Health and Labor Sciences Research Grants in FY2011
(Research on Regulatory Science of Pharmaceuticals and Medical Devices)
Joint Research Report
Research on Development and Manufacturing Information of Drug Substances
— R&D of Drug Substances by the Methodology of Quality by Design —

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Research Summary

Manufacturing methods of drug products have been registered and strictly controlled by the governments. Since companies need to submit an application or notification of change to the regulatory authorities even when they just hope to change Process Parameters (PPs) after marketing, both companies and the regulatory authorities have been consuming a lot of time, labor, and cost. Therefore, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) announced the following policies: the state-of-the-art science and the concept of Quality Risk Management shall be adopted in Research and Development (R&D) and quality control of drug products; and if development is implemented in accord with the above policy, the guideline also indicates principle where the above described can create a basis for flexible regulatory approaches. Although a reasonable quality control and cost reduction will be made possible by these policies, the specific methods for R&D have not been clearly indicated. Therefore, it becomes an urgent task to specifically indicate the whole concept of scientific R&D and reviews based on the actual situations in Japan.

In the last fiscal year, we illustrated the example of scientific R&D, and in order to make the processes of R&D and reviews more efficient, we investigated the actual situations of R&D of drug substances, which in accord with the methodology of so-called Quality by Design (QbD). Based on the information, we created the document sample of R&D report titled The Mock-up Sample of CTD 2.3.S.2 Drug Substances for Sakuramil (Draft) for submitting to the regulatory authority in Japan. In this fiscal year, we refined the document sample in accord with ICH Q11 Guideline, as well as created the example of description in Manufacturing Methods in Application Form (AF) both in Japanese and English versions based on the discussion on the risk-based description taking account of the content of the sample.

Upon the creation, the research group was formed by researchers in the industry, government and academia to analyze and discuss the obtained information. The group members are: National Institute of Health Sciences (NIHS); reviewers and inspectors of PMDA; the industrial circles

(companies participated in the Japan Pharmaceutical Manufacturers Association or Japan Bulk Pharmaceutical Manufacturers Association).

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A. Research Objective

Quality is the basis to ensure the efficacy and safety of drug products, and hence the effort to secure quality has been implemented under strict regulations. Pharmaceutical companies have to create a detailed description of each Process Parameter (PP) in Application Form (AF), and must conduct manufacture within the control range of approved PP. Since submission of an application or a notice of change is necessary when any change is need to be made in PPs or their control ranges by an introduction of new manufacturing equipment or process improvement, etc., both companies and the regulatory authority have consumed a lot of time, labor, and cost. In order to break this situation, ICH created the so-called Q-Trio Guidelines (Q8, Q9 and Q10) to introduce the concept of quality system in pharmaceutical regulations for emphasizing the responsibility and spontaneous effort of companies, and announced the policy that the state-of-the-art science and the concept

of Quality Risk Management should be adopted in R&D, manufacturing control, and quality control of drug products. Moreover, if the product is put into scientific and systematic R&D and demonstrated quality controls based on the results, the guideline also indicates areas where the demonstration of quality controls can create a basis for flexible regulatory approaches.

The implementation of reasonable manufacturing control and quality control are became possible by the above policies, and companies can reduce manufacturing costs including change control costs, while having a consistent manufacturing control and quality control from the stage of development to that of post-marketing. However, regarding the specific methods to implement the above policies, there is no clear description in ICH Guidelines. Therefore, there is a concern that, even if R&D and application for approval are made in accord with the new policies, there will be a delay in development and reviews of drug products if the interpretation of the validity of application contents based on research results is different between the applicant and the authority. It is an urgent to task for the industry, government and academia to corporate for investigation and research on the cases of R&D utilizing the state-of-the-art science in order to clarify the explanation of control strategy justification through J-NDA submission documents.

Meanwhile, ICH started the discussion on the guideline concerning development and manufacture of drug substances (Q11) in Jun, 2008 and has reached the final agreement (Step 4) in Apr, 2012 (the procedure for signing is ongoing at drafting of this report). Q11 is a guideline aiming to adopt the concept indicated in Q-Trio Guidelines for drug substances, and it has been hoped to adopt into Japanese pharmaceutical regulations promptly and smoothly.

