Provisional Translation (as of March 2025)*

Administrative Notice

January 16, 2025

To : Appended Parties

Center for Product Evaluation

Pharmaceuticals and Medical Devices Agency

Example of Documents on Assessment and Control of DNA Reactive (Mutagenic) Impurities attached to Clinical trial Notification

(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).

Assessment and control of DNA reactive (mutagenic) impurities are required based on the "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk"(PSB/PED Notification No. 0214-1 dated February 14, 2024, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)(ICH M7 guideline) and the "Revision of Questions and Answers (Q&A) regarding the Notification of Clinical Trial Plans and Implementation of Clinical Trials for Drugs" (Administrative Notice of the Pharmaceutical Evaluation Division dated August 31, 2022, by the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare), and the contents of the evaluation and control approach are required to be submitted as attachments of clinical trial notifications.

The Quality Group for the Chemical Products, Center for Product Evaluation at PMDA has compiled typical examples of documentation on assessment and control approaches of DNA reactive (mutagenic) impurities attached to clinical trial notifications. We hereby inform you of its availability.

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.

(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 Association

Japan Medical Association

Japan Hospital Association

All Japan Hospital Association

Japanese Society of Hospital Pharmacists

Japan Pharmaceutical Association

Japan CRO Association

Academic Research Organization

Japan Society of Clinical Trials and Research

The Japanese Society of Clinical Pharmacology and Therapeutics

Pharmaceutical Affairs Divisions, Prefectural Health Departments (Bureaus)

Example of Documents on Assessment and Control of DNA Reactive (Mutagenic) Impurities Attached to Clinical Trial Notification (Early Consideration)

January 16, 2025

Center for Product Evaluation
Pharmaceuticals and Medical Devices Agency

I. Background

Assessment and control of DNA reactive (mutagenic) impurities are required based on the "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk"(PSB/PED Notification No. 0214-1 dated February 14, 2024, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)(ICH M7 guideline) and the "Revision of Questions and Answers (Q&A) regarding the Notification of Clinical Trial Plans and Implementation of Clinical Trials for Drugs" (Administrative Notice of the Pharmaceutical Evaluation Division dated August 31, 2022, by the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare), and the contents of the evaluation and control approach are required to be submitted as attachments of clinical trial notifications. In the investigation of clinical trial notifications conducted by the Pharmaceuticals and Medical Devices Agency (PMDA), the evaluation of mutagenic impurities and their control were assessed. However, there were some cases in which investigations required time due to insufficient data and description. Therefore, we decided to compile and publish typical examples based on the operational experiments of the ICH M7 guideline to make investigations more efficient and conduct clinical trials smoothly.

This document provides typical examples of how to prepare materials related to the evaluation and control approach of mutagenic impurities attached to clinical trial notifications. It does not attempt to introduce new regulations or explain how to evaluate and control mutagenic impurities. If the information submitted is sufficient, it is possible to submit documents prepared in different styles or formats. Since the appropriateness of the control approach of mutagenic impurities is determined according to the status of individual products, and additional data may be required during the process of notification assessment, the utilization of consultation by PMDA should be considered if there is any uncertainty regarding the control approach of mutagenic impurities or the content of risk assessment. In addition, this document was prepared taking into account the standard description at the stage of the clinical trial notification, and it does not guarantee the acceptability of the control approach, etc. in the marketing authorization application.

Please note that this document was prepared based on scientific knowledge and findings available as of January, 2025, and that it may change in the future due to newly obtained knowledge and scientific progress.

II. Structure of This Document

For products under clinical development, ICH M7 guideline differs in the content of materials to be attached to clinical trial notifications in the early phase of clinical development (Phase I and IIa studies) and the late phase (Phase IIb and III studies). Furthermore, Phase I studies differ in impurities that should be investigated on the basis of the treatment duration. Therefore, this document presents the following examples.

1. Phase 1 clinical trials for dosing up to 14 days
   （1） When none of the Class 1 or Class 2 impurities, nor impurities in the cohort of concern, are present
   （2） When any of the Class 1, Class 2 impurities, or impurities in the cohort of concern, are present

2. Phase 1 clinical trials greater than 14 days and for Phase 2a clinical trials
   （1） When none of the Class 1, Class 2, or Class 3 impurities, nor impurities in the cohort of concern, are present
   （2） When any of the Class 1, Class 2, or Class 3 impurities, or impurities in the cohort of concern, are present

3. Phase 2b and Phase 3 clinical trials
   （1） When none of the Class 1, Class 2 or Class 3 impurities, nor impurities in the cohort of concern are present
   （2） When any of the Class 1, Class 2 or Class 3 impurities, or impurities in the cohort of concern are present

4. Cases where attachments can be omitted
   （1） In the second and subsequent notifications, when the manufacturing method has not changed since the previous notification, and the dosage, administration and duration of administration have not exceeded those in the conducted clinical trial (except for the case of transitioning from the early development phase (Section 1. and 2.) to the late development phase (Section 3.))
   （2） When using an approved product as an investigational product

1. Phase 1 clinical trials for dosing up to 14 days

（1）When none of the Class 1 or Class 2 impurities, nor impurities in the cohort of concern, are present

(Example of description)

1. Purpose

Based on the ICH M7 Guideline, the hazard assessment and control approach for DNA reactive (mutagenic) impurities that are likely to arise during the manufacturing and storage of the drug substance and the drug product are summarized below.

Since the planned clinical trial is a phase 1 clinical trial for dosing up to 14 days, the assessment was conducted focusing on the Class 1 impurities, Class 2 impurities and impurities in the cohort of concern.

2. Results of hazard assessment of impurities

Regarding impurities arising in the manufacturing of the drug substance and the drug product, toxicity information was investigated by searching the database and literature on impurities derived from raw materials, reagents and intermediates used in the manufacturing process and impurities derived from the manufacturing process, and hazard assessment was conducted based on the obtained information. As a consequence, none of the impurities included in Class 1 impurities, Class 2 impurities or impurities in the cohort of concern were identified.

Degradation products newly formed in the storage of the drug substance and the drug product were evaluated based on the results of stability studies performed with the drug substance and the drug product manufactured by the same manufacturing process as the investigational drug substance and product. As a consequence, none of the impurities included in Class 1 impurities, Class 2 impurities or impurities in the cohort of concern were identified.

