Activity Summary of the 14th Term (April 2018– March 2020)	
Study Group	**Joint Special Project Group 1 (K-T-1)**
Theme	**Roles of development QA for Pharmaceutical Products Lifecycle**

Human resources involved in quality assurance of medicinal products during development stage are limited in many cases. Within that context, roles of development QA in lifecycle of medicinal products were discussed and summarized for more effective and efficient quality assurance. Business that QA should perform according to GMP were classified by priority based on the PIC/S GMP guide. Points to notice in GMP especially for “Development QA” in charge of quality assurance of investigational medicinal products (IMPs) during development stage were discussed.

<The definition of development QA in this study>

• Building and maintenance of Pharmaceutical Quality System during development stage
• Investigational Product GMP.
• Quality Assurance during technology transfer stage to commercial manufacturing.
• Standards of Reliability of Application Data of CMC Documents

<Review method and Discussion>

Team members read and discussed CHAPTER 1 to 9 and Annex 13 of PIC/S GMP Guide, Version PE 009-14, July 2018″

The written requirements were classified into the following (I), (II) and (III) in accordance with the level of involvement of QA. And then, the roles of QA were discussed focusing on the items (II) and (III).

(I) Business that relates to all staff including QA and that QA should understand.
(II) Business that QA may perform or be involved in.
(III) Business that QA obviously performs or should be involved in such as approvals, etc.

According to the PIC/S GMP, roles of development QA are not limited to the quality assurance of IMPs but also building of quality through the lifecycle of medicinal products. In addition, as for IMP manufacturing, judgement of IMP-specific situations is required as discussed based on the Annex 13. QA has responsibilities to understand the risks, complexity and flexibility which are specific to IMP manufacturing, to build and maintain quality system and to ensure it practically functions. For those objectives, a wide range of knowledge about pharmaceutical development and clinical trials is also required.

<Conclusion>

- Based on the PIC/S GMP guide, major points of roles of quality assurance department were discussed and summarized by importance.
- For development QA, it was confirmed that a wide range of knowledge covering overall lifecycle of medicinal products is required.
- Considering “speed” required during the development stage, it was regarded as essential that all personnel involved in GMP should have awareness and knowledge about quality.

Activity Summary of the 14th Term (April 2018– March 2020)	
Study Group	**Joint Special Project Group 1 (K-T-1)**
Theme	**Data integrity during the development phase** **- Focusing on reanalysis of chromatograms -**

Many guidelines on data integrity have been issued, including drafts. In this project, we worked as the development phase topics working group and started to investigate "whether there is data integrity specific for the development phase."

To better understand data integrity, we read and analyzed the book "Practice! Approach for Data Integrity" (in Japanese) and realized that data integrity is required through the drug lifecycle and has the same requirements during the commercial manufacturing phase and the development phase.

Using the FDA Warning Letters, we investigated the compliance status of data integrity at manufacturing sites. There were many findings on the handling of electronic data in the Warning Letters, which were mostly related to arbitrary handling of dynamic data.

Using high-performance liquid chromatography (HPLC) data as dynamic data, we focused on the reanalysis of chromatograms, in which operators' intentions are easily reflected. During the development phase, quality and processes are under consideration and not optimized. Therefore, "manual analysis or reanalysis" of HPLC data is likely to occur more frequently during the development phase than during the commercial manufacturing phase. We thus established the procedures for reanalysis to investigate the actions required in cases of system operating errors and incorrect data handling caused by human errors and poor understanding of data integrity.

Reanalysis is an operation necessary for obtaining quantitative values by appropriate waveform analysis, and the procedures for switching from basic automatic analysis to reanalysis are important to avoid *ad hoc* reanalysis. The purpose of reanalysis is that we understand the nature of data deeply and correctly, furthermore, in order to ensure data integrity, it is important to confirm the principles of ALCOA +, such as data consistent and prevention of falsification and loss.

When reanalysis, which occurs frequently, is conducted during the development phase, the process of data generation and the validity of analysis should be properly determined, and the analysis methods should be modified and improved, which are useful measures to establish analysis methods for the commercial manufacturing phase.

Activity Summary of the 14th Term (April 2018– March 2020)	
Study Group	**Joint Special Project Group 1 (K-T-1)**
Theme	**A Study on Quality by Design and Materials related to CMC/Applications**

The International Council for Harmonisation (ICH) started in 1990, but its original purpose was to standardize the materials necessary for drug approval in Japan, the US, and Europe. Later, a new quality vision to "Develop a harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science" was announced at the GMP Workshop at the ICH Brussels Conference in July 2003, and the concept of Quality by Design (QbD) has emerged as a new ICH concept for quality assurance.

Drug development using the QbD method is necessary to produce quality drugs, and QA needs to understand its details. Therefore, the "Study on Quality by Design and Materials related to CMC/Applications" team read the following ICH guidelines on QbD and related materials such as lecture materials, and the team summarized the outline of, trends in, and important points of each guideline.

- ICH Q8 (Pharmaceutical Development)
- ICH Q9 (Quality Risk Management)
- ICH Q10 (Pharmaceutical Quality System)
- ICH Q11 (Development and Manufacture of Drug Substances)
- ICH Q12 (Lifecycle Management)
- ICH Q13 (Continuous Manufacturing of Dug Substances and Drug Products)
- ICH Q14 (Analytical Procedure Development)

As of October 2019, ICH Q12 is at step 3, so we selected the draft guideline from step 2 and created the deliverable. ICH Q13 and Q14 are at step 1, so there were no ICH guidelines as of October 2019. Therefore, we read the documents issued by public institutions up to this point and created the deliverable.