This research group is formed for the purpose of creating an effective guidance for R&D of drug products in order to implement the new quality assurance policy briefly indicated in ICH guidelines promptly in Japan. The final goal is to promote scientific approval reviews which lead to more secured quality of drug products through this research.

In the research in FY2009, we clarified the requirements of starting materials, etc. based on the discussion on the starting point (starting materials) of drug substance manufacture which determines the processes subject to pharmaceutical regulations by the regulatory authority.

In the research in FY2010, we investigated the actual situation of R&D based on the research result in FY2009, and created the document sample of R&D report titled The Mock-up Sample of CTD 2.3.S.2 Drug Substances for Sakuramil (Excerpt) for submitting to the regulatory

authority.

In FY2011, we revised the document sample to be more harmonized with Q11 Guideline based on Example 4 in ICH Q11 Guideline. For the revision, we disclosed the results of the research in FY2010 on the website of NIHS to request comments from the public, and reflected the obtained comments. Moreover, we considered the points to concern for describing manufacturing processes of drug products developed by the methodology of Quality by Design (QbD)* in AF, and created the example of description in Manufacturing Methods in AF both in Japanese and English versions.

Glossary

- Quality by Design (QbD): A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (ICH Q8(R2))

B. Research Methods

This research group is formed by researchers and technical experts, who belong to Japan Pharmaceutical Manufacturers Association (domestic or foreign companies) or Japan Bulk Pharmaceutical Manufacturers Association, together with reviewers and inspectors of PMDA. As Pfizer Japan Inc. proposed to provide a sample data, this document sample was created based on the development data of Torcetrapib, which was developed by the methodology of QbD. We disclosed the result of FY2011 on the website of Division of Drugs of NIHS, and collected comments from Jun to Sep. We held the research group conference for 5 times (2011: Jun 29, Sep 27, Dec 6; 2012: Jan 19, Mar 27) and subcommittee for 2 times (2012: Jan 13, Mar 15), and then revised the document sample with reference to the obtained comments.

Upon the research, we referred to the following ICH guidelines and papers:

1) Q8 (R2): Pharmaceutical Development (http://www.pmda.go.jp/ich/q/q8r2_10_6_28.pdf)

2) Q9: Quality Risk Management (http://www.pmda.go.jp/ich/q/q9_06_9_1.pdf)

3) Q10: Pharmaceutical Quality System (http://www.pmda.go.jp/ich/q/step5_q10_10_02_19.pdf)

4) Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4) (http://www.pmda.go.jp/ich/q/qiwgq&a_10_9_17.pdf)

5) ICH QUALITY IMPLEMENTATION WORKING GROUP POINTS TO CONSIDER (R2) ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation

(http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html)

6) Guidance Relating to Manufacturing/Marketing Approval Application Registries for Medicines based on the Revised Pharmaceutical Affairs Law (PAB/PCD Notification No. 0210001 as of Feb 10, 2005)

(Consideration for ethical aspects)

There is no item requiring consideration for ethical aspects, since this is a research of the quality guidelines for drug products in Japan, US, and EU, as well as a research of investigating the actual conditions for quality criteria and manufacturing processes, etc.

C. Research Results

I. The creation of the final version of the document sample of Sakuramil

1) The relationship between the target product quality profile of drug products and CQAs of drug substances

In Q11 Guideline, it is recommended to specify Critical Quality Attributes (CQAs) * of drug substances by connecting with Quality Target Product Profile (QTPP)* of drug products and CQAs of products. In the guideline, it is described that "The intended quality of the drug substance should be determined through consideration of its use in the drug product as well as from knowledge and understanding of its physical, chemical, biological, and microbiological properties or characteristics, which can influence the development of the drug product (e.g., the solubility of the drug substance can affect the choice of dosage form). The Quality Target Product Profile (QTPP) and potential CQAs of the drug product (as defined in ICH Q8) can help identify potential CQAs of the drug substance. Knowledge and understanding of the CQAs can evolve during the course of development." In this document sample, we also described QTPP and CQAs of the drug product of Sakuramil as recommended in Q11.

