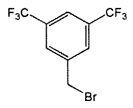
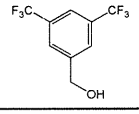
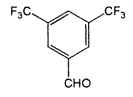
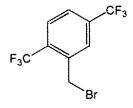
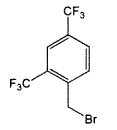
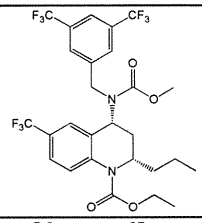
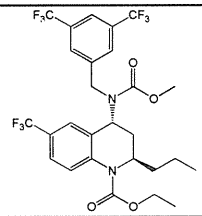
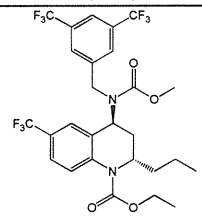
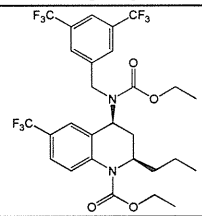
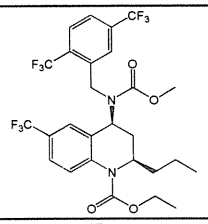
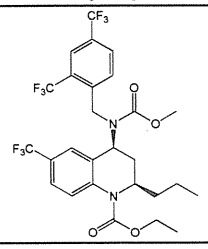
CP-8		Starting material	Alkyl halide functional group based genotoxicity aerting structure. Negative in the Ames Assay.	Control in accordance with ICH Q3A
CP-8-OH		By-product of CP-8	No genotoxicity alerting structure.	Control in accordance with ICH Q3A
CP-8-CHO		By-product of CP-8	No genotoxicity aerting structure.	Control in accordance with ICH Q3A
CP-8-25I		By-product derived from impurity in raw material of CP-8	Alkyl halide functional group based genotoxicity alerting structure. Common structure with CP-8.	Control in accordance with ICH Q3A
CP-8-24I		By-product derived from impurity in raw material of CP-8	Alkyl halide functional group based genotoxicity alerting structure. Common structure with CP-8.	Control in accordance with ICH Q3A
CP-9-E		Enantiomer of Sakuramil drug substance	No genotoxicity alerting structure.	Control in accordance with ICH Q3A
CP-9-D1		Diastereomer 1 of Sakuramil drug substance	No genotoxicity alerting structure.	Control in accordance with ICH Q3A
CP-9-D2		Diastereomer 2 of Sakuramil drug substance	No genotoxicity alerting structure.	Control in accordance with ICH Q3A
CP-9-1		Ethyl homolog of Sakuramil drug substance	No genotoxicity alerting structure.	Control in accordance with ICH Q3A

CP-9-2		2,5-Regioisomer of trifluoromethyl group	No genotoxicity alerting structure.	Control in accordance with ICH Q3A
CP-9-3		2,4-Regioisomer of trifluoromethyl group	No genotoxicity alerting structure.	Control in accordance with ICH Q3A

Appendix-2 Example of Description of Manufacturing Process in Application Form

Step 1 (Critical Step) (Reaction[1)], Extraction, Purification[2)], Phase Separation, and Drying)

Methyl (2*R*,4*S*)-2-propyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline-4-ylcarbamate (CP-6) [1] 『(230 kg)』, tetrahydrofuran 『(1300 L)』, sodium carbonate 『(42.4 kg)』 are combined. Ethyl chloroformate "158~592 kg" is added and the mixture is heated at temperature up to reflux. The mixture is filtered, and the filtrate is quenched with a "50%"[2)] sodium hydroxide solution. To the mixture, *n*-hexane is added and stirred, and the layers are settled and separated. The organic layer is concentrated by distillation with ethanol for the solvents exchange (final concentration 『(1400 L)』). Water ("25 to 35%" weight per weight of ethanol) is added and the mixture is stirred at 『20°C』. The resulting crystalline precipitates are separated, rinsed with ethanol, and dried at 『42.5°C』 to yield Ethyl (2*R*,4*S*)-2-propyl-4-(methoxycarbonylamino)-6-(trifluoromethyl)-3,4-dihydroxyquinoline-1(2*H*)-Carboxylate (CP-7) [2] (product 253 kg, yield 89%).

1) Ethyl chloroformate quantity, tetrahydrofuran volume and sodium carbonate or trisodium phosphate, dodecahydrate are parameters establishing Design Space which control quantity of CP-7-1.
2) Water quantity relative to ethanol quantity, ethanol volume and crystallization temperature are parameters establishing Design Space which control quantity of total impurities.

Step 2 (Critical Step) (Reaction[3)], Extraction, Purification[4)], Phase Separation, and Drying)

CP-7 [2] 『(250 kg)』 from Step 1 and 3,5-bistrifluoromethylbenzyl bromide (CP-8) 『(215 kg)』 are combined in methylene chloride 『(750 L)』. Tetra-*n*-butylammonium bromide 『(50 kg)』 and "50%"[2)] aqueous sodium hydroxide solution 『(750 L)』 are added and stirred, and then methylene chloride and water are added and stirred. The mixture obtained is settled and the layers are separated. The organic layer is washed with diluted hydrochloric acid. The organic layer is concentrated by distillation with ethanol for the solvents exchange (final concentration 『(1800 L)』). Water (20 to 35% weight per weight of ethanol) is added, and then the mixture is cooled at the rate of 0.15 to 0.5°C per minute, followed by stirring at 『18°C』. The resulting crystalline precipitates are separated, rinsed with ethanol, and dried at 『42.5°C』 to yield Ethyl (2*R*,4*S*)-4-{[3,5-bis(trifluoromethyl)benzyl](methoxycarbonyl)amino}-2-propyl-6-(trifluoromethoxy)-3,4-dihydroquinoline-1(2*H*)-carboxylate [3] (Sakuramil) (product 360 kg, yield 90%).

3) Quantity of 3,5-bistrifluoromethylbenzyl bromide (CP-8), volume of methylene chloride and volume of aqueous sodium hydroxide solution are parameters establishing Design Space which control quantity of residua l CP-8.
4) Ethanol volume, quantity of water relates to ethanol, cooling rate and cooling temperature are parameters establishing Design Space which control quantity of residual CP-8.

Step 3 (Packaging)

Sakuramil drug substance [3] is packaged in polyethylene bags, closed with a tie-wrap, which is then stored in "fiber drums".

