GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 1: GLP regulations**
Subgroup	**L-1-1**
Theme	**GLP for drugs**

The course of action of the Subgroup 1, Study Group 1 in the 13th term has been set as "The mainstays of our activities are to collect and analyze cases found in the GLP compliance assessments for drugs, to discuss GLP-related topics/issues to propose countermeasures against them, and to organize GLP survey/inspection case report meetings. These activities intend to have members develop an understanding on GLP for drugs and contribute to improving member's skills as QA personnel through discussions taken place in the examinations of the issues. We also collaborate with the supervisory authority (PMDA) and Study Group 2 through information analyses concerning GLP training meetings and compliance assessments." According to the policy, continuing from the 12th Term (FY2014-2015), we planned to classify PMDA's instructions, search provisions for their rationales, and prepare a list of cases on the basis of the GLP survey/inspection case reports provided by members of the Japan Society of Quality Assurance (JSQA). Some forty people gathered, who expected to the presented Course of Action. However, actual activities in this term had been mainly comprised of consideration for the gathering of drug GLP compliance assessment cases and associated measures because the case reports intended to be used for the examination were not mostly submitted to the JSQA-GLP Division. Thus, as a measure for examination of cases, we analyzed deviation matters noted in the GLP Guidebook and cases obtained from a drug GLP fact-finding questionnaire given to all the members in the JSQA-GLP Division. Additionally, as the other activities, we also reviewed revisions to the practical QAU textbooks that the GLP Division made in this term and examined what group members had doubted and wanted to ask questions that arose during their works in their respective facilities.

We prepared the deliverable with the contents that the results of activities in the 13th term could be understood concretely and in detail so that it would be useful to the members who would conduct case analyses in the next term and thereafter. It was prepared dividing into two main parts: "The case gathering and analysis of GLP compliance assessments" and "The improvement of QAU skills."

In the part of "The case gathering and analysis of GLP compliance assessments," we described the results of "consideration of case gathering method" and "examination of case reports" For the former result, we included the following items as the results of consideration of measures to address the declining number of GLP compliance assessment case reports: "Consideration of reasons why cases cannot be reported," "Improvement of report formats and preparation of new formats for case gathering," "Documentation of the purpose and significance of case gathering," and "Preparation of a template of presentation material for GLP survey/inspection case report meetings." For the latter result, we described the analysis results of the following: a case report from one member facility, deviation matters which were reported in a GLP training meeting and obtained from the drug GLP fact-finding questionnaire. From the questionnaire, we learned that half of the GLP Division members had never undergone a drug GLP compliance assessment. This suggests that there are some members who cannot submit reports even if they want to. It was also thought to be a factor that may be inhibiting the gathering of cases.

On the other hand, in the part of "The Improvement of QAU skills," we included the following items "Taking part in revising practical QAU textbooks," "Questions following GLP training meetings," "Doubts and questions at hand" and "Themes for further investigation." For "Themes for further investigation," we created seven teams comprised of small numbers and studied in each team. The theme of each team was "Materials storage," "Acting as deputy of a study director," "Simplification of inspection of refrigerators," "Storage periods for common materials and management of environmental measurement data," "Management of electronic raw data," "Management method of equipment: the need for SOPs and use records," and "Digitalization of SOPs and its practical use." Some of these themes may deserve continuous examination, and others may need further examination at the division level rather than the subgroup or study group level. We hope that they will contribute to activities in the next term and beyond.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 1: GLP regulations**
Subgroup	**L-1-2**
Theme	**QA assessment points identified from virtual tests and case studies of medical devices and regenerative medical products**

Subgroup 2, Study Group 1, GLP Division, was organized in April 2004 (Term 7) and has since then made responses to the GLP Ordinance for Medical Devices, responded to institutional revisions, and engaged in comparisons and differential analyses of Japanese and foreign safety study guidelines. Additionally, since Term 11, we have discussed such problems and issues at hand that occur in members' daily activities in the context of "case studies." This term, we established regenerative medical products GLP as a new theme and, as in the past, established "case study" as one activity providing a venue for helping resolve problems faced by members. As a result, we discussed a total of 8 cases during these two years and derived conclusions as a subgroup.

