Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Joint Special Project Group 1 (K-T-1)**
Theme	**Understanding of Sakura Bloom Tablets Mocks**

The team studying "Understanding of Sakura Bloom Tablets Mocks" aims to understand the Sakura Bloom Tablets P2 Mock and deepen the understanding of the latest QbD concept not only from the technical point of view of formulation development, but also from the viewpoint of QA. In addition, the team has been working to ensure that the deliverable created is widely used as educational material at each company. Also, in response to the publication of Sakura Bloom Tablets Application Form Mock in February 2017, it also touches on the connection between P2 Mock and the approval application form.

By the way, in the process of reading and understanding the mocks, we described as the discussion results in this deliverable the items that are difficult to understand, and the items we would like to confirm as the conclusion changes depending on interpretation. We also conducted questionnaires about these mocks for K-T-1 members and described the results in the discussion contents. In addition, we sent questions to Sakura Bloom Tablets Mock Sub-group* that created these mocks, and received responses and comments. In addition to the results of our discussions, the answers are shown in the discussion contents.

In summarizing the results of these studies, we emphasize "not only to deepen understanding on pharmaceutical technology but also to make it more useful for QA personnel and for employees on site, and be easy to understand", we described the outline of the large flow and points of QbD on the deliverable. Also, comparing the idea of P2 Mock and important terms to recipes of "Niku-jaga" dish, we summarized the points in an easy-to-understand manner.

It would be greatly appreciated if this deliverable would be useful in understanding and implementing the ideas of QA-related persons in each company in the development by the QbD approach, which will be the mainstream of CMC development in the future.

*Japan Agency for Medical Research and Development(AMED)
Study project for regulatory harmonization & evaluation of drugs etc.
Studies on quality control approach to new development and change in manufacturing of drugs
“Studies on quality assurance throughout the drug product lifecycle”
Sakura Bloom Tablets Mock Sub-group

Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Joint Special Project Group 1 (K-T-1)**
Theme	**Management Review at development stage**

The process of Quality Management Review of Pharmaceutical products (Commercial products) is being generalized through the guidance indicated in the sharing research reports of Health Labour Science Research. However, it is supposed that each company individually conducts Quality Management Review at development stage including the decision whether to do it and how to do it.

In addition, GMP activities from development to the new-drug application (NDA) and/or post-marketing of Pharmaceutical products, it is considered that the manufacturing, the supply, and the quality assurance departments of Investigational Medicinal Products need to establish the appropriate management and the policies based on ICH Q10 and other related international guidelines from the global point of view.

For this reason, we performed questionnaires to understand the current status of Management Review of the companies in KT-1 group.

Based on the results of the questionnaires and each case of the team member’s companies, we presupposed Management Review at the development stage at a certain CMC Research Institute and discussed Quality Management Review at development stage referring to ICH Q10 and the sharing research reports of Health Labour Science Research.

We assumed the position corresponding to the "Senior Management" defined in ICH Q10, and the position corresponding to the "Management" reporting directly to the "Senior Management". On this basis, we discussed the Management Review at the development stage by the "Management", and prepared "Guidance on quality Management Review at developed stage".

This guidance shows the specific procedures and background concepts of Quality Management Review at the development stage. It would be great if you could refer it as a guide for carrying out Management Review at development stage.

Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Joint Special Project Group 1 (K-T-1)**
Theme	**Quality Culture**

Background

As a topic for this term, Quality Culture group has worked on the "Quality Culture" to obtain an understanding of requirements in the pharmaceutical industry. We first focused on a Quality Control required by regulatory agencies, also known as an academic background of Quality Culture, by learning the history and the evolution. Then, as an issue closely related to Quality Culture, we discussed further Data Integrity, Deviation, and CAPA (Corrective Action and Preventive Action) in order to make Quality Culture easier to grasp.

Achievement and Plans for the Future

Understanding Quality Culture based upon the history and the evolution of Quality Control, the intent of regulatory agencies for pharmaceutical companies is to achieve a continuous quality improvement through the lifecycle of drugs. For Data Integrity, we researched the "Dos and Don'ts" of data integrity processes and shared this understanding among each site. For Deviation and CAPA, we realized some gaps of understanding in a system of GMP that we deal with on a daily basis. Therefore, "risk-based approach to GMP", as a slogan of this group was determined and as a result, we would like to continuously maintain the concept of regulatory by grasping a proper understanding of the terms used in the guidelines. And further, promote the continuous improvements of Pharmaceutical Quality System in order to work on issues that are related to the vision and responsivities of QA.

Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Joint Special Project Group 1 (K-T-1)**
Theme	**Comprehension and practices of Quality Risk Management throughout the life cycle of drugs (II)**

The International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) adopted the Step 4 guideline ICH Q9 "Quality Risk Management" (QRM) on November 9, 2005. In Japan it was issued as the "Guidelines for Quality Risk Management" by the Director, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau (PFSB), Ministry of Labour, Health and Welfare (MLHW), and the Director, Compliance and Narcotics Division, PFSB, MLHW (PFSB/ELD No.0901004 and PFSB/CND No. 0901005) on September 1, 2006. Later on, the notification "Concerning Utilization of Quality Risk Management within Pharmaceutical Quality System" was issued by the Compliance and Narcotics Division, PFSB, MLHW on July 7, 2017 during our activity.

In the previous term, our goal was to comprehend QRM, and to practice QRM effectively both (1) when actual troubles, etc. occur and (2) for preventive actions, validations, etc. Consequently, after reading and understanding the "ICH Q9 Briefing Pack", we made the QRM mockup (1) for coping with troubles, gathering and investigating the cases of troubles from the member companies.

In the present term, our goal was set to practice QRM (2) for validations, etc. which was the remaining case of the previous term. QRM is carried out in many cases throughout the lifecycle of drugs and is necessary for preventive actions, validations, and so on. It is relatively easier for us to identify the risks and to evaluate the severity (1) for coping with troubles. However, QRM processes are more complex (2) for preventive actions, validations, etc. in order to previously prevent any troubles as part of development, production, laboratory control, material management, etc. and the following points were considered to be the key practical elements impacting the quality of QRM itself;

- how much risk should be identified
- what are necessary for sufficient risk identification
- where risk evaluation criteria to be set.

Therefore, the goal of our team in the present term was set to clarify the issues of the way of risk identification and risk assessment during QRM (how to ensure the objectivity of scoring, where evaluation criteria to be set).

Some of specific images and key elements of QRM (2) for validation, etc. could be clarified this time by practicing QRM for process validation with regard to the mixing process of solid formulation as an example, and by establishing the practice manual. We would be delighted if this deliverable helps you, who are struggling to practice QRM, by reading and understanding our way to the practice manual and the manual itself.

Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Joint Special Project Group 1 (K-T-1)**
Theme	**Discussion on the various problems of GMP under drug research and development phase**

In GMP activities from drug development to NDA / ANDA / post-marketing, the unit of manufacturing and the relating quality assurance unit need to establish policies for appropriate action and ways of thinking to close individual issues by a global standpoint.

Quality assurance of investigational products is being undertaken by each company systematically. However, since there is no direct descriptions of our specific concerns in "Standards for Manufacturing Control and Quality Control for Investigational Products (GMP for Investigational Products) No. 0709002 published on July 9, 2008" and overseas regulations related to GMP, there are many parts which depend on the policy and judgment of each company. It might be difficult to understand whether the individual understand / thought is compliance with the Regulatory authorities' request in regulations.

Therefore, our team had taken up up daily troubles / concerns / stress from QAs of investigational products development, had widely shared consideration and problems for them, and had summarized opinions that would be a solution or proposal as follows.

We hope our deliverables would be considered as " Case report of·Investigational products' GMP, JSQA version".

Vendor Management: Investigation on raw material (inc. API) suppliers and CMOs, Differences in the problem level in quality between Japan and overseas, Summrizing the impact of raw materials on investigational products quality, etc.

Investigational Products development: Evaluation for impurities during each phase / entire development period, Treatment of the change control in the development period, Development of placebo manufacturing, etc.

QC: Pros and cons on acceptance test of raw materials (inc. APIs), Introduce to Data Integrity, Quality assurance of raw data/records, etc.