2) Description of the validity of starting materials selected in accord with the principles for the selection in Q11

In Q11 Guideline, it is requested for applicants to explain the validity of the selection of starting materials to the regulatory authority, and therefore the following information is necessary to show the validity:

- The ability of analytical procedures to detect impurities in the starting material
- Impurities in starting materials in subsequent process and the fate of their derivatives
- The degree of contribution of specifications of starting materials to quality control strategies for drug substances

In this document sample, we discussed the validity of the selection of starting

materials by adding the figure for impurities in starting materials and the fate of their derivatives.

3) Use of appropriate terminology

We unified terminology and kept its consistency through close examination of the document sample.

4) Addition of explanation

Since we obtained comments for the document sample of FY2010 asking for the reason of the description, we described reasons when explanation is necessary, so that the background and reason of description can be understood simply by reading this document sample.

II. Description in Manufacturing Methods in AF

1) Introduction

In the quality regulation system in Japan, process parameters (PPs) pre-determined in Manufacturing Methods in Application Form (AF) should be described separately in 2 categories based on the assessment result of the impact on final products when they are changed. We discussed how to describe AF in cases where R&D in accord with QbD are implemented, and created the sample of description in Manufacturing Methods in AF based on the discussion. The background and objective of the creation of the sample are described in the following.

2) Current AF

AF is required to be submitted only in Japan, and it is a component of Module I (regional requirements) in CTD format. Quality of drug products and the appropriateness of manufacturing methods and process control are reviewed based on the information described in Module II and III in CTD, and items described in AF are subject to regulations of the Pharmaceutical Affairs Law. Meanwhile, the description of Module III itself is subject to pharmaceutical regulations in Europe and US. In Q11 Guideline, it is also mentioned at the beginning of "4.Description of manufacturing process and process controls" that "The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance." Information should be provided to adequately describe the manufacturing process and process controls (see ICH M4Q (3.2.S.2.2)." Internationally, the description written in "Description of Manufacturing Process and Process Controls" in CTD 3.2.S.2.2 is subject to pharmaceutical regulations.

Figure 1

In the approval system in Japan, when describing manufacturing methods and process control in Manufacturing Methods, it is required to select whether those are included in items that require applications for partial changes in approval for any

change (hereinafter referred to as “items requiring approval for partial change”)* or items that can be changed by simply submitting a minor change notice (hereinafter referred to as “items requiring only a minor change notice”).* For drug substances of chemical entities, the followings are examples of items requiring approval for partial change: changes in the reaction process; changes in the outline of process operations after the final intermediate and raw materials used; changes in the outline of process operations (when the process is important) and raw materials used; changes in information on the test method and judgment criteria when important intermediates and important processes are tested as part of the release test; changes in items that require particularly strict control among those related to the starting materials, important intermediates, and control criteria and methods for raw materials; changes in test methods and judgment criteria that require particularly strict control among those used to guarantee that parameters related to the final and important processes, as well as these processes, are adequately controlled.

In order to flexibly utilize the operating conditions described in AF, the system to set target/set values* is adopted in Japan. Regarding PPs which are determined as target values, the acceptable ranges of target/set values is set in the standard operating procedures (SOPs). As a matter of course, manufacturing equipment should be controlled and set in accord with the pre-determined PPs at the time of manufacture. However, in the actual situations in manufacture, it is assumed that there are cases where values are varied within certain ranges, and do not accord with the pre-determined PPs. It is not appropriate to regard every deviation of PPs as a violation of approval, and hence not allow their shipment.

Therefore, for PPs which do not have impact on quality when they are varied within the range of variation, it is considered reasonable to define those PPs as target/set values and specify their ranges of variation in the product master formula or SOPs instead of AF. By the introduction of target/set values, it became possible to accept variations as long as they are within the pre-determined ranges, and if actual measured values are not within the range of variation in the commercial production, it also became possible to assess the validity of drug products manufactured under deviated conditions by the specifications GMP deviation control.

3) Risk-based description of manufacturing methods of Sakuramil

By a system which allows the flexible application of regulations, it became possible to classify items into those requiring approval for partial change or those requiring only a minor change notice at the time of application, as well as to describe PPs as target/set values.