Additionally, in this term, we envisioned virtual test articles in the subgroup for QAU assessment points concerning hemocompatibility study (other than hemolytic toxicity study), which is an area in which members have little experience conducting QAU assessment, as well as regenerative medical products, held discussions of test operations that will become assessment points in the testing of those virtual test articles from the standpoint of the risk-based approach, and extracted assessment points.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 1: GLP regulations**
Subgroup	**L-1-3**
Theme	**GLPs for agricultural chemicals, chemical substances, etc.**

In Subgroup 3 of Study Group 1, we discussed problems in the GLPs for agricultural chemicals, chemical substances, etc. During this term, we actively adopted the “consultation by e-mail” in addition to the “discussion about questions or problems at hand”. The purpose of the consultation by e-mail is the improvement in the GLP management of our own test facility by referring to the status of the GLP management of other test facilities. For example, in the consultation by e-mail about the inspection of the draft study plan by the QAU, the statuses of many facilities were gathered and it was found that the draft study plan came to be not inspected by the QAU in many facilities dealing with the GLPs for agricultural chemicals and chemical substances as well as the facilities dealing with the GLP for drugs, after the Pharmaceuticals and Medical Devices Agency (PMDA) stated that the QAU must not cooperate in preparing the study plan. We tend to be under the illusion that the GLP management of our own test facility is the best and only way. So, the consultation by e-mail is the suitable way to look at the GLP management from different viewpoints.

Following the previous term, the 2nd training meeting on the GLP for agricultural chemicals was held in cooperation among Food and Agricultural Materials Inspection Center (FAMIC), Japan Crop Protection Association and Japan Society of Quality Assurance (JSQA). In this training meeting, the questions and answers which had not been understood enough in the 1st training meeting were taken up again and we gained deeper understanding of them. The question and answer about the starting point of the archiving of documents was a good example. The starting point of the archiving was definitely shown and the long-standing doubt was believed to be cleared up. This training meeting on the GLP for agricultural chemicals will be held every other year.

It is said that there are six GLP programs in Japan. Our group summarized the differences between the GLPs for drugs and agricultural chemicals (chemical substances). The summarized document was used as the lecture material in the 8th GLP basic training course organized by JSQA. In the document, we took up the above-mentioned issue about the inspection of the draft study plan by the QAU and indicated that the QAU is not prohibited from inspecting the draft study plan in the GLPs for agricultural chemicals and chemical substances. In addition, with regard to the MAD (Mutual Acceptance of Data) system, we took up a problem in the MAD system among the GLPs in Japan. The unification of the GLPs in Japan is thought to be difficult now, but it is desired that the GLPs at least cooperate with each other.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 1: GLP regulations**
Subgroup	**L-1-4**
Theme	**Overseas GLPs**

JSQA has been studying overseas GLPs and compiled ‘Comparison of implementation of GLP between the US, the UK and Japan’ in 2008, and ‘Comparison of implementation of GLP between China, Korea and Japan’ in 2014 with questionnaire.

GLP Study Group 1, Sub-group 4 performed the survey of QA associations in 8 regions (the UK, France, Germany, Sweden, the US, China, Korea and Taiwan) who had concluded Memorandum of Understanding (MOU) between JSQA in the 12th period (the former term) regarding three topics (Archive, Process-based inspections, and Deviation). By this questionnaire, GLP implementation of these three topics was compared and the results were compiled.

In this term, we studied the topics further with the aim of presenting the results at the international meeting. We made out the poster with close investigation of the results and presented it at the 5th Global QA Conference (5th GQAC) held in Edinburgh, the UK in November, 2017.

As for the overseas topic, a draft document of FDA GLP Modernization was announced, which included many new important items. We tackled its tentative translation and went over the content. Since the document wasn’t finalized during the period, we decided not to finalize our tentative translation as a product document but to share it among the group as a reference. This would be useful when the FDA GLP Modernization document advances towards the next step, and we start to study it again.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 1: GLP regulations**
Subgroup	**L-1-5**
Theme	**Overall GLP issues and training**

We conducted the following activities and announced the outcomes of these activities to the public through presentations at academic conferences and making them available on the JSQA website and other media. We also trained GLP-QA personnel and study scientist/staff and helped upgrade their knowledge and skills through education and training on quality.