Alternative manufacturing process

In Step 1, trisodium phosphate, dodecahydrate 〖(101.4 kg)〗 [1)] can be used instead of sodium carbonate 〖(42.4 kg)〗 [1)] as alternative base.

Appendix-3 Reference Information: Manufacturing Method in Application Form

Reference only

Step 1 (Critical Step) (Reaction[1)], Extraction, Purification[2)], Phase Separation, and Drying)

Methyl (2*R*,4*S*)-2-propyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline-4-ylcarbamate (CP-6) [1] 『(230 kg)』 [Note 1)], tetrahydrofuran 『(1300 L)』 [Note 1)], sodium carbonate 『(42.4 kg)』 [Note 1)] are combined. Ethyl chloroformate "158~592 kg" [Note 2)] is added and the mixture is heated at temperature up to reflux. The mixture is filtered, and the filtrate is quenched with a "50%" [Note 3)] sodium hydroxide solution. To the mixture, *n*-hexane is added and stirred, and the layers are settled and separated. The organic layer is concentrated by distillation with ethanol for the solvents exchange (final concentration 『(1400 L)』 [Note 1)]). Water "25 to 35%" [Note 4)] weight per weight of ethanol) is added and the mixture is stirred at 『20°C』 [Note 3)]. The resulting crystalline precipitates are separated, rinsed with ethanol, and dried at 『42.5°C』 [Note 3)] to yield Ethyl (2*R*,4*S*)-2-propyl-4-(methoxycarbonylamino)-6-(trifluoromethyl)-3,4-dihydroxyquinoline-1(2*H*)-Carboxylate (CP-7) [2] (product 253 kg, yield 89%).

1) Ethyl chloroformate quantity, tetrahydrofuran volume and sodium carbonate or trisodium phosphate, dodecahydrate are parameters establishing Design Space which control quantity of CP-7-1.
2) Water quantity relative to ethanol quantity, ethanol volume and crystallization temperature are parameters establishing Design Space which control quantity of total impurities.

Step 2 (Critical Step) (Reaction[3)], Extraction, Purification[4)], Phase Separation, and Drying)

CP-7 [2] 『(250 kg)』 [Note 1)] from Step 1 and 3,5-bistrifluoromethylbenzyl bromide (CP-8) 『(215 kg)』 [Note 1)] are combined in methylene chloride 『(750 L)』 [Note 1)]. Tetra-*n*-butylammonium bromide and "50%" [Note 3)] aqueous sodium hydroxide solution 『(750 L)』 [Note 1)].are added and stirred, and then methylene chloride and water are added and stirred. The mixture obtained is settled and the layers are separated. The organic layer is washed with diluted hydrochloric acid. The organic layer is concentrated by distillation with ethanol for the solvents exchange (final concentration 『(1800 L)』 [Note 1)]). Water (20 to 35% weight per weight of ethanol) is added, and then the mixture is cooled at the rate of 0.15 to 0.5°C per minute, followed by stirring at 『18°C』 [Note 5)]. The resulting crystalline precipitates are separated, rinsed with ethanol, and dried at 『42.5°C』 [Note 5)] to yield Ethyl (2*R*,4*S*)-4-{[3,5-bis(trifluoromethyl)benzyl](methoxycarbonyl) amino}-2-propyl-6-(trifluoromethoxy)-3,4-dihydroquinoline-1(2*H*)-carboxylate [3] (Sakuramil) (product 360 kg, yield 90%).

3) Quantity of 3,5-bistrifluoromethylbenzyl bromide (CP-8), volume of methylene chloride and volume of aqueous sodium hydroxide solution are parameters establishing Design Space which control quantity of residua l CP-8.
4) Ethanol volume, quantity of water relates to ethanol, cooling rate and cooling temperature are parameters establishing Design Space which control quantity of residual CP-8.

Step 3 (Packaging)

Sakuramil drug substance [3] is packaged in polyethylene bags[Note 6], closed with a tie-wrap, which is then stored in "fiber drums" [Note 7].

Alternative manufacturing process

In Step 1, trisodium phosphate, dodecahydrate 『(101.4 kg)』 [Note 1] can be used instead of sodium carbonate 『(42.4 kg)』 [Note 1] as alternative base.

Note 1) Scale dependent values, minor notification matter
Note 2) This quantity is one of parameters establishing Design Space. This parameter is critical, however, risk affecting on DS CQA is low through control strategy established to operate process parameter good enough within the specified range. In consequence, this parameter is defined as medium risk and described as range of notification.
Note 3) Target/Set values (Range is noted and controlled in MBR and SOP)
Note 4) This quantity is one of parameters establishing Design Space. This parameter is critical, however, risk affecting on DS CQA is low through control strategy established to operate process parameter good enough within the specified range. In consequence, this parameter is defined as medium risk and described as range of notification.
Note 5) Temperature is target/set value (Range is described/controlled in MBR/SOP)
Note 6) Material of primary container is described.
Note 7) Secondary container to ensure stability is described

Appendix-4

The flow diagram showing the outline of manufacturing process development indicated in the chapter of the background of manufacturing process development for Sakuramil drug substance (2.3.S.2.6) is provided below. This flow diagram starts from the timepoint of decision of "manufacturing methods for the application," and the following items implemented during the period from early stage development to the decision of manufacturing the manufacturing methods are described as "Prior Knowledge & Experience" : investigation results; risk assessment; change of manufacturing process; selection of the starting materials, etc.

In the development of manufacturing process for Sakuramil drug substance, all elements of so-called QbD approach described as a "more enhanced approach" in ICH Q11 are included.