(Checklist)

- ✓ Are impurities likely to arise during the manufacturing and storage of the drug substance and the drug product considered?
- ✓ Are Class 1 impurities, Class 2 impurities, and impurities in the cohort of concern evaluated?
- ✓ Are the risk assessment and control of nitrosamines conducted based on the relevant notifications ("Self-inspection on Risks of Contamination with Nitrosamines in Drugs"(PSEHB/PED Notification No. 1008-1, PSEHB/PSD Notification No. 1008-1, PSEHB/CND Notification No. 1008-1 dated October 8, 2021) etc.)?

（2）When any of the Class 1, Class 2 impurities, or impurities in the cohort of concern, are present

(Example of description)

1. Purpose

Based on the ICH M7 Guideline, the hazard assessment and control approach for DNA reactive (mutagenic) impurities that are likely to arise during the manufacturing and storage of the drug substance and the drug product are summarized below.

Since the planned clinical trial is a phase 1 clinical trial for dosing up to 14 days, the assessment was conducted focusing on the Class 1 impurities, Class 2 impurities and impurities in the cohort of concern.

2. Hazard assessment and control approach for impurities

Regarding impurities arising in the synthesis of the drug substance, toxicity information was investigated by searching the database and literature on impurities derived from raw materials, reagents and intermediates used in the manufacturing process and impurities derived from the manufacturing process, and hazard assessment was conducted based on the obtained information. As a consequence, impurities in the cohort of concern, Class 1 impurities, or Class 2 impurities are listed in Table 2-1. In addition, no newly formed degradation product was detected in the stability studies performed with the drug substance manufactured by the same manufacturing method as the drug substance used for the investigational drug product.

Regarding impurities arising in the manufacturing of the drug product, toxicity information was investigated by searching the database and literature on impurities derived from raw materials, reagents and intermediates used in the manufacturing process and impurities derived from the manufacturing process, and hazard assessment was conducted based on the obtained information. As a consequence, impurities in the cohort of concern, Class 1 impurities or Class 2 impurities are listed in Table 2-1. In addition, no newly formed degradation product was detected in the stability studies performed with the drug product manufactured by the same manufacturing process as the investigational drug product.

Table 2-1. Impurities classified as the cohort of concern, and impurities classified as Class 1 or Class 2

Name and structure of impurities	Origin	ICH M7 Class	Control approach for mutagenic impurities*
Impurity A [Structural formula] ※ Describe the structure of the impurities	By-products	cohort of concern	Apply Option 1, control at or below the acceptable limit (50 ppm) ** in the drug substance.
Impurity B [Structural formula]	By-products	Class 1	Apply Option 1, control at or below the acceptable limit (3,620 ppm) *** in the drug substance.
Impurity C [Structural formula]	Starting material	Class 1	Apply Option 2, control at or below the acceptable limit (240 ppm) **** in the starting materials.

Impurity D [Structural formula]	Starting material	Class 2	Option 3 Since the purge study in the manufacturing process confirms that the impurity is removed to less than the acceptable limit (100 ppm) **** even when added to the starting material in quantities exceeding the control value, it is controlled at or below (1,000 ppm) in the starting material in accordance with Option 3.
Impurity E [Structural formula]	Starting material	Class 2	Option 4 The risk assessment using the estimated purge factor resulted in a negligible risk of remaining above the acceptable limit (100 ppm) **** in the drug substance; therefore, we apply Option 4 in ICH M7 Guideline.

* ICH M7 Guideline-based control methods for impurities

**Calculated from the literature ([Example Reference]).

***Calculated from ICH M7 guidelines.

****Calculated from in-house data ([Example Reference]).

3. Conclusion

The hazard assessment and control approach for DNA reactive (mutagenic) impurities of the investigational product in the planned clinical trial were evaluated. It was concluded all identified impurities can be controlled.

(Checklist)

- ✓ Are impurities likely to arise during the manufacturing and storage of the drug substance and the drug product considered?
- ✓ Are Class 1 impurities, Class 2 impurities, and impurities in the cohort of concern evaluated?
- ✓ Are chemical structures of Class 1 impurities, Class 2 impurities, and impurities in the cohort of concern presented?
- ✓ Have any control plans been described for mutagenic impurities?
- ✓ Are the appropriate acceptable daily intakes selected according to the duration of the clinical trial?
- ✓ Are the risk assessment and control of nitrosamines conducted based on the relevant notifications ("Self-inspection on Risks of Contamination with Nitrosamines in Drugs"(PSEHB/PED Notification No. 1008-1, PSEHB/PSD Notification No. 1008-1, PSEHB/CND Notification No. 1008-1 dated October 8, 2021) etc.)?

2. Phase 1 clinical trials greater than 14 days and for Phase 2a clinical trials

（1） When none of the Class 1, Class 2, or Class 3 impurities, nor impurities in the cohort of concern, are present

(Example of description)

1. Purpose

Based on the ICH M7 Guideline, the hazard assessment and control approach for DNA reactive (mutagenic) impurities that are likely to arise during the manufacturing and storage of the drug substance and the drug product are summarized below.

Since the planned clinical trial is a phase 1 clinical trial greater than 14 days, the assessment was conducted focusing on Class 1 impurities, Class 2 impurities, Class 3 impurities, and impurities in the cohort of concern.

2. Results of hazard assessment of impurities

Regarding impurities arising in the manufacturing of the drug substance and the drug product, toxicity information was investigated by searching the database and literature on impurities derived from raw materials, reagents and intermediates used in the manufacturing process and impurities derived from the manufacturing process, and hazard assessment was conducted based on the obtained information. As a consequence, none of the impurities in Class 1 impurities, Class 2 impurities, Class 3 impurities, or impurities in the cohort of concern were identified.

Degradation products newly formed in the storage of the drug substance and the drug product were evaluated based on the results of stability studies performed with the drug substance and the drug product manufactured by the same manufacturing process as the investigational drug substance and drug product. As a consequence, none of the impurities included in Class 1 impurities, Class 2 impurities, Class 3 impurities, or impurities in the cohort of concern were identified.