GDP: Guidance about transportation for in-house and courier, Damage on shipments and trouble during transportation, Transportation study and stability guarantee, etc.

Organization Structure: Organization and structure of GMP for investigational products, Resource allocation, reservation, recruitment and training, etc.

QA: Self-inspection and Audit, Awareness / influence and business area of Development QA, etc.

Activity Summary of the 13th Term (April 2016 – March 2018)	
Study Group	**Joint Special Project Group 2 (K-T-2)**
Theme	**Audit Methodologies at Clinical/Medical Laboratories for Clinical Trials**

Good Clinical Laboratory Practice (GCLP) is being used in the US and Europe, and since 2008, JSQA has been considering this topic in a Joint Special Project. The Good Clinical Laboratory Practice (GCLP) will be relevant for Quality assurance of contract laboratories including central laboratories, pharmacogenetic laboratories conducting analysis of clinical samples. Due to the recent revision of Japanese regulations (GCP Ordinance, guidance, etc.), the quality assurance of sample analyses from clinical trials and the storage of records have been reinforced. The related investigator sites (trial facilities), sponsors, etc. are working to respond to these changes.
Joint Special Project Group 2 discussed the issues of GCLP during the last term. The group determined to discuss topics related to recent environmental changes, planned activities and worked on each theme as listed below.
Through this project, we attempted to present specific cases by using the results of questionnaires, and working on the above tasks so that our output will be helpful for each participant in clinical trials.
We hope that our output will also contribute to JSQA members' daily auditing activities.

Group 1: Discussion of the current situation and the quality improvements of the equipment for clinical trials
We have had poster presentations every year at "Conference on CRC and Clinical Trials" in Japan. In 2016, we collected information about the situation of the quality control for equipment from investigator sites through questionnaire, which were sent to JSQA GCP members. Following that improvements were discussed. In 2017, we focused on imaging and special equipment. And then we summarized these points in the 13th term activity report.

Group 2: Audit methodologies for Bioanalysis
For the bioanalysis forum supporters at the 8th JBF symposium, we had oral/poster presentations based on the questionnaire results of "The audit correspondence in bioanalysis". In addition, for the bioanalysis technicians of the JSQA GLP member companies, the questionnaire results on "Bioanalysis Temperature Management in Clinical Trials" were presented at "The 9th JBF Symposium". Furthermore, we began to prepare educational materials and checklists for primary analysts and/or auditors at bioanalysis facilities. We will continue considering these in the 14th term of JSQA.

Group 3: Changes due to environmental conditions in GCLP
We reviewed the historical and environmental changes related to GCLP up to the present, and discussed the current issues and prospects related to GCLP. Events related to GCLP were summarized in a chronological table. Furthermore, GCLP changes were organized and documented including the regional and international harmonization. The outline of main guidelines were explained in the activity report for the 13th term of JSQA.

Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Joint Special Project Group 3 (K-T-3)**
Theme	**Issues for Regenerative Medicines**

Regenerative medicine is really expected to treat the disease which has no effective treatment method so far. On the other hand, the risk of regenerative medicine is not lower than that of pharmaceuticals and medical devices. Its safety remains unknown because it is the newest therapy. Therefore, we need ~~for~~ more advanced quality risk management when we develop a new regenerative medical product.

Through the 13th activity term, we studied the challenges in developing regenerative medicine from both sides of conducting the clinical study and the chemistry, manufacturing and control (CMC).

Clinical study group

For the early realization of regenerative medical products, we should quickly shift to clinical trials to get approval from the stage of clinical research. Accordingly, we compared the requirements of 'Law on the Safety of Regenerative Medicine' with the regulatory requirements on 'Law on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics'.

This study is still ongoing. However, we have revealed some differences between the regenerative medicine provision plans and clinical trial protocol notification.

CMC group

We discussed the requirements of quality for the regenerative medical products from the point of view of science and risk-based control. The materials we considered are listed below:

- PMDA review reports of four approved regenerative medical products
- Evaluation index of next-generation medical devices
- Notifications related to regenerative medicine over the past two years

We cannot control the quality of regenerative medical products by only the specifications. We also cannot handle them uniformly without precedents. Thereby we have to identify all risks to be subjected to comprehensive risk management for each product.