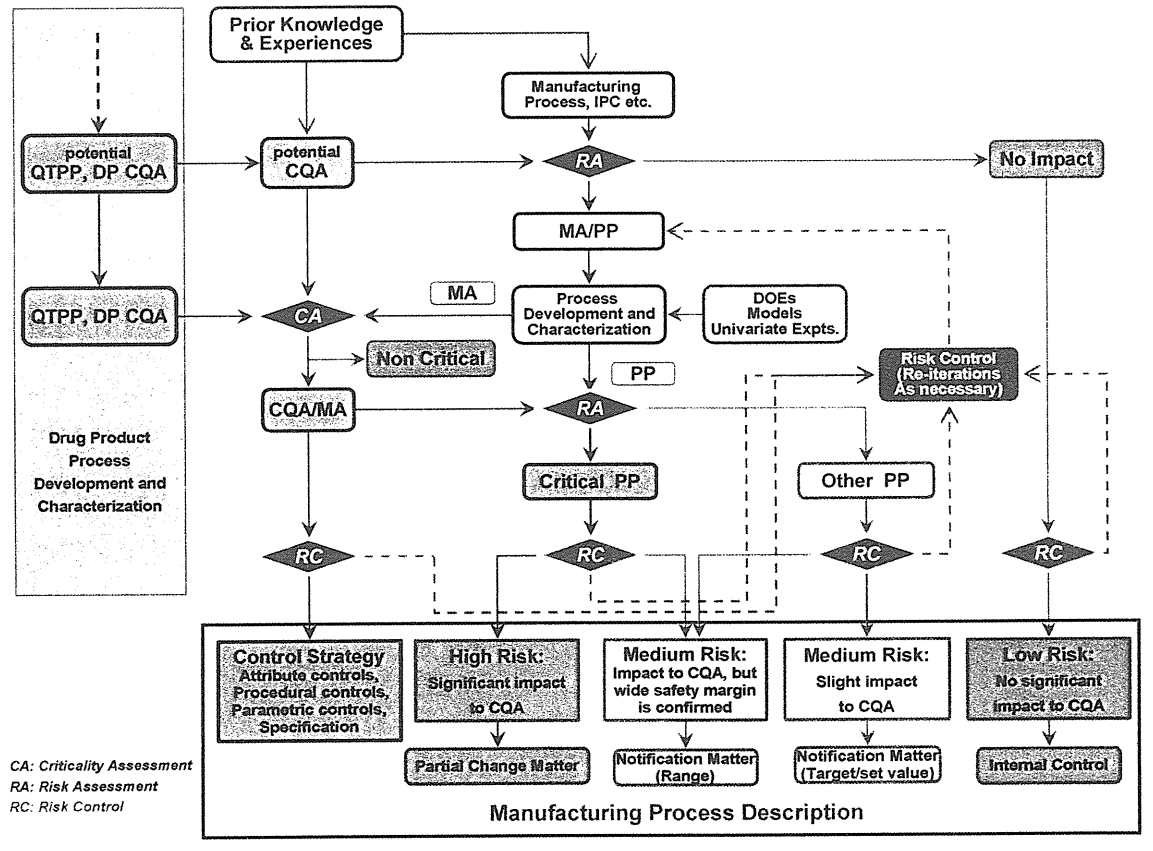


Figure Flow diagram of the outline of manufacturing process development for drug substances

Note: In this flow diagram, we used the terms: Criticality Assessment (CA) for the assessment of Quality Attribute (QA) and Material Attribute (MA). These terms are used for clearly distinguish these from Risk Assessment (RA) based on the concept of POINT TO CONSIDER (*R2*) created by ICH Q-IWG that "Quality Attribute criticality is primarily based upon severity of harm and does not change as a result of risk management."

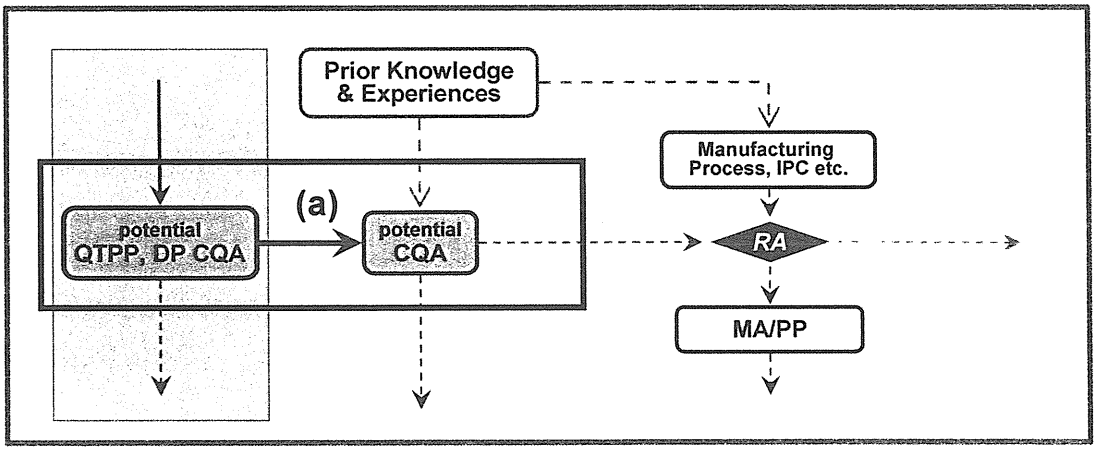
The chapter of the background of manufacturing process development (2.3.S.2.6) in Sakuramil S2 Sample is made up by the following 6 sections, and we indicate the relationship between the content of these sections and the flow diagram of overview in the following.

2.3.S.2.6 Background of manufacturing process development

1) Critical Quality Attribute (CQA) expected for Sakuramil drug substance.

This section corresponds to (a) in the below flow diagram of the outline of manufacturing process development for drug substances.

In this section, the process to specify the expected CQA of drug substance from Quality Target Product Profile (QTPP) of drug product is described. Since Sakuramil drug substance is an insoluble compound, it is formed as tablet after making spray-dry dispersed in-process materials by dissolving the drug substance in manufacturing process. Therefore, physical attributes (crystalline form, particle size distribution) of Sakuramil drug substance have no impact on drug products; and hence the focal point for the development of manufacturing process for Sakuramil drug substance is the control of impurities.