(Checklist)

- ✓ Are impurities likely to arise during the manufacturing and storage of the drug substance and drug product considered?
- ✓ Are Class 1 impurities, Class 2 impurities, Class 3 impurities* and impurities in the cohort of concern evaluated?
- ✓ Are the risk assessment and control of nitrosamines conducted based on the relevant notifications ("Self-inspection on Risks of Contamination with Nitrosamines in Drugs" (PSEHB/PED Notification No. 1008-1, PSEHB/PSD Notification No. 1008-1, PSEHB/CND Notification No. 1008-1 dated October 8, 2021) etc.)?

*No comprehensive (Q)SAR is expected at an early development stage (phase 1 clinical trials greater than 14 days and 2a clinical trials).

（2）When any of the Class 1, Class 2, or Class 3 impurities, or impurities in the cohort of concern, are present

(Example of description)

1. Purpose

Based on the ICH M7 Guideline, the hazard assessment and control approach for DNA reactivity (mutagenic) impurities that are likely to arise during the manufacturing and storage of the drug substance and the drug product are summarized below.

Since the planned clinical trial is a phase 1 clinical trial greater than 14 days, the assessment was conducted focusing on Class 1 impurities, Class 2 impurities, Class 3 impurities, and impurities in the cohort of concern.

2. Hazard assessment and control approach for impurities

Regarding impurities arising in the synthesis of the drug substance, toxicity information was investigated by searching the database and literature on impurities derived from raw materials, reagents and intermediates used in the manufacturing method and impurities derived from the manufacturing process, and hazard assessment was conducted based on the obtained information. As a consequence, impurities in the cohort of concern, Class 1 impurities, Class 2 impurities, or Class 3 impurities are listed in Table 2-1. In addition, no newly formed degradation product was detected in the stability studies performed with the drug substance manufactured by the same manufacturing process as the drug substance used for the investigational drug product.

Regarding impurities arising in the manufacturing of the drug product, toxicity information was investigated by searching the database and literature on impurities derived from raw materials, reagents and intermediates used in the manufacturing process and impurities derived from the manufacturing process, and hazard assessment was conducted based on the obtained information. As a consequence, impurities in the cohort of concern, Class 1 impurities, Class 2 impurities, or Class 3 impurities are listed in Table 2-1. In addition, no newly formed degradation product was detected in the stability studies performed with the drug product manufactured by the same manufacturing process as the investigational drug product.

Table 2-1. Impurities classified as the cohort of concern, and impurities classified Class 1, Class 2 or Class 3

Name and structure of impurities	Origin	ICH M7 Class	Control approach for mutagenic impurities*
Impurity A [Structural formula] ※ Describe the structure of the impurities	By-products	Class 2	Apply Option 1, control at or below the acceptable limit (3,620 ppm) ** in the drug substance.
Impurity B [Structural formula]	By-products	Class 3	Apply Option 2, control at or below the acceptable limit (240 ppm) *** in the starting materials.

*ICH M7 Guideline-based control methods for impurities

**Calculated from in-house data([Example Reference])

***Calculated from ICH M7 guidelines.

3. Conclusion

The hazard assessment and control approach for DNA reactive (mutagenic) impurities of the investigational product in the planned clinical trial were evaluated. It was concluded all identified impurities can be controlled.

(Checklist)

- ✓ Are impurities likely to arise during the manufacturing and storage of the drug substance and the drug product considered?
- ✓ Are Class 1 impurities, Class 2 impurities, Class 3 impurities* and impurities in the cohort of concern evaluated?
- ✓ Are chemical structures of Class 1 impurities, Class 2 impurities, Class 3 impurities *, and impurities in the cohort of concern presented?
- ✓ Have any control plans been described for mutagenic impurities?
- ✓ Are the appropriate acceptable daily intakes selected according to the duration of the clinical trial?
- ✓ Are the risk assessment and control of nitrosamines conducted based on the relevant notifications ("Self-inspection on Risks of Contamination with Nitrosamines in Drugs" (PSEHB/PED Notification No. 1008-1, PSEHB/PSD Notification No. 1008-1, PSEHB/CND Notification No. 1008-1 dated October 8, 2021) etc.)?

*No comprehensive (Q)SAR is expected at an early development stage (phase 1 clinical trials greater than 14 days and Phase 2a clinical trials).

3. Phase 2b and Phase 3 clinical trials

（1） When none of the Class 1, Class 2 or Class 3 impurities, nor impurities in the cohort of concern are present

(Example of description)

1. Purpose

Based on the ICH M7 Guideline, the hazard assessment and control approach for DNA reactive (mutagenic) impurities that are likely to arise during the manufacturing and storage of the drug substance and the drug product are summarized below.

Since the planned clinical trial is a Phase 3 clinical trial, Class 1, 2, and 3 impurities, which are actually or potentially existing, and impurities in the cohort of concern were evaluated. A list of impurities assessed by (Q)SAR is also provided.

2. Manufacturing method of investigational products

2.1 Manufacturing process for the drug substance

The manufacturing process flow diagram for the drug substance is shown in Figure 2.1-1.

