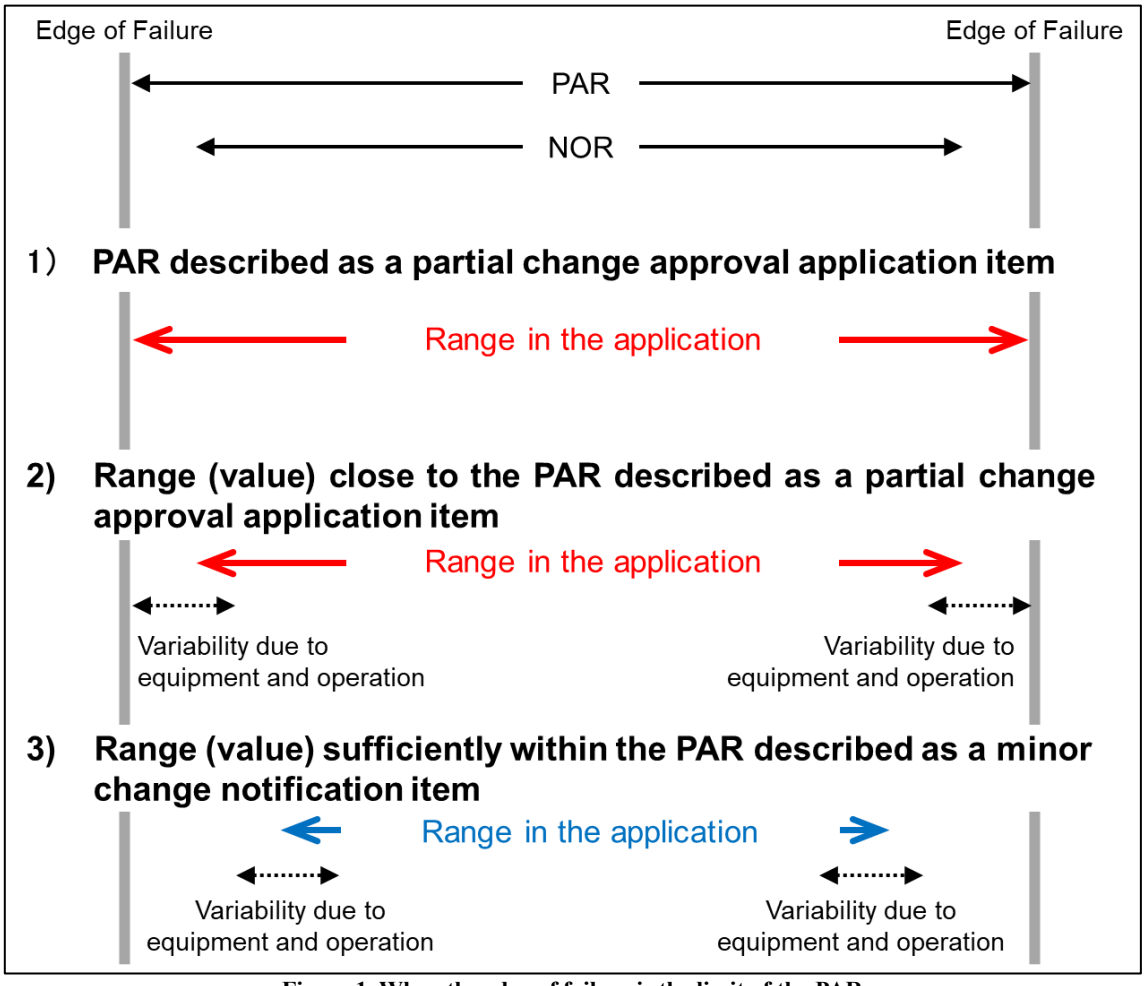

Figure 1. When the edge of failure is the limit of the PAR

(2) When the Edge of Failure Is Not Identified, and the Parameter Is a CPP

CPP is a process parameter whose variability has an impact on CQAs and therefore should be monitored or controlled to ensure the process produces the desired quality[2]. Even when the edge of failure has not been identified within the range evaluated for the impact of variation of the process parameter on CQAs, it is reasonable to consider that the edge of failure exists relatively close to or just outside the PAR limits. Therefore, since the possibility that variation of the process parameter outside the PAR may affect CQAs cannot be excluded, deviation from PAR is not acceptable in this case as well. Accordingly, the process parameter must be described in the Manufacturing Method section of the application based on the same concept as described in (1) above (Figure 2).