◆ Activity outcomes

1 Preparation of questions and draft answers for the GLP Training Workshop and their submittal to PMDA
2 Questions about the GLP Training Workshop and discussion of views with PMDA
3 Proposal on GLP related issues and solutions to PMDA
4 Research activities by working group
  4.1 Differences in high-risk cases between GLP study and and non-GLP studies using the risk-based approach
  4.2 Study of ways of operating electronic data archives using servers: possibilities for the use of external servers
5 Proposal of these training themes, implementation, and management for the GLP Basic Training Course and GLP Advanced Training Course
6 Public presentation of outcomes
  6.1 A risk-based approach is useful for quality assurance of non-clinical studies, 137th Annual Meeting of the Pharmaceutical Society of Japan [Sudo, et al. FARUMASHIA, Vol. 53, No. 2 suppl., p 166, 2017.]
  6.2 Guidance for GLP facilities on the implementation and maintenance of a risk-based Quality Assurance programme (MHRA), Japanese translation released on December 27, 2017, via the JSQA website

In the discussion meeting with PMDA, we proposed “The operation concerning the archive of electronic data using an external server” to PMDA and discussed solutions to this issue.

In the research activities by working group, we identified differences in high-risk cases between GLP and non-GLP studies in using the risk-based approach and discussed what the differences are and whether over-operation and over-procedure processes exist. In operation concerning the archive of electronic data using an external server, we identified electronic data storage patterns and discussed operations for each pattern. We utilized these two research outcomes as educational themes for the GLP Basic and GLP Advanced Training Courses and helped upgrade the knowledge and technical skills of QA personnel.

In the GLP Advanced Training Course, we invited a lecturer from PMDA for the first time to conduct training on “Quality assurance for computerized systems” and built a new training model based on collaboration among other groups and PMDA. These activities received high satisfaction ratings from participants.

In publicly presenting outcomes, we presented “A risk-based approach is useful for quality assurance of non-clinical studies” in the Pharmaceutical Society of Japan for the purpose of improving research quality in academia, which is a part of the drug development value chain. Additionally, we provided the information to JSQA members via the JSQA website to expansion of the knowledge for risk-based approach on QA.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 2: Quality management of non-GLP studies**
Subgroup	**L-2-1**
Theme	**Quality of CMC studies**

We considered CMC studies based on the fact that the overall research theme of Study Group 2 in this term's activities was "to prepare forms for 'records (worksheets)' that are important for tracing 'study protocols' providing the starting point for studies and studies themselves based on the essence of manuals and quality standards for quality assurance that supports efficacy, which is a topic that was considered up to the 12th Term" (CMC team). Additionally, we considered conducting a similar examination for investigational medicinal products and decided to examine the preparation of forms for processing instructions and records, and labolatory records for investigational medicinal products (team examining GMP for IMP).

The CMC team selected "stability study (long term testing)" and "validation of analytical procedures," which have different timing in CMC studies as well as different objectives and assessment criteria positioning, as target studies, and then considered the preparation of forms for "study protocols" and "worksheets" for them. We received information on study protocols and worksheets from the companies of participating team members and held discussions based on it. As part of these discussions, we narrowed items down to those needed to ensure quality in study protocols and worksheets and then studied reasons why each item was "necessary" or "unnecessary." Based on the results, we prepared forms for each and provided "reasons" clarifying the team's thinking as annotations.

In the team examining GMP for IMP, we borrowed the situations of "Sakuramil S2 Mock" (FY2011) and "Sakura Bloom Tablets P2 Mock" (FY2013) in the MHLW Grant-in-Aid for Scientific Research study report and considered the preparation of forms for processing instructions and records, and labolatory records for investigational medicinal substances and investigational medicinal products with a view to the production and quality testing of the virtual investigational product "L2-1 tablet." As we considered differences between drug GMP and investigational medicinal product GMP in our examination for form preparation, we prepared the forms while engaging in discussion designed to deepen team members' understanding of production/quality control for investigational medicinal products (substances) and demonstrate that perspective.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 2: Quality management of non-GLP studies**
Subgroup	**L-2-2**
Theme	**Discussion on essential structures and contents of study protocols and record-sheets in pharmacology studies for application use**

In the past JSQA activities, it had already been discussed and compiled as “essence of reliability” how we can improve quality of pharmacological studies for application use. However, the environments surrounding drug discovery are rapidly changing at the global level, and now not only quality but efficiency of studies is further required for researchers. On the basis of these backgrounds, we have further focused on the issues about study protocols which are the starting point for reconstitution of studies and thought to be important for eliminating arbitrariness in the studies.