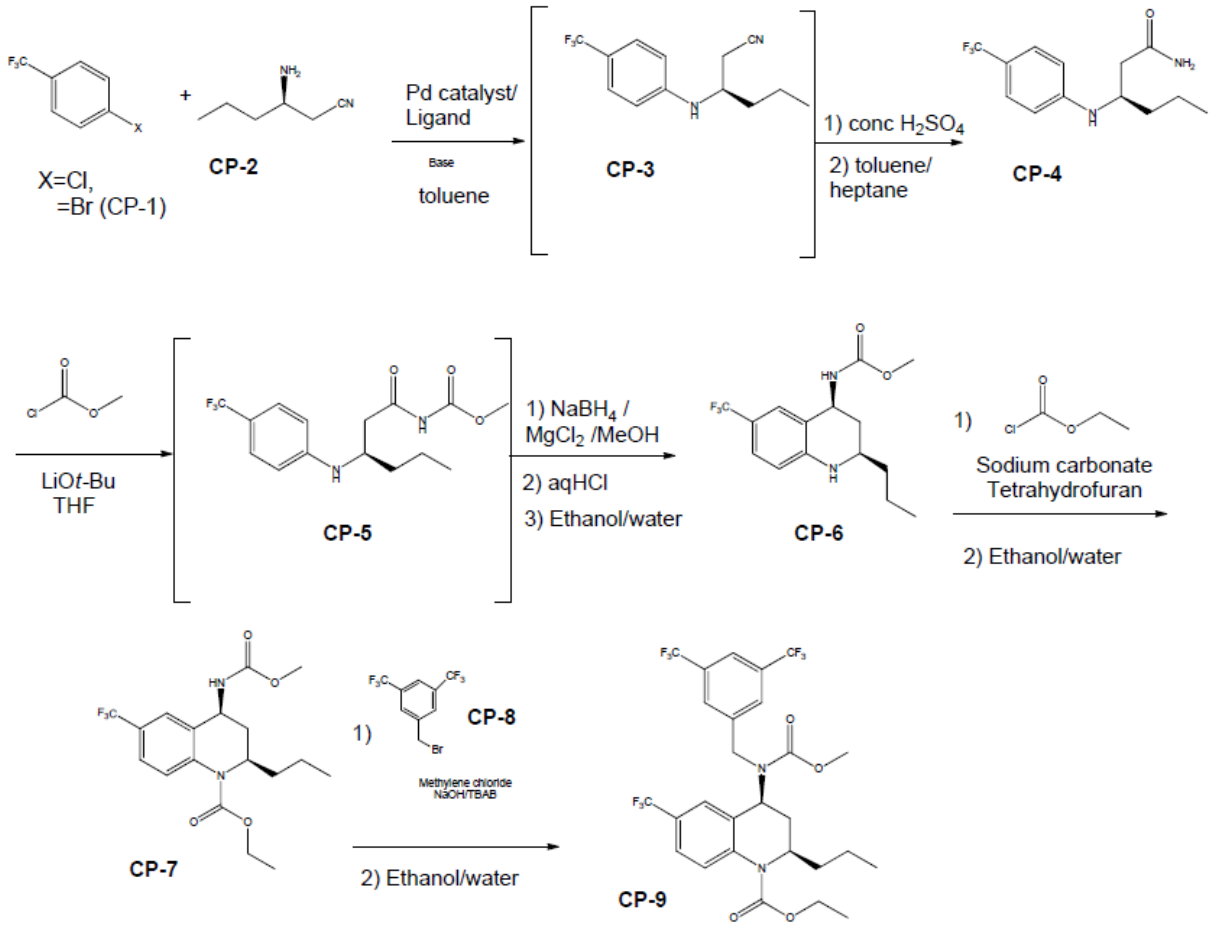

Figure 2.1-1. Synthetic route of the drug substance

(Source: S2 mock-up of the drug substance of sakramil; https://www.nihs.go.jp/drug/section3/H23SakuramillMockJ.pdf)

2.2 Manufacturing method of the drug product

The flow diagram of the manufacturing process of the drug product is shown in Figure 2.2-1.

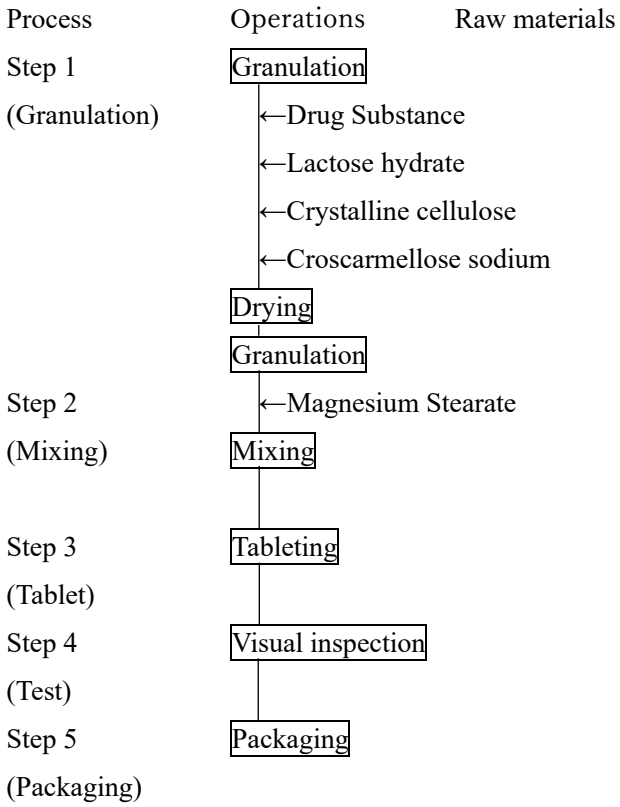

Figure 2.2-1. Manufacturing diagram of the drug product

3. Hazard assessment of impurities

Regarding actual and potential impurities likely to arise in the manufacturing and storage of the drug substance and the drug product, toxicity information was investigated by searching the database and literature, and hazard assessment was conducted based on the obtained information.

For the drug substance, the results of hazard assessment are shown in Table 3-1. There were no impurities that are possibly present in the investigational product classified as Class 1 impurities, Class 2 impurities, or impurities in the cohort of concern. Using bacterial mutagenicity tests, *in vivo* tests and (Q)SAR that predicts the outcome of bacterial mutagenicity tests as a computerized toxicological assessment, impurities were classified into Class 3, Class 4 or Class 5 impurities. As a result, none of them are classified as Class 3 impurities. In addition, no newly formed degradation product was detected in the stability studies performed with the drug substance manufactured by the same manufacturing process as the drug substance used for the investigational drug product.

For the drug product, the identified impurities are derived from the manufacturing process of the drug substance and are appropriately controlled by establishing control approach and acceptance criteria based on acceptance limits for the drug substance. In addition, as a result of the stability studies performed with the drug product manufactured by the same manufacturing process as the investigational drug, no degradation product was found. Based on the above, it was concluded that no impurities are subject to ICH M7 Guideline in the drug product.

Potential impurities that may increase in the future during storage will be additionally assessed by the time of marketing authorization application.