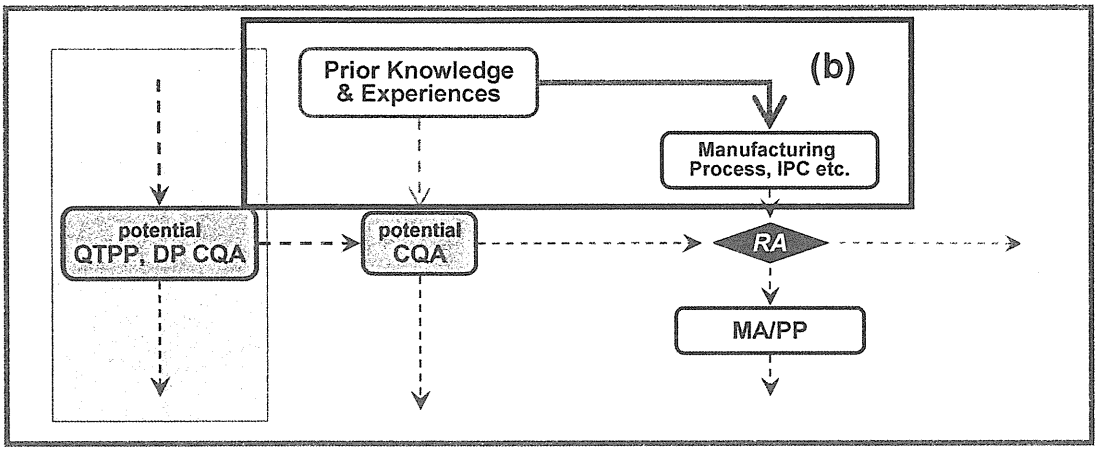


The corresponding part in the flow diagram of the outline of manufacturing process development for drug substances

2) Background of development

This section corresponds to (b) (expressed as "Prior Knowledge") in the below flow diagram of the outline of manufacturing process development for drug substances.

In Sakuramil S2 Sample, we itemize tasks (disadvantages) in each route from manufacturing methods in early development (Route A) through to manufacturing methods for the application (Route C), and indicate how those tasks were improved.

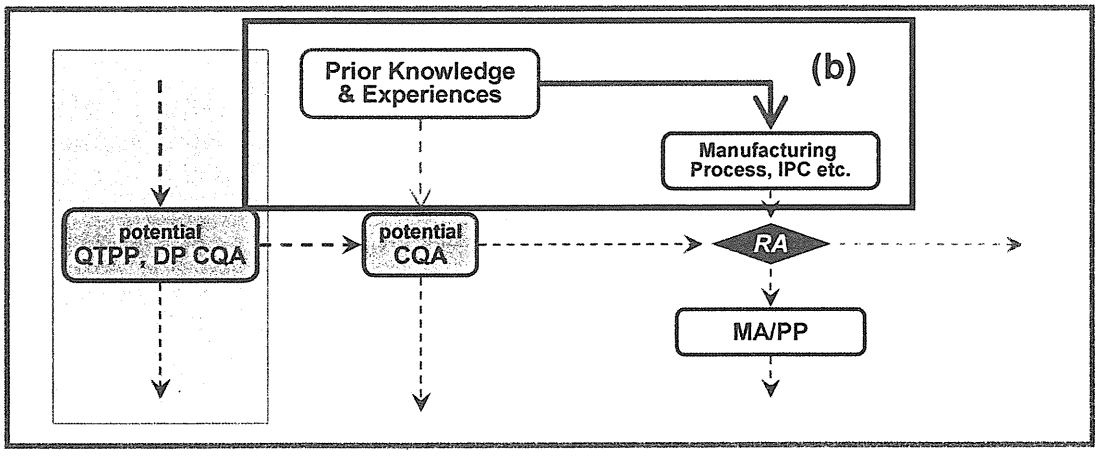


The corresponding part in the flow diagram of the outline of manufacturing process development for drug substances

3) Validity of starting materials and selection of manufacturing methods for commercial production

This section corresponds to (b) (expressed as "Prior Knowledge") in the below flow diagram of the outline of manufacturing process development for drug substances.

Regarding the validity of specifying 2 final reaction processes as the manufacturing methods for commercial production of Sakuramil drug substance, as well as the validity of selecting CP-6 and CP-8 as the starting materials, we discuss the rationale of setting control items/cction limits by reflecting the results of Risk Assessment (RA) for Material Attributes (MA).



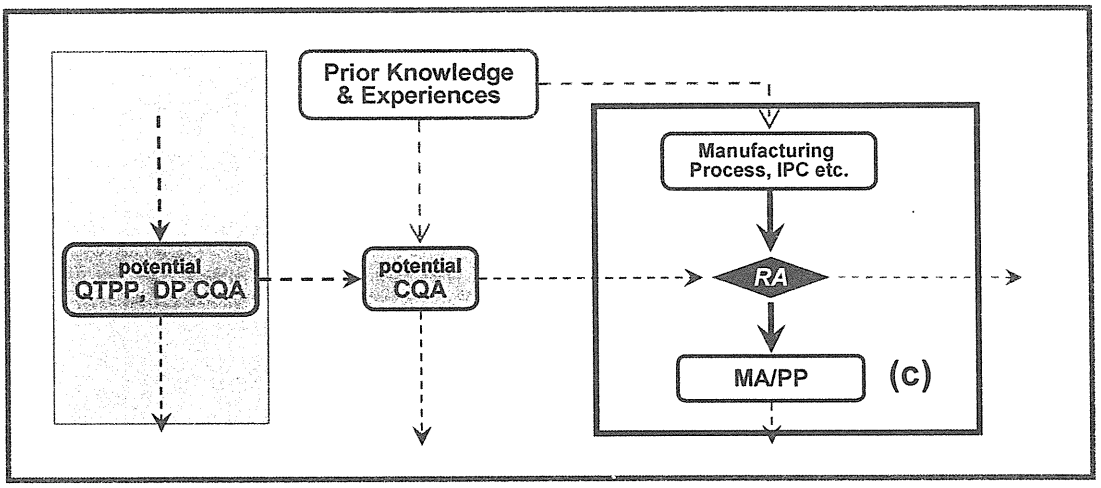
The corresponding part in the flow diagram of the outline of manufacturing process development for drug substances

4) Risk assessment for the development of knowledge space and control strategies

This section corresponds to (c) in the below flow diagram of the outline of manufacturing process development for drug substances.

To specify the impact of manufacturing process on Sakuramil drug substance CQA (impurities), we conducted Risk Assessment (RA) for the impact of manufacturing process on drug substance CQA. Further, in order to specify the manufacturing process parameter (PP) which affects drug substance CQA, we divide manufacturing process into unit operations (focus area) and specify the unit operation (focus area) where critical impurities left in the drug substance (drug substance CQA) produce/are introduced/are eliminated by RA.

In addition, there are many cases where RA is implemented repeatedly according to process investigations conducted multiple times, and MA and PP of intermediates are specified by that. In this section, to avoid the scheme to become complicated, we show the one case.