Understanding QbD is increasingly necessary for QA by each company. We hope that this deliverable will help QA personnel understand and implement the QbD method since it will become the mainstream of CMC development in the future.

Activity Summary of the 14th Term (April 2018– March 2020)	
Study Group	**Joint Special Project Group 1 (K-T-1)**
Theme	**Learning of basic knowledge of GMP and quality management**

Our team study GMP and Quality management.

- Study of Total Quality Management (TQM) which is the basis of ICH Q10 Pharmaceutical Quality System.
- Study of draft revision of the GMP Ministerial Ordinance.
- Study of KPI management.
- Study of Cause and effect diagrams, Control chart, Process capability index, and Pareto figure.

Firstly, we thoroughly read books of Dr. Eizaburo Nishibori, Dr. Kaoru Ishikawa, and Dr. Kosaku Yoshida (he is Dr. Deming's only one Japanese staff member), all of whom are pioneering leaders of TQM in Japan, to well understand quality management and roles of the quality assurance unit.

Secondly, we have studied a draft revision of the Japanese GMP to be issued, with the use of released documents. We plan to apply for that the questions raised in the discussion to public comments on Japanese GMP.

Thirdly, we have studied the performance indicator and make a training material about KPI management.

About Cause and effect diagrams, Control chart, Process capability index, and Pareto figure, which are also introduced in ICH Q9, have been compiled as KT1's internal materials. If you are interested, let's join KT1 and learn together!

Activity Summary of the 14th Term (April 2018– March 2020)	
Study Group	**Joint Special Project Group 2 (K-T-2)**
Theme	**Methodologies for Auditing Clinical Trials at Clinical/Medical Laboratories**

Good Clinical Laboratory Practice (GCLP), the reference of reliability assurance in CROs such as clinical laboratories or specified testing facilities, has attracted attention in the US and Europe. A Joint Special Project of JSQA has been also discussing this topic since 2008. GCLP will be relevant to quality assurance at contract laboratories including central laboratories and pharmacogenetic laboratories analyzing samples from clinical trials. Due to the recent revision of Japanese regulations (GCP Ordinance, guidance, etc.), the quality assurance of analysis of samples from clinical trials and the retention of records have been reinforced. Relevant investigation sites (trial facilities), sponsors, etc. are working to respond to these changes. In addition, cancer gene panel testing is now covered by National Health Insurance, and the search for biomarkers is heating up.

The Joint Special Project 2 Group (K-T-2) discussed issues with GCLP during the last term. The group decided to discuss topics related to recent environmental changes, planned activities, and worked on the individual themes listed below.

In this project, we attempted to present specific examples, such as survey results, and we worked on the above tasks to help each participant in clinical trials.

We hope that JSQA members find our findings useful when routinely conducting audits.

Group 1: Discussion of the current state of the handling/testing of clinical samples and quality improvement.

We have a poster every year at the “Conference on CRCs and Clinical Trials” in Japan. At the 18th conference (Sep 2018), we conducted a survey on temperature control for clinical samples and IMP. We identified issues with temperature control and discussed improvements. At the 19th conference (Sep 2019), we compiled incidents from K-T-2 members and shared their root causes and CAPAs.

Group 2: Auditing methodologies in bioanalysis

We had a poster for the bioanalysis forum supporters at the 10th JBF symposium based on a survey on "Auditing PK and biomarker testing." In addition, we summarized points to consider when auditing genetic and biomarker testing.

Group 3: GCP training materials for analysts

We explained the GCP training materials for people new to clinical sample analysis in the report of JSQA activities for the 14th term.

Activity Summary of the 14th Term (April 2018– March 2020)	
Study Group	**Joint Special Project Group 3 (K-T-3)**
Theme	**Issues in Regenerative Medicine**

Regenerative medicine is expected to treat diseases that have no effective treatment method so far. However, regenerative medicine involves risks on par with those of pharmaceuticals and medical devices. Its safety remains unknown because it is the newest therapy. Therefore, we need better quality risk management when developing a new regenerative treatment.
Through the 14th term, we studied challenges in developing regenerative medicine from both sides, i.e. conducting a clinical study and chemistry, manufacturing, and control (CMC).

[Clinical study group]

We compared the requirements of the 'Ministerial Ordinance on the Act on the Safety of Regenerative Medicine' with the regulatory requirements of the 'Japanese GCP Guidelines' and the 'Ministerial Ordinance on the Clinical Research Act.' By focusing on Specific Clinical Research, we identified some differences between these regulations.

[CMC group]

Continuing from last term, we discussed the requirements for quality assurance of regenerative treatments from the point of view of science and risk-based control. The materials we considered are listed below:

- PMDA review reports of regenerative treatments approved after 2017
- Notifications related to regenerative medicine over the past two years

We summarized important points in terms of indications or components as follows:

1. Recently, aspects of treatment of target diseases (indications or performance) have been classified as high-risk:
   - From autologous to allogeneic
   - From simple to complex pharmacological mechanisms
2. Autologous versus "off the shelf"

Even today, the regenerative treatments that have been approved in Japan are mainly "autologous".

- Autologous products always have temporal restrictions for patient treatment.
- Concerns specific to off-the-shelf products include donor eligibility, qualification, reproducibility, stability of the master cell bank, and scaling. That is very complicated, as indicated by the phrase **'The Process Is the Product.'**

3. Post-marketing evaluation in all patients treated with a product is of critical importance.