Table 3-1. Results of assessment of mutagenicity of impurities and management of mutagenic impurities

Name and structure of impurities	Origin	(Q)SAR System 1*	(Q)SAR System 2 **	Results of mutagenicity tests using bacteria	ICH M7 Class	Control approach for mutagenic impurities ***
Impurity A [Structural formula] ※ Describe the structure of the impurities	Raw materials	Inactive	Inconclusive	N/A	Class 4	N/A
Impurity B [Structural formula]	Reagents	Inactive	Negative	N/A	Class 5	N/A
Impurity C [Structural formula]	Raw materials	Plausible	Positive	Negative	Class 5	N/A

N/A: Not applicable

* Software: [Example Software Name] version 5.0.1(Expert rule-based)

** Software: [Example Software Name] version 1.3.0.0(Statistical-based)

***ICH M7 Guideline-based control methods for impurities

4. Control approach and measurement of impurities

4.1 Class 1, Class 2 or Class 3 impurities

As a result of hazard assessment, no impurities were classified as Class 1, Class 2, or Class 3.

4.2 Class 4 or Class 5 impurities

As a result of hazard assessment, Impurity A, Impurity B and Impurity C were identified as Class 4 or Class 5 impurities. Since Class 4 and Class 5 impurities are treated as non-mutagenic impurities, control of the impurities is considered unnecessary.

5. Nitrosamines

Nitrosamines were evaluated with reference to "Self-inspection on Risks of Contamination with Nitrosamines in Drugs"(PSEHB/PED Notification No. 1008-1, PSEHB/PSD Notification No. 1008-1, PSEHB/CND Notification No. 1008-1 dated October 8, 2021) etc.

The risk assessment of nitrosamine contamination during the synthetic process of the drug substance resulted in no risk of nitrosamines contamination.

The drug substance and excipients contained in the drug product, as well as the manufacturing process and

packaging materials of the drug product, were also subjected to a risk-assessment for the contamination of nitrosamines. As a result, there was no risk of contamination of nitrosamines.

6. Conclusion

The hazard assessment and control approach for DNA reactive (mutagenic) impurities of the investigational product in the planned clinical trial were evaluated. It was concluded all identified impurities can be controlled.

(Checklist)

- ✓ Are process flow diagrams of the drug substance synthesis and the drug product manufacturing contained?
- ✓ Are actual and potential impurities likely to arise during the manufacturing and storage of the drug substance and the drug product assessed?
- ✓ Is there a list of impurities (including chemical structures) assessed by two (Q)SAR prediction methodologies?
- ✓ If results of (Q)SAR are anything other than “positive” or “negative,” such as “inconclusive,” or if the results differ between two (Q)SAR, is there a justification for classifying the results?
- ✓ Is there any information for the *in silico* (Q)SAR system used in the assessment?
- ✓ Is there a risk-assessment of the manufacturing process after the starting material(s) selected by referring to the "Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)"(Notification No. 710-9 dated July 10, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) (ICH Q11 Guideline), etc.?
- ✓ Are the risk assessment and control of nitrosamines conducted based on the relevant notifications ("Self-inspection on Risks of Contamination with Nitrosamines in Drugs" (PSEHB/PED Notification No. 1008-1, PSEHB/PSD Notification No. 1008-1, PSEHB/CND Notification No. 1008-1 dated October 8, 2021) etc.)?

（2） When any of the Class 1, Class 2 or Class 3 impurities, or impurities in the cohort of concern are present

(Example of description)

1. Purpose

Based on the ICH M7 Guideline, the hazard assessment and control approach for DNA reactive (mutagenic) impurities that are likely to arise during the manufacturing and storage of the drug substance and the drug product are summarized below.

Since the planned clinical trial is a Phase 3 clinical trial, Class 1, 2, and 3 impurities, which are actually or potentially existing, and impurities in the cohort of concern were evaluated. A list of impurities assessed by (Q)SAR is also provided.

2. Manufacturing method of investigational products

2.1 Manufacturing process for the drug substance

The manufacturing process flow diagram for the drug substance is shown in Figure 2.1-1.