In pharmacological studies with undefined forms, it is not realistic to conduct studies based only on protocols prescribing details of the studies, and this is different from the other fields such as PK and CMC studies in which study procedures are defined and standardizable. Furthermore, prescribing details in the protocols needs a considerable amount of time and would increase risks of erroneous descriptions in pharmacological studies with undefined forms.

Due to these circumstances, we tried to propose a simple combination of study protocol and record-sheet, which provides a study outline and supplement the study protocol, respectively, for pharmacology studies for application use. The minimal requirements for contents in the study protocols and record-sheets were also discussed.

The study number and study director must be clearly noted in the study protocol. Essential items to be provided are (1) study objectives; (2) names of the test articles, important reagents, and main devices; (3) test systems (e.g., species, strain, sex and supplier in the case of animals studies, and name, supplier, and culture methods in the case of cell-based assays); (4) group components; (5) outline of procedures (e.g., grouping, administration of the test articles, and evaluation methods in the case of animals studies, and assay methods or principals in the case of cell-based assays and biochemical assays); (6) methods of data processing and statistical analysis; and (7) decision criteria. The inclusion of other items may be left to the judgment of the individual facilities.

As for record-sheet requirements, in addition to the distinctive information of individual sheets, the record-sheet must include details of the study records at a resolution available for confirmation of its consistency with the study protocols and reports. Additionally, it needs to include appropriate maintenance and storage records of study materials to confirm their quality. In the preparation of a record-sheet, therefore, it was considered to be important for researchers to understand the minimal requirements beyond the undefined forms between studies. We considered the “5W1H” items (when, where, who, what, why, and how) to be important as notation requirements, and proposed to keep a simple structure to enable the items to be read easily.

In addition, we enhanced our own understanding during the above discussions by preparing mock-ups of study protocols and record-sheets based on typical examples of animal studies and cell-based assays.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 2: Quality management of non-GLP studies**
Subgroup	**L-2-3**
Theme	**Discussion of study protocols and worksheets in Drug Metabolism and Pharmacokinetic (DMPK) studies**

Previously, Study Group 2, GLP Division examined what items should be kept in mind to ensure quality in non-GLP studies and compiled the deliverables as the "essence of reliability." It was thought that such documents with the essence of reliability would be sufficient from the point of view of quality, hence, studies could be implemented with simplified study protocols, thereby research efficiency got improved. However, we found out that, even now, detailed study documents are prepared in many study facilities. We speculated it is because most study facilities think simple study protocols with only the essence of reliability is not always practical, and because past deliverables cannot fully explain how to applicate the essence of reliability in their studies.

Therefore, in this term, we have promoted activities aimed at proposing sample study protocols and worksheets that reflect the essence of reliability in three groups: Chemistry, Manufacturing and Control (CMC), pharmacology, and DMPK.

In group 3, we examined study protocols and worksheets for DMPK studies. To begin, we divided the group into an *in vivo* study team and an *in vitro* study team, and each team selected one typical study that forms the foundation of new drug application (*in vivo* study: pharmacokinetics of L-1323 in rats after single oral administration; *in vitro* study: *In vitro* metabolite profiling of ^{14}C-L-1323 in rat, monkey and human liver microsomes; L-1323 was the virtual test substance). For each of the selected studies, we first shared information on current circumstances in examining members' facilities, and then discussed whether or not description of individual items is necessary in the study protocol. Secondly, we prepared sample study protocols and worksheets based on the results of this examination. During preparation, we engaged in brainstorming on "scientificity" and "usability" which are important elements together with "quality," in order to consider how they should be incorporated. We then added hints that are useful for practical application from the point of view of scientificity and quality as commentary and worked to promote readers' understanding of notation content.

Finally, we considered by comparing the results of our examination with pharmacology studies. We found that, although the essential thinking vis-à-vis quality was almost the same, there were several differences in the extent to which it was noted in study protocols. These differences were thought to be attributable to factors that included the following: (1) most methodologies of DMPK studies are relatively established, (2) DMPK studies are conducted in accordance with various guidelines, and (3) many test facilities conduct DMPK studies in accordance with GLP principles.