However, regarding what procedures should be taken to include the description of manufacturing methods in AF, both the industry and the regulatory authority hardly have any experience, and hence it was difficult for applicants and regulatory personnel to share the achievement of QbD. Therefore, we clarified the manufacturing process development and risk management of Sakuramil, and created the flow diagram covering items for R&D through to items described in AF (the figure in Appendix of the document sample – 4).

Regarding the creation of this flow diagram, we reflected the opinions concerning the criticality in “Points to Consider: Relationship between risk and criticality created by ICH Q-IWG (Quality Implementation Working Group)”. In the above document, it is mentioned that “Risk includes severity of harm, probability of occurrence, and detectability, and therefore the level of risk can change as a result of risk management. Quality Attribute criticality is primarily based upon severity of harm and does not change as a result of risk management. Process Parameter criticality is linked to the parameter’s effect on any critical quality attribute. It is based on the probability of occurrence and detectability and therefore can change as a result of risk management.” In accord with this understanding, CQAs are determined only by severity of harm in this flow diagram.

PPs other than those judged to have no impact by risk assessment are identified in a typical scheme of R&D of drug substances in accord with QbD (the development of Sakuramil is also a typical example). We included those PPs in the Design of Experiments (DoE), and assessed the degree of impact on CQAs by variation of each PP. As a result of analysis by DoE, we concluded that if PPs have no negative impact on quality unless they are varied in unrealistic range, it is not necessary to regard them as CPPs but as “other PPs” even when they are considered to have significant impact on CQAs from statistical and functional perspectives (Critical Process Parameter (CPP)* in the definition in Q8). In addition, “other PPs” includes PPs that cause no statistically significant variation on CQAs as a result of DoE, and considered to have hardly any impact on CQAs. Meanwhile, we regard PPs as CPPs if they have a negative impact on CQAs when varied within the assumable ranges. Hence, we added PPs which are proved to have no impact by risk assessment, and classified PPs into 3 stages.

Need of description and classification of minor notification/partial change in AF are resulted from risk assessment and obtaining the agreement from the regulatory authority are included in the process of risk communication.

Therefore, description of those items will be determined on a case-by-case basis as the description includes reliability of the used model, quality system of applicants, and robustness of supply chains, etc.

In this document sample, we assumed that it is possible to classify PPs by the level of risk when they are judged CPPs by risk assessment: if risk can be reduced by risk control, those CPPs are ranked as medium risk; or otherwise, those CPPs are ranked as high risk. Based on this assumption, PPs are classified into the following categories: (1) CPPs ranked as high risk; (2) CPPs ranked as medium risk; (3) other PPs ranked as medium risk; (4) PPs judged to have no impact by the risk assessment.

We considered that, when describing PPs in AF, PPs can be regarded as items that can be changed by simply submitting a minor change notice if they are other PPs, or PPs which are CPPs but their risk level was decreased to medium by setting appropriate control strategies for risk control. Further, we proposed a measure to set PPs with appropriate ranges depending on judgment of applicants. By introducing this measure, it becomes possible to change PPs within the pre-determined ranges in accord with quality system manufacturing companies, as well as to change the ranges themselves by submitting a minor change notice.

The risk of variation in PPs is different depending on whether Design Space (DS)* is set or not. We decided to describe the components of DS in AF because it is necessary to know which components constitute DS during the reviews, inspections and change controls over product life cycle.

Glossary

- Critical Quality Attribute (CQA): A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8(R2))
- Quality Target Product Profile (QTPP): A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product (ICH Q8(R2))
- Items subject to partial change approval application: When changing manufacturing methods, the content of change needs to be submitted to the regulatory authority with attachment to prove the validity the change. The change is made only after those are reviewed and approved.
- Items that can be changed by simply submitting a minor change notice: When changing manufacturing methods, the content of change needs to be submitted to the regulatory

authority within 30 days after shipment of products. Materials to support the validity of the change should be stored within the companies.