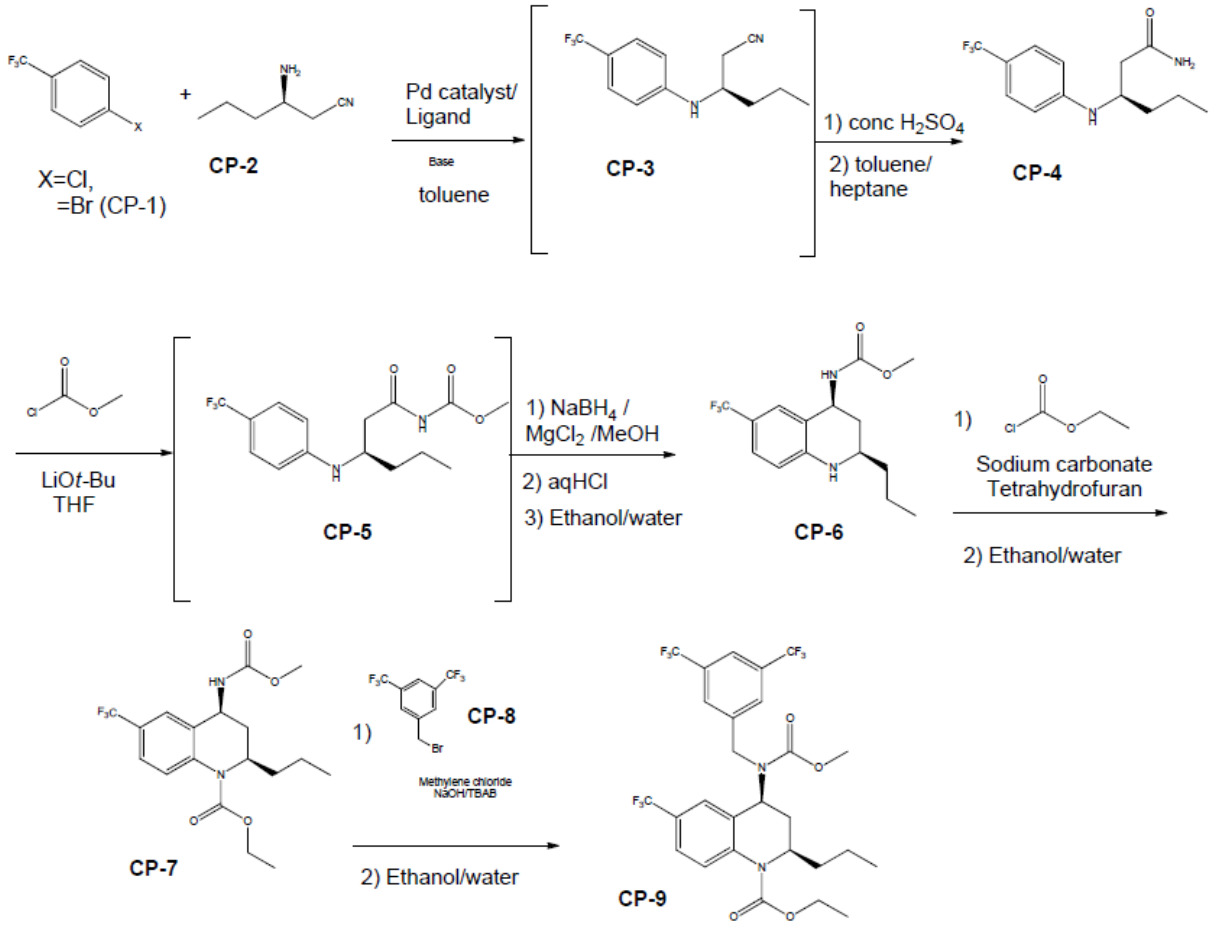

Figure 2.1-1. Synthetic route of the drug substance

(Source: S2 mock-up of the drug substance of sakramil; https://www.nihs.go.jp/drug/section3/H23SakuramillMockJ.pdf)

2.2 Manufacturing method of the drug product

The flow diagram of the manufacturing process of the drug product is shown in Figure 2.2-1.

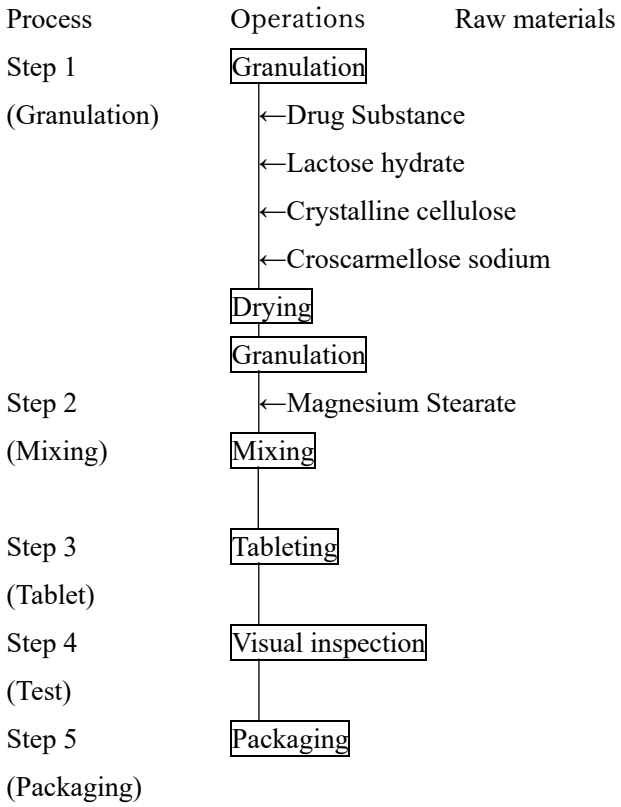

Figure 2.2-1. Process flow diagram of the drug product

3. Hazard assessment of impurities

Regarding actual and potential impurities likely to arise in the manufacturing and storage of the drug substance and the drug product, toxicity information was investigated by searching the database and literature, and hazard assessment was conducted based on the obtained information.

For the drug substance, the results of hazard assessment are shown in Table 3-1. For potential impurities in the investigational product, none of the impurities in the cohort of concern is identified, but Class 1 and Class 2 impurities were identified. Using bacterial mutagenicity tests, *in vivo* tests and (Q)SAR that predicts the outcome of bacterial mutagenicity tests as a computerized toxicological assessment, impurities were classified into Class 3, Class 4 or Class 5 impurities. For identified impurities, each control approach was designed and is shown in Section 4. In addition, no newly formed degradation product was detected in the stability studies performed with the drug substance manufactured by the same manufacturing process as the drug substance used for the investigational drug product.

For the drug product, the identified impurities are derived from the manufacturing process of the drug substance and are appropriately controlled by establishing control strategies or acceptance criteria based on acceptance limits for the drug substance. In addition, as a result of the stability studies performed with the drug product manufactured by the same manufacturing process as the investigational drug, no degradation product was found. Based on the above, it was concluded that no impurities are subject to ICH M7 Guideline in the drug product.

Potential impurities that may increase in the future during storage will be additionally assessed by the time of marketing authorization application.

Table 3-1. Results of assessment of mutagenicity of impurities and management of mutagenic impurities

Name and structure of impurities	Origin	(Q)SAR System 1*	(Q)SAR System 2 **	Results of mutagenicity tests using bacteria	ICH M7 Class	Control approach for mutagenic impurities***
Impurity A [Structural formula] ※ Describe the structure of the impurities	Raw materials	Plausible	Positive	N/A	Class 1	Option 1
Impurity B [Structural formula]	Reagents	Plausible	Known Positive	N/A	Class 1	Option 2
Impurity C [Structural formula]	Reagents	Plausible	Positive	Positive	Class 2	Option 1
Impurity D [Structural formula]	Intermediate	Plausible	Positive	Positive	Class 2	Option 1
Impurity E [Structural formula]	Raw materials	Plausible	Positive	Positive†	Class 2	Option 3
Impurity F [Structural formula]	Intermediate	Plausible	Positive	N/A	Class 3	Option 4
Impurity G [Structural formula]	Raw materials	Inactive	Inconclusive	N/A	Class 4	N/A
Impurity H [Structural formula]	Reagents	Inactive	Negative	N/A	Class 5	N/A
Impurity I [Structural formula]	Raw materials	Plausible	Positive	Negative	Class 5	N/A

N/A: Not applicable

* Software: [Example Software Name] version 5.0.1 (Expert rule-based)

** Software: [Example Software Name] version 1.3.0.0 (Statistical-based)

***ICH M7 Guideline-based control methods for impurities

† It has been described in the literature and no Ames studies have been conducted (reference: [Example Reference]).

4. Control approach and measurement of impurities.

4.1 Acceptance limits and acceptance criteria for Class 1 impurities

As a result of the hazard assessment, it will be confirmed that Impurity A and Impurity B, which are classified as Class 1 impurities, are below the impurity-specific acceptable limits.