Preparing simple study protocols that omit items other than the essence of reliability would lead to faster and more efficient implementation of studies, however, it is necessary to keep in mind that some items should not be omitted depending on the study content. Hence, it is necessary for study directors to comprehend the essential meaning of individual items and make decisions on their inclusion after fully considering what is needed for study reconstruction and precise test operation. Nonetheless, it may be difficult to make such decisions for inexperienced study directors, and thus it is recommended that "simplification of study protocols" be pursued depending on the level of experience with consulting experienced study directors and/or QA personnel. We hope our samples will be referred by such study directors during refining their study protocols and worksheets.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 2: Quality management of non-GLP studies**
Subgroup	**L-2-4**
Theme	**Study of training programs for Reliability Criteria**

This term (FY2016-2017), Subgroup 4, Study Group 2, GLP Division, Japan Society of Quality Assurance conducted activities on the discussion theme “Study of training programs for Reliability Criteria: Upgrading training item lists for personnel involved with Reliability Criteria (study divisions, quality assurance divisions, etc.) and preparation of training materials “research integrity”.

In the previous term, the Training Subgroup (L-2-3) of Study Group 2 compiled a list of training items for personnel involved in Reliability Criteria studies for the purpose of having them put to use in education and training planning by facilities. This list targets not only personnel involved in the implementation of Reliability Criteria studies but also all personnel associated with study implementation. Training can be selected from the list in accordance with each person’s position and level of experience.

This term, we conducted a further review of the items of the previous term’s list so that more detailed and necessary training will be made available to personnel involved with Reliability Criteria studies. We also established four “character” patterns corresponding to how people are associated with studies and summarized the points of view for each training item that are thought to be necessary for each character.

Moreover, we also took up the issue of “research integrity,” which is the foundation upon which researchers conduct fair-minded research, and prepared training materials for it in this term.

As questions arise concerning data fabrication, data falsification, and other wrongdoings in various industries, we engaged in repeated discussion on what fair-minded research is by referring to past materials and deliverables. We will provide training materials on “research integrity,” which serves as the foundation of research and covers all aspects of research, including the exploratory stage, not just studies in which “Reliability Criteria” are applied for approval applications the exploratory stage. This material is comprised of a general discussion and detailed discussion points, with explanations provided on each slide, making it possible to choose training content to fit targeted trainees in each facility.

It is thought that most of the instances of research misconduct that come to light in the pharmaceuticals industry lately were caused by declining awareness and morals vis-à-vis study quality. We hope that the training materials concerning the “training item lists” and “research integrity” that we prepared this term will prove useful in training conducted by facilities and thus help prevent such misconduct and improve awareness and morals among people involved in research.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 3: Computerized systems**
Subgroup	**L-3-1 (System Operation and Management)**
Theme	**Quality assurance procedures for computerized systems - Proposal for system operation and management -**

In recent years, the use of devices and computerized systems for the efficient execution of operations associated with drug research, development, manufacture, and application has become essential in the pharmaceuticals industry.

Various computer systems are even used in GLP studies of non-clinical studies for submittal to regulatory authorities. They include devices to control test environments; measurement devices for study assessments; computer systems used in data collection, processing, and editing; and document management systems for applications.

Operation and management procedures for computerized systems had been examined as part of the activities of relevant issue examining team until the previous term. However, with the issuance of OECD-GLP No. 17, we believe there is a need to consider anew the operation and management of devices and systems. Thus, for this term, (April 2016 to March 2018), we attempted to prepare activity guidelines for a “proposal for system operation and management.” In addition to GLP demands, we established the deliverable based on actual operations seen in the GLP organizations of companies in the industry.

We executed our activities in accordance with the following procedure 1) to 5).

1) Confirmation of regulatory classifications
2) Identification of the devices and computerized systems used in GLP facilities
3) Collection of information on operations in GLP facilities
4) System level classification
5) Proposal of specific procedures for system operation at each level

We hope that facilities will find the system operation and management procedures provided in this deliverable useful in improving their system operations.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 3: Computerized systems**
Subgroup	**L-3-1 (Supplier Utilization Study Team)**
Theme	**Quality assurance procedures for computerized systems "'Storage of electronic records in outsourced materials storage facilities' and "use of cloud computing' in non-clinical research in Japan"**

With recent advances in IT technologies and lower costs, the use of cloud computing in corporate activity is moving from a cutting-edge and forward-looking initiative toward an application of ordinary infrastructure. Using computing systems as a service without possession of physical resources, and not having data storage media containing possessed electromagnetic records, are becoming very commonplace.