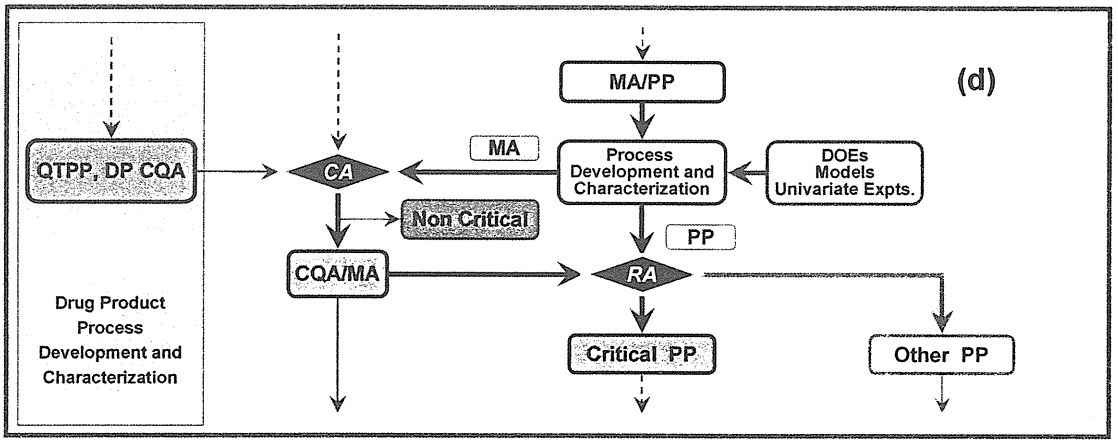
The corresponding part in the flow diagram of the outline of manufacturing process development for drug substances

5) Design space of unit operations of each step in drug substance manufacture

This section corresponds to (d) in the below flow diagram of the outline of manufacturing process development for drug substances.

Regarding the focus area (Step 1 and Step 2 of reaction process and crystallized process) specified by risk assessment (RA), we investigate the impact of process parameter (PP) on quality attribute/material attribute by the multivariate design of experiments, and show the investigation result including the establishment of Design space/Knowledge space. Also, we briefly describe the investigation result concerning the experiments assuming the worst case scenario, experiments for addition, scale effect, etc. Further, we conduct RA of criticality for each unit operation (focus area) from the obtained results, and consider Critical Process Parameter (CPP).

We conducted RA for the investigation result on the design of experiments (DOE), and judged PP as CPP in cases where the variation of PP is related to the variation of drug substance CQA with statistical/functional significance, and at the same time, PP has negative impact on drug substance CQA when it is varied within the realistically assumable range. Also, we judged PP as other PP in cases where PP has no negative impact on drug substance CQA unless it is varied with an unrealistic range, as well as in cases where there is no relationship observed between the variation of Pp and drug substance CQA.

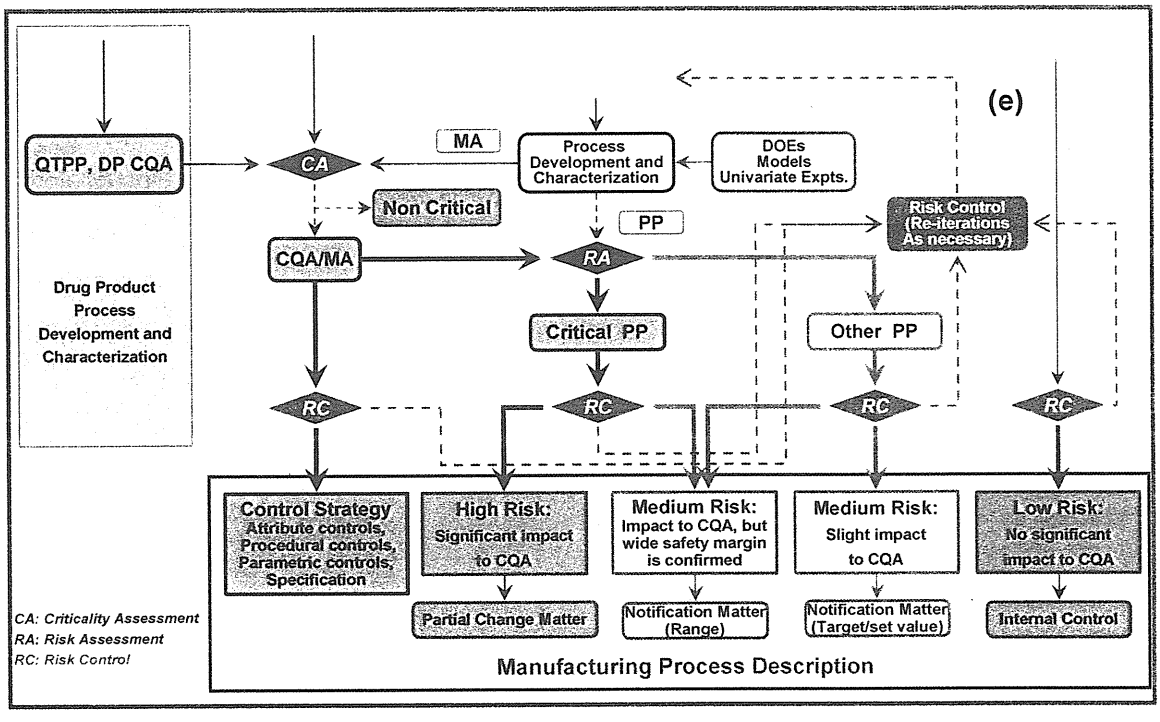


The corresponding part in the flow diagram of the outline of manufacturing process development for drug substances

6) Assessment of criticality of manufacturing process

This section corresponds to (e) in the below flow diagram of the outline of manufacturing process development for drug substances.

We considered the final RA results obtained from overall design space and control strategies for the specified CPP and critical quality attributes.



The corresponding part in the flow diagram of the outline of manufacturing process development for drug substances

Reference

ICH Q11 DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES

3.1.3 Approaches to Development

An enhanced approach to manufacturing process development would additionally include the following elements:

- Identifying potential CQAs associated with the drug substance so that those characteristics having an impact on product quality can be studied and controlled;
- Defining an appropriate manufacturing process;
- A systematic approach to evaluating, understanding and refining of the manufacturing process, including;
  - Identifying, through e.g., prior knowledge, experimentation and risk assessment, the material attributes (e.g. of raw materials, starting materials, reagemts, solvents, process aids, intermediates) and process parameters that can have an effect on drug substance CQAs;
  - Determining the functional relationships that link material attributes and process parameters to drug substance CQAs;
- Using the enhanced approach in combination with QRM to establish an appropriate control strategy which can, for example, include a proposal for a design space(s) and/or real-time release testing (RTRT).