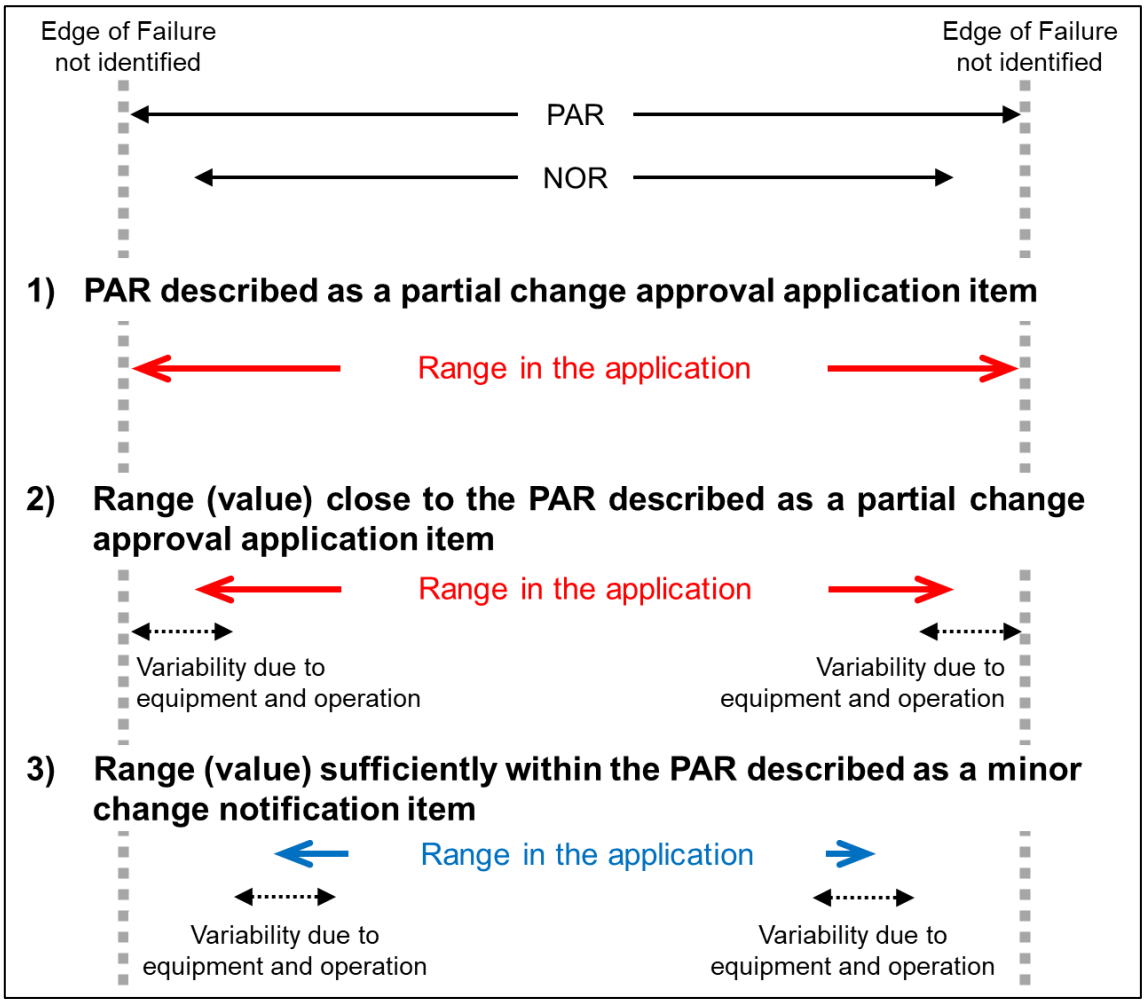

Figure 2. When the edge of failure is not identified, and the parameter is a CPP

(3) When the Edge of Failure Is Not Identified, and the Parameter Is Not a CPP, but the Possibility of Affecting Product Quality Cannot Be Reasonably Excluded

When the process parameter is an EC other than a CPP and the edge of failure has not been identified, PAR or a range (value) within PAR may be described in the Manufacturing Method section of the application as an item subject to minor change notification.

The appropriateness of determining that the process parameter is not a CPP and describing it as an item subject to minor change notification must be explained in CTD Modules 2.3 and 3, or CTD Module 1.13, taking into account the impact of the parameter on CQAs and the results of studies related to PAR.

3. Re-evaluation of Change Categories in Product Lifecycle Management

The change categories for process parameters established after approval are not fixed and should be continuously re-evaluated in the lifecycle management of the product. For example, the initially assumed margin relative to the PAR limits or the risk profile of the manufacturing process may change due to the addition of manufacturing sites, changes in manufacturing equipment, or the accumulation of manufacturing experience over a long period of time. Even if a parameter was initially designated as an item subject to minor change notification at the time of the initial approval, if sufficient margin from the limits of the PAR can no longer be secured under a new manufacturing environment (corresponding to case 2) in Figures 1 and 2), it should be noted that the change category and the parameter range (value) should be appropriately reviewed through change control procedures.

4. References

1） Revision of the Guideline on Quality Risk Management (PSEHB/PED Notification No. 0831-1 and PSEHB/PSD Notification No. 0831-2, dated August 31, 2023; ICH Q9 Guideline)

2） Revision of the Guideline on Pharmaceutical Development (PFSB/ELD Notification No. 0628-1, dated June 28, 2010; ICH Q8 Guideline)