Even in non-clinical research, services claiming to support GLP are starting to be offered by various suppliers, and it is conceivable that the storage of electromagnetic records outside the laboratory, such as in data centers and outsourced materials storage facilities, would have great benefits for non-clinical research facilities. However, introducing such services into non-clinical study settings is considered to present high-level challenges.

We, the Supplier Utilization Study Team of Subgroup 1, Study Group 3, Japan Society of Quality Assurance (hereinafter "the Subgroup"), have been examining issues envisioned in the use of the aforementioned services and technologies in non-clinical research and countermeasures since Term 10 (2010 to 2011). Additionally, in Term 11 (2012-2013), we conducted a survey to shed light on the "use of cloud computing" and "storage of electronic records in outsourced materials storage facilities."

At the beginning of our examination, Wanbishi Archives Co., Ltd., was, in fact, the only outsourced materials storage facility that supported GLP in Japan. However, since then, Amazon Web Service and Instem Cloud have started cloud services for non-clinical research fields. Given this, our Cloud Study Team conducted a questionnaire similar to that of Term 11 and attempted to observe any changes taking place in awareness and usage vis-à-vis external suppliers among domestic drug manufacturers and CROs.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 3: Computerized systems**
Subgroup	**L-3-1 (SEND examination)**
Theme	**Quality assurance procedures for computerized systems "Examination of reliability assurance for SEND"**

Study Group 3, GLP Division, began examination activities concerning SEND (Standard for Exchange of Nonclinical Data), which is a data standard for non-clinical toxicology studies, in the previous term (FY2014-FY2015). In the previous term's deliverable (Material No. 15L12), we reached the conclusion that, given time and technical considerations, the method of preparing SEND data packages (SEND data, Define files and nSDRG files) through cooperation (outsourcing, etc.) with a specialized company is efficient, at least at the beginning, and that SEND-related knowledge should be prepared so that specific requests for data composition, structure, etc., can be issued as experience is gained. Additionally, the formulation of methods concerning SEND's reliability assurance was mentioned as a task to be tackled.

This term, we decided, based on the results of our examination of the previous term, to examine methods concerning SEND's reliability assurance on the premise that the preparation of SEND data packages would be outsourced. The Examination Team prepared a consideration points for reliability assurance by third parties within the process of preparing SEND data packages from a preliminary questionnaire for the selection of an outsourcing contractor prior to the preparation of SEND data packages and study data. The team then summarized points to bear in mind for SEND-related reliability assurance. In addition, JSQA held a discussion meeting concerning SEND with outside organizations (Japan Pharmaceutical Manufacturers Association and CDISC Japan User Group).

1. Concerning the preliminary questionnaire to outsourcing contractors for the work of preparing SEND data packages

We prepared the preliminary questionnaire for the selection of an outsourcing contractor by referring to the main items mentioned in "Itaku-saki Sentaku-ji no Omo-na Ryuiten" (main points to consider when selecting outsourcers) of the deliverable of the previous term (Material No. 15L12) and the content of Partnership-level Points to Consider, SEND between Organizations, SEND Implementation Wiki, which is available to the public on PhUSE.

The questionnaire is a list of points to be checked when a sponsor (including QA personnel in some cases) selects a facility to outsource work in the work of preparing SEND data packages. It is assumed that the questionnaire will be used when sending preliminary questions in writing to outsource contractors.

2. Concerning the reliability assurance consideration points in the work of preparing SEND data packages

We prepared the reliability assurance consideration points to be used when third parties prepare SEND data packages by conducting an examination based on the standpoint of reliability assurance in the process of preparing SEND data packages and by referring to the content of the "SDTM inspection item list" that was created for quality certification in the Study Data Tabulation Model (SDTM), which is a data standard for clinical studies by JPMA.