3.2 Submission of Manufacturing Process Development Information

3.2.1 Overall Process Development Summary

- List of drug substance CQAs;
- Brief description of the stages in the evolution of the manufacturing process and control strategy;
- Brief description of the material attributes and process parameters identified as impacting drug substance CQAs;
- Brief description of the development of any design spaces.

Appendix-5

Regarding regulatory flexibility

In the end of "Introduction" in ICH Q11, regulatory flexibility is described as the following:

> **ICH Q11 DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES (Excerpt from Introduction)**
>
> Introduction
>
> ..... As discussed in ICH Q8 for drug product, a greater understanding of the drug substance and its manufacturing process can create the basis for more flexible regulatory approaches. The degree of regulatory flexibility is generally predicated on the level of relevant scientific knowledge provided in the application for marketing authorisation.

As some proposals expecting regulatory flexibility are also included in Sakuramil S2 Sample, we describe the outline of the proposals in the following. This needs to be understood that these proposals are expecting items discussed by Research on Regulatory Science of Pharmaceuticals and Medical Devices, and that not all applications are approved in the actual application, even though the supporting material for the application is the exactly equivalent to the sample, since the following elements are considered in the actual application: the reliability of methods and tools, the level of facilities conducted R&D, the reliability including the situation of quality risk management and quality system in accordance with ICH Q9 and Q10, etc, implemented by the applicants.

1) Description of manufacturing methods

We indicated the differences in the description of manufacturing methods between the sample and the conventional approach. When using the conventional approach, description of set/target values, etc. for all parameters are required in manufacturing methods of drug substance. We proposed that description of target/set values is not necessary for parameters in cases where the more enhanced approach was used in development such as the sample, since it is clear that these have no impact on quality.

Parameter	Target/Set value	Traditional approach	QbD approach	Justification of QbD
CP-6	230 kg	note	note	Impact on CP-7-1 generation
THF	1300 L	note	note	Impact on CP-7-1 generation
Na_2CO_3	42.4 kg	note	note	Impact on CP-7-1 generation

Ethyl chloroformate	206 kg	note	note	Impact on CP-7-1 generation
Reaction temperature	reflux	note	note	Impact on CP-7-1 generation
50% NaOH aq	1000 L	note	Not noted	No impact on quality
n-Hexane	700 L	note	Not noted	No impact on quality
Concentrated volume	2000 L	note	Not noted	No impact on quality
EtOH volume	1400 L	note	note	Minor impact on impurity residue
Quantity of Water addition	25 - 35%	note	note	Impact on impurity residue (critical)
Crystalization temperature	20°C	note	note	Minor impact on impurity residue
Drying Temperature	42.5°C	note	note	Possibility to produce degradation product

QbD approach: more enhanced approach

2) Proposal to specify PP described with range as items that can be changed by simply submitting a minor change notice

We indicate an example where PP described with range are specified as items that can be changed by simply submitting a minor change notice in the description of reference information of manufacturing methods (Attachment-2) in the application form.

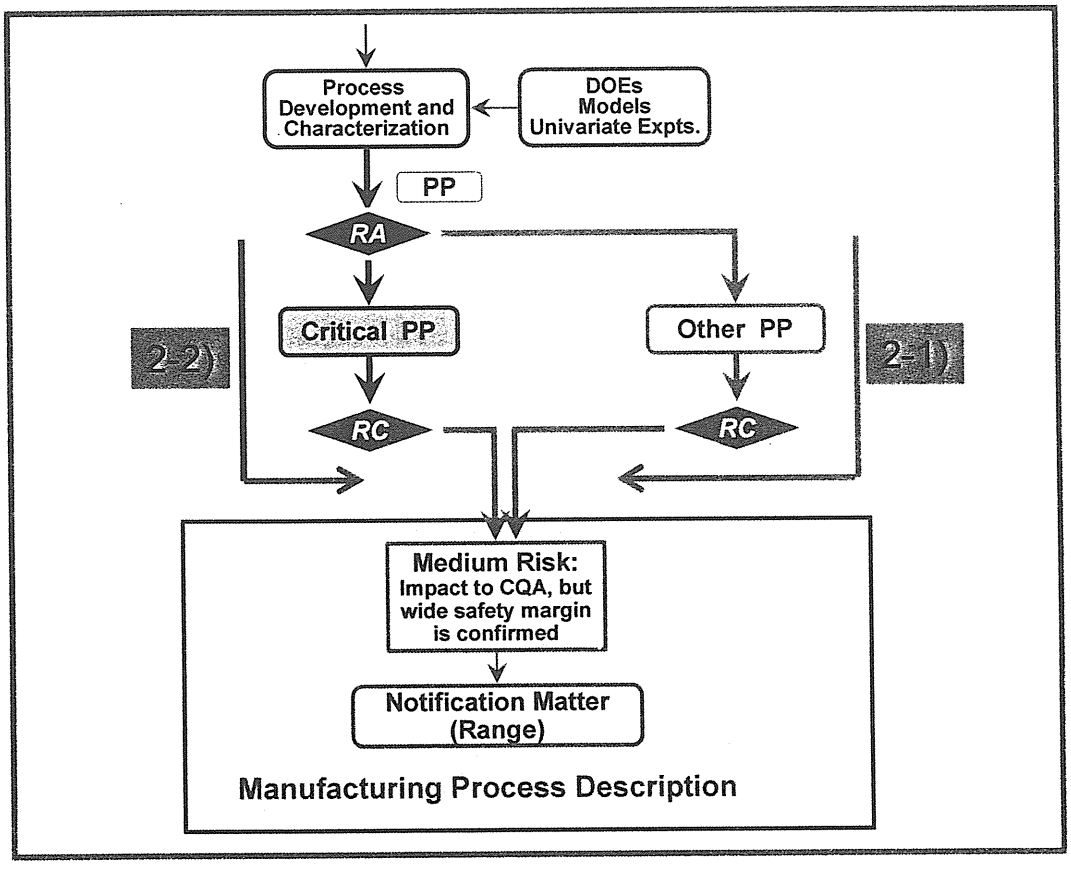
Different from established proven acceptable ranges (PAR) obtained from univariate experimentation, in this case, the impact of PP when it is varied is investigated by the research of DOE. The knowledge concerning the relationship between Edge of Failure (EOF) and PP has been deepened, and this can be considered that risk is sufficiently decreasing. However, as a matter of course, if PP is deviated from pre-determined range, even though deviation is within the range of DS determined by DOE, it is necessary to conduct verification of quality in accord with GMP specifications, and shipment of the products will not be allowed if the deviation is judged inappropriate as a result of verification.