- Target/Set values: Target values are defined as values obtained as a result of implementing a manufacturing process (e.g., values obtained by measurement), where as Set values refer to values pre-determined in order to establish the condition for a manufacturing process. Whether target values and/or set values should be established and whether these values need an application for partial change in approval or simply a minor change notice suffices in order to change them should be determined on a case-by-case basis for each manufacturing process (PFSB/ELD Notification No. 0210001 as of Feb/10/2005).
- Critical Process Parameter (CPP): A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (ICH Q8(R2))
- Design Space (DS): The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8(R2))

D. **Consideration**

In Japan, some marks have been used when describing PPs in AF in order to distinguish items requiring only a minor change notice and items requiring approval for partial change, as well as to distinguish the target value/set value, and others (Table 1). There was no regulation existed or operated regarding range description of PPs while regarding those PPs as items requiring only a minor change notice. This may because it has been considered there are risks if PPs described with ranges can be changed by simply submitting a minor change notice. This example of Sakuramil is based on the assumption that it is possible to describe PPs with their ranges with the following conditions: drug substances are manufactured in accord with QbD; DS was set by DoE; and parameters can be operated at a medium risk level.

The rationale of the above is that, unlike the cases of verified Proven Acceptable Range (PAR)* obtained from the univariate experiments, it can be considered that the risk has been

sufficiently decreased regarding the case of the document sample, because impact of PPs when they are varied is investigated by DoE, and knowledge of the knowledge of the relationship between Edge of Failure (EOF)* and PPs has been deepened.

However, as a matter of course, if PPs are deviated from pre-determined, it is necessary to conduct verification of quality in accord with GMP control procedure even though deviation is within the range of DS determined by DoE, and shipment of the products will not be allowed if the deviation is judged inappropriate as a result of verification.

Table 1

In the description sample of AF, cases are classified into 3 categories depending on the relationship between DS of PPs and EOF (Figure 2). The 3 categories are the following: cases where EOF exists within the range of planned DS, and the end of DS is close to EOF (Critical Process Parameters (CPPs) ranked as high risk); cases where EOF exists within the range of planned DS but the end of DS is far from EOF by setting the range of PPs to be smaller than DS (CPPs ranked as medium risk); cases where there is no EOF within the range of planned DS (other PPs ranked as medium risk).

Figure 2

A major element when judging the risk of PPs is “a distance” between the limit of DS determined by DoE (the end of the range of PPs) and EOF. Further discussion is necessary for determining how much distance is considered to provide sufficient risk reduction. We made a proposal that it is effective to adopt the concept of process capability index (Cpk) into risk assessment of PPs (Figure 2). It may be possible to consider that the risk is sufficiently reduced if Cpk is not less than 1.5 and fraction defective is not more than 10 ppm. The degree of risk will be a further discussion topic since it is varied depending not only on the probability of occurrence but also on severity and detectability of damages, and hence it may be difficult to set uniformly.

Figure 3

The risk of variation of PPs is different depending on whether DS is set or not. Since it is important to know which components constitute DS during reviews , inspections and change controls over product life cycle, we considered that it is necessary to describe the components of DS in AF so that they are easily understood.

In addition, there are opinions submitted from the industry: it would be better if it is not necessary to describe all

PPs used in DoE in AF; and it also would be better if it is not necessary to describe PPs which are verified to have no impact or less probability on quality as a result of DoE and risk assessment (other PPs, no impact) in AF and they can be regarded as in-house control values. Unlike US where changes are reported in annual reports, in order to understand manufacturing processes from the description in AF, the Japanese regulatory authority requests to describe PPs in AF even it has less probability to have impact on quality. We need to discuss further on how much information should be described on the application, as well as to discuss on the establishment of a system of annual reporting, etc.

The concept of manufacturing control or quality control for drug substances/products developed by the methodology of QbD is different from conventional concepts, it will be necessary to have more scientific and risk-based GMP inspections. After receiving the first regular inspection, the inspectors are changed from PMDA to the local prefectural governments. However, uniform inspections are required for manufacturing medicinal product with QbD. Therefore, it is necessary to transfer the inspected information from the PMDA to the local prefectural governments appropriately.

E. Conclusion

In cases where DS is set, the way of describing manufacturing methods in AF can be different depending on company policies and the risk level of PPs. In this research, we considered the risk of PPs by focusing on the relationship between PPs and EOF, and concluded that the range description of PPs is possible as items which can be changed by simply submitting a minor change notice.