It is assumed that the sponsor (including QA personnel in some cases) will use the consideration points when ensuring the reliability of a SEND data package prepared by an outsourcing contractor in the case of outsourcing, and that a third party who is other than the preparer will use the consideration points when ensuring the reliability of a SEND data package in the case of in-house package preparation (checking of the preparation process and QC work).

In our examination activities for this term, we concluded that it is necessary to formulate quality certification standards for SEND data as a point to remember in SEND-related reliability assurance. Because SEND is not subject to GLP regulations, GLP-compliant reliability assurance is considered unnecessary. However, examination of standards for compliance in ensuring quality of a certain standard and certifying quality for electronic data in applications to authorities is needed. The QMS of ISO 9001 is an example of a means for that. Reasons for this include the fact that SEND requires quality certification that is specialized for production and the need to also consider data integrity with final reports and raw data. We intend to make research that enables us to propose best practices for SEND-related reliability assurance by understanding SEND's characteristics and clarifying the scopes that can be covered by GLP and by ISO 9001 a topic for the next term.

We hope that this deliverable, which contains 1) the preliminary questionnaire and 2) the consideration points, will prove useful to people involved in SEND data package preparation and reliability certification. We should note that we plan to make corrections to the preliminary questionnaire and consideration points as necessary while sharing pertinent information with SEND-related external parties.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 3: Computerized systems**
Subgroup	**L-3-2 (interest group on QA role for CSV)**
Theme	**Upgrade of the skills of QA staff members who handle CSV and electronic data** **"The Roles of QA staff in quality assurance of computerized system"**

We have investigated the following two themes:

- Main theme: development of CSV-QA staff, who are engaged in the auditing of CSV processes
- Sub-theme: questionnaire survey on CSV of measuring instruments and manufacturing equipment

The main theme includes three topics:

- Questionnaire survey on development of CSV-QA staff
- Evaluation of effectiveness of GLP advance training course
- Support for creating the practical text for QA staff

Questionnaire survey on development of CSV-QA staff was conducted for members of the GLP Division of JSQA. This questionnaire survey revealed the following matters:

- Nearly half of CSV-QA staff in Japanese laboratories felt that they had sufficient abilities, but the rest did not.
- The majority of Japanese laboratories didn't have an effective training program for CSV-QA staff.

Based on the results of this survey, it became clear that many laboratories needed support for education and training for CSV-QA staff. JSQA can provide support for that, through provision of the training course and publication of the practical text.

For the GLP advanced training course, we conducted the following activities.

- Before the training course, we prepared the training plan with the evaluation questionnaire on training to be completed by the students.
- After the training course, we analyzed the survey results, considered the improvement measures and summarized them in the training report.

Study group 3 of GLP division prepared the "Investigation of computerized system" section of the practical text for QA staff. In order to ensure that the reliability of the text is secured and that the text is published within the deadline, we conducted review of the draft of the section and progress of the management of creation of the section.

As mentioned above, we investigated the current situation of the training of CSV-QA staff and conducted activities related to the training of CSV-QA staff.

As the sub-theme, we surveyed how much CSV of measuring instruments and manufacturing equipment is classified. The investigation clarified the following matters:

- Most of them are classified as software category 3.
- The implementation status of CSV varied depending on relevant regulations and others, but most of them were validated simply.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 3: Computerized systems**
Subgroup	**L-3-2 (Regulations examination)**
Theme	**Upgrade of the skills of QA staff members who handle CSV and electronic data** **Consideration of "the application of GLP Principles in computerized systems"**

1. Purpose of activities

Data life cycle and other new items were added to "Application of GLP Principles to Computerised Systems," Advisory Document of the Working Group on Good Laboratory Practice, OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring Number 17 (hereinafter referred to as "AD No. 17"), which is a set of guidelines concerning the computerization of GLP that was issued by the OECD in 2016, and consistency with GAMP 5, EU-GMP Annex 11, and 21 CFR Part 11 is established.

As a result, AD No. 17 has a significant amount of additional content compared to OECD Consensus Document No. 10, which had been referred to heretofore, and therefore it was decided that AD No. 17 would replace No. 10. Accordingly, employees involved with GLP will be required to accurately understand AD No. 17 from the standpoint of life cycle-based electronic data management. We therefore considered requirements of AD No. 17 by answering questions concerning AD No. 17 that were solicited from Study Group 3 members.