4.1.1 Impurity A

Since the maximal daily dose (MDD) in the planned clinical trial is 1000 mg/day, the acceptable limit for Impurity A was calculated as follows. The acceptable intake (AI) was 117 μg/day based on ICH M7 guideline.

Acceptable limit = AI μg/day ÷ MDD g/day

=117 μg/day ÷ 1.0 g/day

=117 ppm

Based on the above, the acceptable limit for Impurity A in the drug substance was set as 117 ppm.

Impurity A in the drug substance batches used in the planned clinical trial was measured, and no Impurity A was detected (below 1 ppm).

4.1.2 Impurity B

Since the maximum daily dose (MDD) in the planned clinical trial is 1000 mg/day, the acceptable limit for Impurity B will be 600 ppm when Option 1 of "Impurity: Guideline For Residual Solvent" (PMSB/ELD Notification No. 307 dated March 30, 1998, by the Director of Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare) (ICH Q3C Guideline) is applied. Impurity B is derived from raw materials and is not newly generated or concentrated in the manufacturing process.

Based on the above, Impurity B was controlled by the residual amount in the raw material, which is considered to be a root cause of contamination, and the acceptance limit was set as 600 ppm (Option 2).

Impurity B in the raw material used for synthesis of the drug substance batches used in the planned clinical trial was measured and resulted below the acceptance limit (<600 ppm).

4.2 Acceptance limits and specifications for Class 2 or Class 3 impurities

As a result of hazard assessment, Impurity C, Impurity D and Impurity E were identified as Class 2 impurities, and Impurity F was identified as Class 3 impurities. Impurity C and Impurity D are controlled by Option 1 and tested to ensure that they are below the acceptable limits for the drug substance. As a result of examining the behavior in the synthesis process, Impurity E was judged to be manageable by Option 3. Impurity F is controlled according to Option 4 because the effects on process parameters and levels of residual impurities are well understood and determined to be below the acceptable limit.

4.2.1 Impurity C and Impurity D

Since the treatment duration in the clinical trial is >1-10 years, the acceptable intake (AI) for Less-Than-Lifetime (LTL) exposures is 10 μg/day as an AI for individual impurities based on Threshold of Toxicological Concern (TTC). In addition, since the maximum daily dose (MDD) in the planned clinical trial was 1000 mg/day, the acceptable limit for mutagenic impurities was calculated as follows.

Acceptable limit (individual impurities) = AI (μg/day)÷ MDD (g/day)

=10 (μg/day) ÷ (1.0 g/day)

=10 ppm

Based on the above, the specification for individual impurities in the drug substance are determined as 10 ppm and controlled with Option 1.

No Impurity C was detected in the drug substance batches used for the clinical trial (below LOD (0.3 ppm)).

No Impurity D was detected in the drug substance batches used for the clinical trial (below LOD (0.3 ppm)).

4.2.2 Impurity E

The behavior of Impurity E at each synthetic step was assessed on a laboratory scale.

In the Step 1, when Impurity E was added at levels 1, 2 and 3 times higher than the specification for raw material (1.3%), the Impurity E contents in intermediate yielded in the Step 1 were less than 30% of the acceptable limit (10 ppm) based on the TTC (3.0 ppm, 2.1 ppm and 1.9 ppm, respectively). In addition, in the intermediate yielded in Step 2 produced with raw material containing three times as much Impurity E as the specification, the content of Impurity E was less than 30% (<1.5 ppm) of the acceptable limit (10 ppm) based on TTC.

For Impurity E, the drug substance was analyzed for 1 ppm of quantitation limits to follow the Impurity E in the drug substance and its intermediates. As shown in Table 4.2.2-1, all drug substance batches contained Impurity E contents (below 3 ppm) that were less than 30% of TTC acceptable limit (10 ppm).

Table 4.2.2-1. Content of representative drug substance batches (Impurity E)

Drug substance batch number	Impurity E content (ppm)
ABC-1	<1
ABC-2	<1
ABC-5	<1
ABC-6	<1

Based on the above, it was considered appropriate to set the acceptable limit at 1.3% for Impurity E in raw material.

4.2.3 Impurity F

For Impurity F, with reference to Org. Process Res. Dev. 2013, 17, 2, 221-230 (Risk Assessment of Genotoxic Impurities in New Chemical Entities: Strategies to Demonstrate Control), a scientific risk-assessment was performed based on physical processes designed to remove chemical reactivity, solubility, volatility and impurities, and an estimated purge factor for removal of impurities by the process was calculated. In addition, based on Regul Toxicol Pharmacol, 2017; 90: 22-8 (A consortium-driven framework to guide the implementation of ICH M7 Option 4 control strategies), the purge factor ratio was calculated from the estimated purge factor and the purge factor required to reduce the mutagenic impurity to the acceptable limit. As a consequence, the purge factor ratio was 2.3×10^3, which is concluded that Impurity F will not be left in the drug substance. Therefore, Impurity F can be controlled with Option 4.

Table 4.2.3-1. Results of risk assessment using estimated purge factors (Impurity F)

Process		Reactivity	Solubility [a]	Volatility	Other	Purge factor
Drug substance Step 2	Reaction	100 [b]	1	1	1	100
	Work up	1	1	1	1	1
	Crystallization/ solid-liquid separation	1	10	1	1	10
	Washing	1	10	1	1	10
	Drying	1	1	1	1	1
Drug substance Step 3	Reaction	100 [c]	1	1	1	100
	Crystallization/ solid-liquid separation	1	1	1	1	1
	Washing	1	1	1	1	1
	Drying	1	1	1	1	1
Drug substance Step 4	Dissolution with heat	10 [d]	1	1	10 [e]	100
	Crystallization/ solid-liquid separation	1	1	1	1	1
	Washing	1	1	1	1	1
	Drying	1	1	1	1	1

Estimated purge factor	1×10^8
Required purging factor(F= I/L)	43000
Purging factor ratio(f/F)	2.3×10^3
Origin	Intermediate
Initial concentration(I)	430000 ppm
AL(L)	10 ppm

a The solubility of Impurity F in the solvents used in each process step was confirmed and evaluated. Solubility was set to 1 for operations not applicable to solid-liquid separation and liquid-liquid extraction because they have no removal ability based on solubility.

b Since Impurity F is consumed in the reaction, the chemical reactivity is set to 100.

c Since it was confirmed experimentally that Impurity F decomposes when dissolved in a solvent and a reagent used in the reaction, the reactivity was set to 100.

d When Impurity F was heated and dissolved in a solvent, it was experimentally confirmed that it showed a tendency to decompose, so that the reactivity was set to 10.

e Based on the removal ability of activated carbon added at the time of heating and dissolution, the other element was set to 10.