2-1) Range description of other PP which is not specified as CPP

The amount of Ethyl chloroformate in reaction process in Step 1, when it is investigated by the multivariate design of experiments, although it has subtle impact on drug substance CQA, the production of impurities are less than one third of the determined specifications even when using excessive amount which is not used in normal manufacture, and there was no EOF observed in the investigated area. Based on the result, it can be judged that the amount of Ethyl chloroformate is not CPP but other PP ranked as medium risk. Therefore, we proposed the obtained design space as an item that can be changed by simply submitting a minor change notice which can be described with range.

2-2) Range description of CPP which risk is sufficiently decreased

By investigating the amount of water in crystallized process in Step 1 by the multivariate design of experiments, it was specified as CPP because it is statistically/functionally related to drug substance CQA. However, since its risk level is decreased to medium level by a control strategy of setting its area as smaller than the confirmed design space, we proposed it as an item that can be changed by simply submitting a minor change notice.



The corresponding part in the flow diagram of the outline of manufacturing process development for drug substances

3) Specifications of drug substance

We indicated the differences in the setting of specifications of drug substance between the sample and the conventional approach. When using the conventional approach, specified drug substance CQA is set as specifications of drug substance, and tested in drug substance. But when the more enhanced approach was used in development, its relationship with manufacturing PP/material attribute can be clarified. Therefore, we proposed to minimize the specifications set for drug substance by adopting the followings: control using design space, use of in-process control test results, upstream control of material attributes, etc. of starting material and intermediates, etc.

DS CQA	limit	Is CQA tested on drug substance/ included in drug substance specification		QbD Justification
		Traditional approach	QbD approach	
Related Substances (1)				
CP-9-1	≤ 1.0%	Yes/Yes*	No/Yes	DS in Step 1
CP-8	≤ 0.10%	Yes/Yes	No/Yes	DS in Step 2
Related Substances (2)				
Other (each)	≤ 0.10%	Yes/Yes	Yes/Yes	
Total impurities	≤ 0.5%	Yes/Yes	Yes/Yes	
GTIs				
CP-6	≤ 10 ppm	Yes/Yes	Yes/Yes	
Total (CP-3, -4, -5, -6)	≤ 25 ppm	Yes/Yes	No/Yes	DS in Step 2
Residual solvent				
Ethanol	≤ 5000 ppm	Yes/Yes	No/Yes	IPC in Step 2 : LOD ≤ 0.40%
Tetrahydrofuran	≤ 720 ppm	Yes/Yes	No/No	After Step 1, this is removed significantly than that of conc limit in Q3C through manufacturing process.
n-Hexane	≤ 290 ppm	Yes/Yes	No/No	After Step 1, this is removed significantly than that of conc limit in Q3C through manufacturing process.
Dichloromethane	≤ 600 ppm	Yes/Yes	Yes/Yes	(Propose skip test)
Assay	98 - 102%	Yes/Yes	Yes/Yes	

QbD methodology : more advanced approach

*CQA is tested in DS or not/CQA is included in DS specification.

平成23年度厚生労働科学研究費補助金
（医薬品・医療機器等レギュラトリーサイエンス総合研究事業）
医薬品の製造開発から市販後に及ぶ品質確保と改善に関する研究

平成23年度　分担研究報告書 製剤の開発・製造情報に関する研究

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日米EU医薬品規制調和国際会議(ICH)は、製品研究開発と品質管理に最新の科学と品質リスク管理の概念を取り入れることにより規制の弾力的な運用を実施するという方針を打ち出し、合理的な品質管理とコスト削減の道が開かれた。しかし、運用方法については殆ど示されていないので、我が国の実情も踏まえ、科学的な製品研究開発と審査のあり方を具体的に示すことが急務となった。本分担では製剤工程開発の実情を調査した上で、承認申請の事例研究を実施する。この作業を通じて、規制当局へ提出される研究開発レポートの実物モデルの作成を含め、研究開発レポート及びその評価に関するガイダンスを作成することを目的とする。

ICHQ8-10実施作業部会（Q-IWG）では本研究班の実物モデルを基にした研修資料に採用されることとなり、21年度はその作成に参画した。継続してQ-IWGの議論を参考にしながら、管理戦略の事例に基づくシナリオ作成、近赤外吸収スペクトル測定法(NIR)の製剤工程管理への適用事例研究、及びリアルタイムリリース試験（Real Time Release Testing: RTRT）における含量均一性評価のための試料数と評価（Large-N）という具体的なテーマに取り組んだ。

本年度は多数のサンプル数による含量均一性試験につき，推奨されるべき判定基準について既に国外で公表されている案、米国製品品質研究所（PQRI）主催のワークショップにおける議論の要点を調査・精査すると共に、統計学的な手法により、試験法の妥当性について検討した。RTRTにおける試験規格については生産者危険がより重要であるものの、従来法の試験規格との間に、生産者危険の観点で、ある程度の整合性が必要であると結論した。

NIRの製剤工程管理への適用事例研究では、実際の実験により得られた知見を基に、各極薬局方およびガイドラインなどを参考に、NIRメソッドの構築、分析法バリデーション、メソッドトランスファーおよびメソッドメンテナンスの実施方法を具体的に検討した。

RTRTを採用する場合の試験方法について，承認申請書（AF : Application Form）への記載方法について事例研究を行った。AFへの記載内容をCTD（M2/QOS及びM3）あるいは製品作業手順書（SOP）の記載内容と比較しながら検討し，特に「システム適合性」，「キャリブレーション」，「バリデーション」及び「再バリデーション」のAFへの記載内容について種々の議論を行い、次年度の研究班においても継続して検討することとした。