Glossary

- Proven Acceptable Range (PAR): A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria (ICH Q8(R2))
- Edge of Failure (EOF): An edge where quality becomes not compliant with related quality properties when operated within certain parameters.

F. Health Hazard Information

Not applicable

G. Research Presentation

Paper Presentation

- Sakai-Kato K., Nanjo K., Kawanishi T., and Okuda H., "Rapid and sensitive method for measuring the plasma

concentration of doxorubicin and its metabolites" Chem. Pharm. Bull. Chem Pharm Bull (Tokyo). 2012;60(3):391-6.

- K. Sakai-Kato, K.Ishikura, Y. Oshima, M. Tada, T., Suzuki, A. Ishii- Watabe, T. Yamaguchi, N. Nishiyama, K. Kataoka, T. Kawanishi, H. Okuda, “Evaluation of intracellular trafficking and clearance from HeLa cells of doxorubicin-bound block copolymers.” Int J Pharm. 2012 Feb 28;423(2):401-9.
- Ohno A, Kawanishi T, Okuda H, Fukuhara K., A New Approach to Characterization of Insulin Derived from Different Species Using (1)H-NMR Coupled with Multivariate Analysis. ChemPharm Bull (Tokyo). 2012;60(3):320-4.
- Okuda H, Revised Points in the Individual Monograph – (2) Newly Listed and Listed Drug Products, Pharmacies, 62(6) 2667-2674 (2011)
- Okuda H, Major Revised Points of The Japanese Pharmacopoeia of Sixteenth Edition, Journal of Tokyo metropolitan society of health system pharmacists, 61, 8-14 (2012)

Conference Presentation

- Okuda H, Objective of ICH Q11 Guideline and the Outcome of Research Group Conference of FY2010 Health and Labour Sciences Research Grants – Working together toward smooth implementation of Q11 – Aug 5, 2011 (Tokyo)

H. Application/Registration status for intellectual property right

Not applicable

Figure 1

Approval System in Japan

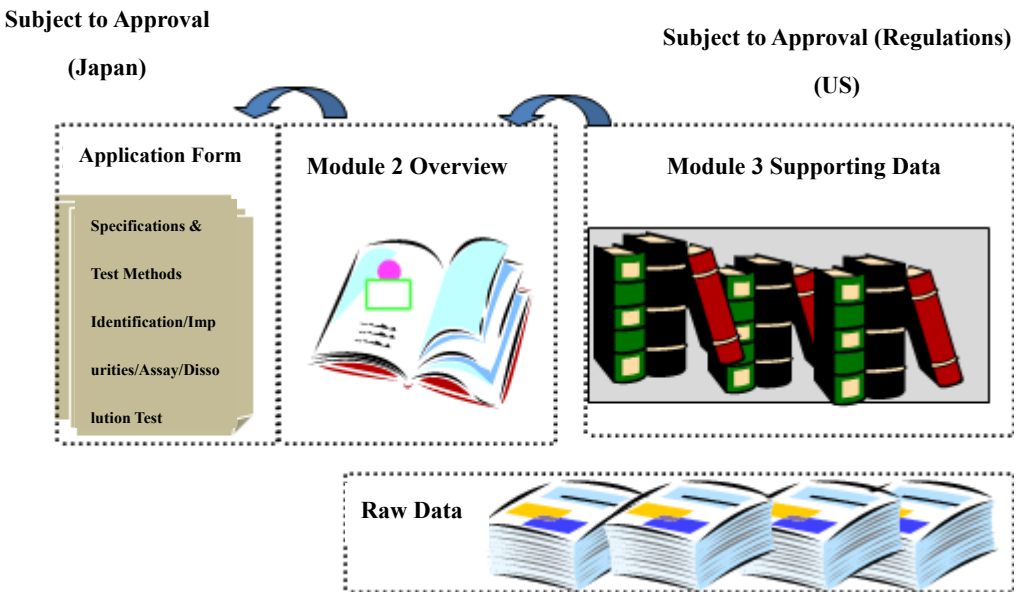
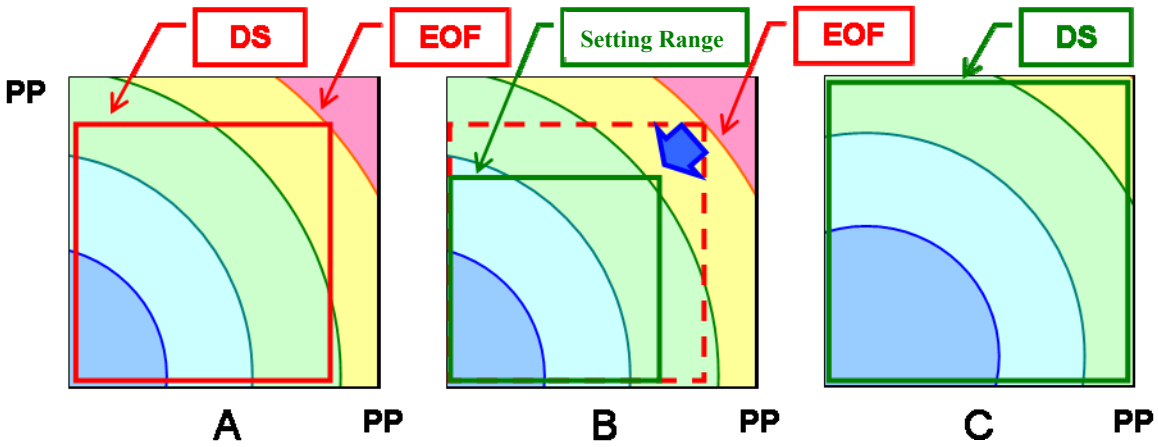