4.3 Class 4 or Class 5 impurities

As a result of hazard assessment, Impurity G, Impurity H and Impurity I were identified as Class 4 or Class 5 impurities. Since Class 4 and Class 5 impurities are treated as non-mutagenic impurities, control of the impurities is considered unnecessary.

5. Measurement results of impurities

Analysis of mutagenic impurities in drug substance batches is shown in Table 5-1.

Table 5-1. Analytical results of mutagenic impurities

Mutagenic impurities	Acceptable limit (Criteria)	Lot No.				
		ABC-1	ABC-2	ABC-3	ABC-5	ABC-6
Impurity A	117 ppm	<0.4 ppm	<0.4 ppm	<0.4 ppm	—	—
Impurity B	600 ppm [a]	—	—	—	<600 ppm	—
Impurity C	10 ppm	<0.3 ppm	<0.3 ppm	<0.3 ppm	—	—
Impurity D	10 ppm	<0.3 ppm	<0.3 ppm	<0.3 ppm	—	—
Impurity E	1.3% [b]	<1 ppm	<1 ppm	—	<1 ppm	<1 ppm

a Control in raw materials according to Option 2.

b Control in raw materials according to Option 3.

6. Nitrosamines impurities

Nitrosamines were evaluated with reference to "Self-inspection on Risks of Contamination with Nitrosamines in Drugs"(PSEHB/PED Notification No. 1008-1, PSEHB/PSD Notification No. 1008-1, PSEHB/CND Notification No. 1008-1 dated October 8, 2021) etc.

The risk assessment of nitrosamine contamination during the synthetic process of the drug substance resulted in no risk of nitrosamines contamination.

The drug substance and excipients contained in the drug product, as well as the manufacturing process and packaging materials of the drug product, were also subjected to a risk-assessment for the contamination of nitrosamines. As a result, there was no risk of contamination of nitrosamines.

7. Conclusion

The hazard assessment and control approach for DNA reactive(mutagenic) impurities of the investigational product in the planned clinical trial were evaluated. It was concluded all identified impurities can be controlled.

(Checklist)

- ✓ Are process flow diagrams of the drug substance synthesis and the drug product manufacturing contained?
- ✓ Are actual and potential impurities likely to arise during the manufacturing and storage of the drug substance and drug product assessed?
- ✓ Is there a list of impurities (including chemical structures) assessed by two (Q)SAR prediction methodologies?
- ✓ If results of (Q)SAR are anything other than “positive” or “negative,” such as “inconclusive,” or if the results differ between two (Q)SAR, is there a justification for classifying the results?
- ✓ Is there any information for the *in silico* (Q)SAR used in the assessment?

- ✓ Is there a risk-assessment of the manufacturing process after the starting material(s) selected by referring to the "Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)" (Notification No. 710-9 dated July 10, 2014 by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) (ICH Q11 Guideline), etc.?
- ✓ Are any control plans described for mutagenic impurities?
- ✓ Are the appropriate acceptable daily intakes selected according to the duration of the clinical trial?
- ✓ Are the risk assessment and control of nitrosamines conducted based on the relevant notifications("Self-inspection on Risks of Contamination with Nitrosamines in Drugs"(PSEHB/PED Notification No. 1008-1, PSEHB/PSD Notification No. 1008-1, PSEHB/CND Notification No. 1008-1 dated October 8, 2021) etc.)?

4. Cases where attachments can be omitted

Attached documents can be omitted by giving a description in the “remark” field under “documents attached to the notification” of the clinical trial notification with reference to the following examples. It is also acceptable to include the following descriptions in attached documents.

（1）In the second and subsequent notifications, when the manufacturing method has not changed since the previous notification, and the dosage, administration and duration of administration have not exceeded those in the conducted clinical trial (except for the case of transitioning from the early development phase (Section 1. and 2.) to the late development phase (Section 3.))

(Example of description) The submission of a document on the assessment and control of DNA reactive (mutagenic) impurities is omitted, because there has been no change in the manufacturing process of the drug substance and the drug product since the previous clinical trial notification was submitted (number of notification: [Enter Number]; date of notification: [Enter Date]), and the dosage, dose frequency per day and duration of dosing do not exceed those in the previous clinical trial notification.

(Checklist)

- ✓ Is it specified that there is no change in the manufacturing process?
- ✓ Is it specified that the dosage, administration and the duration of administration do not exceed those in the previous clinical trial notification?
- ✓ Is it specified that no new impurities have been detected by stability studies etc.?

（2）When using an approved product as an investigational product

(Example of description) The submission of a document on the assessment and control of DNA reactive (mutagenic) impurities is omitted, because the investigational product is identical to [Example Drug Name], which is an approved drug in Japan, and the dosage and administration should not exceed the dosage and administration of the approved drug. The manufacturing process for the drug substance and the drug product has not changed, and the expected duration of administration does not exceed the duration of administration of the approved drug.

(Checklist)

- ✓ Are the drug substance and drug product identical* to the medicinal product approved in Japan? Even if the drug is identical to an approved drug in Japan, if the approved drug is not subject to ICH M7 Guideline (e.g., a drug indicated for advanced cancer), a document on assessment and control of DNA reactive (mutagenic) impurity have not been previously assessed, and therefore the data cannot be omitted.
- ✓ Does the dosage and administration of the investigational product not exceed the maximum daily dose of the approved product?
- ✓ If the duration of administration of the investigational product is prolonged compared with the standard duration of administration of the approved product, it is necessary that the acceptable intake not be reduced based on the Less-Than-Lifetime (LTL) concept.

* It is necessary that the drug substance and the drug product are manufactured in the same manufacturing

site/facility according to the same manufacturing procedure as the approved drug. For an investigational drug with different salt or different solvates, the manufacturing process is considered to be different, and therefore it is necessary to submit documents in principle.

End