管理戦略のライフサイクルにおける課題検討においては、商業生産段階における品質面およびビジネス面での継続的改善を促すためには、上市後に想定される変更（サイト、スケール、設備など）について、具体的なケースを想定して対処法（管理戦略）を考案し、一連の知識を含めて工場へ移転することが有効であることを事例をあげて示した。技術移転及び承認後の変更管理において、中間品のCQAにフォーカスした管理戦略の必要性を提案し、継続的改善を促進するための薬事規制のあり方について議論した。

これらの研究班による検討内容は、国際調和された考え方の国内への具体的な導入だけでなく、Q-IWGのPoints to Consider（PtC）作成の議論に反映され、国際調和に直接貢献できたと考えられる。

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A．研究目的

日米 EU 医薬品規制調和国際会議(ICH)は、製品研究開発と品質管理に最新の科学と品質リスク管理の概念を取り入れることにより規制の弾力的な運用を実施するという方針を打ち出した（参考文献１）。新しい品質保証の概念における製品開発研究(Enhanced Approach)の具体例を示し、規制当局と企業が共通の基盤に立って医薬品開発研究を評価することを可能とさせる。これら新技術の導入の際に考慮すべき要因が例示されれば、企業に対しては新技術の円滑な開発と高品質の医薬品製造が、規制当局に対してはそれらの一層の科学的な評価が可能になることが期待される。結果として、医薬品開発期間の短縮、審査期間の短縮が可能になる。

今年度は昨年度の本分担の成果及び ICHQ8-10 実施作業部会（Q-IWG）の検討状況を参考にしながら、管理戦略の事例に基づくシナリオ作成、近赤外吸収スペクトル測定法（NIR）の製剤工程管理への適用事例研究、リアルタイムリリース試験（RTRT）における含量均一性評価のための試料数と評価（Large-N）、RTRT 適用時の承認申請書（AF：Application Form）の記載内容，という具体的なテーマに取り組む。

リアルタイムリリース試験（RTRT：Real Time Release Testing）を採用し、多量のサンプルにより大量のデータをリアルタイムで生成することができれば，工程管理および工程能力を向上させることが可能になる。一方、このようなシステムで含量均一性試験を行う際には，限られたサンプルをロットからランダムにサンプリングすることを前提とする、薬局方に規定されるような従来のロット出荷試験の方法及び許容基準が妥当であるのかと言う疑問がある。RTRT において適用される Large-N における UDU（Uniformity of Dosage Unit、製剤均一性）試験につき，既に国外で公表されている判定基準案を調査すると共に、推奨されるべき判定基準について検討することを目的とした。

近赤外吸収スペクトル測定法（以下 NIR）の製剤工程管理への適用事例研究では、多変量検量モデル/モデルフリー計算式（以下 NIR メソッド）の開発・検証から実適用に至るまでの、ライフサイクルに亘る課題の認識や効果的な運用方法について研究することを目的とした。事例として検量モデルおよびモデルフリーな適合性判定計算式を用い、製剤開発と連動した NIR メソッドの構築と分析法バリデーション、生産工場への技術移転における NIR メソッドのト

ランスファー、ならびに継続的なNIRメソッドのメンテナンスの実施方法を提案し、NIRメソッドのライフサイクルに亘る性能保証の手法を検討した。

AFの記載事項は承認後の製剤の品質を恒常的に保証するための企業側のコミットメントとして極めて重要と判断される。RTRT適用時のAFの記載内容をCTD（M2/QOS及びM3）あるいは製品作業手順書（SOP）の記載内容と比較しながら検討し，特に製造時の打錠工程中の錠剤の製剤均一性をNIRにより測定し，多数のサンプル数による判定基準を採用した場合の試験方法につき，最終的にMock作成を目的として事例研究を行った。

管理戦略は製品実現を達成するために重要な要素であり、ICH Q-IWGでも活発に議論されている。製品ライフサイクルにおいて管理戦略の展開をどのように取り扱うべきか、特に、承認後の継続的改善を促すための管理戦略に関わる課題を検討することを目的とした。

B．研究方法

RTRTにおける含量均一性評価のための試料数と評価（Large-N）では、現行のUDU試験規格、すなわち通常のサンプルサイズの含量均一性試験の判定基準と、これまでPhRMA（参考文献2、3）やEP（参考文献4）から提案されてきたRTRT用の判定基準を比較するため、検査特性（OC）曲線を作成し、それぞれの試験規格の品質保証性能について比較検討した。また、国内外でのLarge-N規格についての動向を調査するため、関連する会議、ワークショップに参加し知見を得ることに努めた。

近赤外吸収スペクトル測定法の製剤工程管理への適用事例研究では、検量モデルを用いた事例として錠剤中の主薬含量測定法、およびモデルフリーな適合性判定計算式を用いた事例として混合均一性のモニタリング法を採用した。これらのNIRメソッドを実際の実験を通じて構築し、実験により得られた知見を基に、各極薬局方（参考文献5，6，7）ならびにガイドライン（参考文献8，9）を参考にすることで、NIRメソッドの構築、分析法バリデーション、NIRメソッドトランスファーおよびNIRメソッドメンテナンスの実施方法を検討した。

NIRによるRTRTのAF記載内容の検討では、打錠工程中の個々錠剤の薬物含量をNIRにより測定し，Large-Nによる製剤均一性判定基準を採用する場合の試験方法につき，AFへの記載内容をCTDあるいはSOPの記載内容と比較しながら検討した。特に「システム適合性」，「キャリブレーション」，「バリデーション」及び「再バリデーション」のAFへの記載内容について，種々の具体的な事例を用いて行政側及び企業側からの視点に基づき考察を行った。なお，具体的な事例としてはサクラ錠AF Mock及び製剤機械技術学会PAT委員会の作成した記載例を用いた。また，行政側と企業側の議論の中から作成された簡潔記載モデルについても議論された。

管理戦略の事例に基づくシナリオ作成では、管理戦略の構築、検証と製品ライフサイクルとの関係について明らかにした（図1）。更に製品ライフサイクルを通じた管理戦略の課題を抽出し、具体的な考察を行なった。

国際会議・学会の際には、何らかの発表を行い本研究班からのデータ・意見の発信、およびフィードバックの収集に務めた。

C．研究結果

RTRTにおける含量均一性評価のための試料数と評価（Large-N）