Table 1

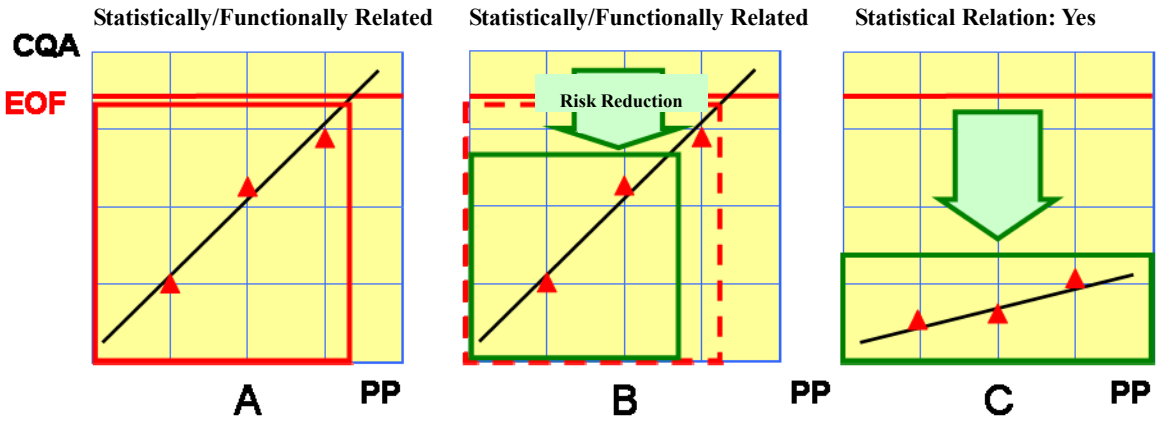
	Other than Target Value		Target Value
	Single Point Description	Range Description	
Partial Change	●	● – ●	<< ● >>
Minor Change	" ● "		< ● >

Figure 2

Concept of Risk of PPs When Setting DS from the Results of DoE



The image of the relationship between CQA and PPs in the above figure is indicated in the below figure:



A.	Cases where Edge of Failure (EOF) exists within the range of planned Design Space (DS), and the end of DS (the range of Process Parameters (PPs)) is close to EOF
B.	Cases where EOF exists within the range of planned DS but the end of DS is far from EOF by setting the range of PPs to be smaller than DS
C.	Cases where there is no EOF within the range of planned DS, and the realistically expected range of PPs is far from EOF

Figure 3

Concept of Realistically Assumable Range of PP