2. Activity outcomes

We received 60 questions, held discussions with team members on each, and summarized the results. The item receiving the most questions was "1.3 Personnel, roles, and responsibilities." This item was followed by "1.1.3 Qualification," "1.2 Risk management," and "3.6 Periodic review." The following provides a summary.

1.3 Personnel, roles, and responsibilities:

There were many questions concerning the roles of operation managers and quality assurance departments. In particular, there were questions about the qualifications and education needed to understand and evaluate CSV. We responded that the use of outside training, etc., should be promoted.

1.2 Risk management:

There were questions about risk management when GLP data and non-GLP data are mixed in the same system. We answered that management should be based on access authorization and physical separation.

3.6 Periodic review:

To questions concerning who should conduct reviews, how reviews should be conducted, and how records should be kept, we answered by providing concrete examples.

We also answered questions concerning items that received relatively little attention before, such as the roles of suppliers, electronic data archiving, and electronic data storage.

We anticipate that AD No. 17 will become broadly understood in Japan and that CSV based on its principles will be practiced.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 3: Computerized systems**
Subgroup	**L-3-2 (GxP comparison)**
Theme	**Upgrade of the skills of QA staff members who handle CSV and electronic data "Comparative examination of GxPs in computerized system-related guidance"**

Many forms of computerized system-related guidance have been issued in Japan and abroad, and companies must respond according to their needs. Moreover, it has been reported that, in recent PMDA-based GLP inspections, it takes more time for the inspections concerning computerized systems, and demand for use of computerized systems is growing year by year.
Our examination team discussed operations relating to computerized systems, we found that companies handle the matter in various ways. Additionally, members raised questions concerning the difficulty of decision-making vis-à-vis what should actually be done and to what extent. Members also expressed the view that there seem to be gaps in how responses are made among GxPs. Our examination team therefore considered the proper management of GLP computerized systems while also examining the following points.

(1) Comparative examination of GxPs

We conducted a comparative examination with focus on the following content in order to consider the main causes of gaps and common items among GxPs in the operation of computerized systems. We limited the scope of our examination to GLP/GCP/GMP.

- History and background
- Computerized systems and data handling
- Viewpoints and tendencies of regulatory authorities

(2) ALCOA

Because ALCOA was mentioned among the common items in our comparative examination of GxPs, we summarized ALCOA in the form of important keywords.

(3) Collection of computerized system-related guidance

We collected forms of computerized system-related guidance and then arranged and considered them from the following perspectives. It should be mentioned that we limited our examination to guidance forms primarily targeting GLP/GCP/GMP that were issued in Japan, the United States, or Europe. We also added guidance drafts in order to also examine the latest information.

- Categorization (domains [GLP/GCP/GMP], targets [CSV/data])
- Recent trends and relevance from the past

（4） Comparison of data integrity guidance

From our collection of computerized system-related guidance forms, we found that data integrated guidance is a common item and recent trend among GxPs. We therefore conducted a comparison of recently issued forms of data integrated guidance.

Our examination team successfully executed examination activities by taking full advantage of the expertise possessed by members who have practical experience with individual GxPs. The deliverable incorporates the elements of each GxP results and also has content with a global perspective. We hope it will prove useful as an aid in the proper management of computerized systems by companies.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 4: Quality assurance for non-clinical studies (Eastern Japan)**
Subgroup	**L-4-1**
Theme	**Examination of frequent questions/issues** **GLP, Reliability Criteria, and other general matters**

Study Group 4 mainly conducts activities in Eastern Japan area. Members belong to quality assurance departments, Research laboratories and QC departments. Our activities theme is the examination of topics concerning allover the quality assurance. Adopting a free discussion style, we primarily considered "frequent questions/issues in work" that members routinely encounter in their daily work.

In the first half of the term (FY2016), We were divided into three groups at random to discuss "frequent questions/issues in work" as a whole study group. And in the second half of the term (FY2017), we discussed matters in three separate subgroups: "GLP," "Pharmacology/Pharmacokinetics," and "Quality." During the 13th term, we discussed a total of 64 issues with focus on ensuring quality in daily work.

In addition, we held various seminars and lecture meetings in order to improve the quality assurance skills of the study group's members and to broaden their viewpoints. At the seminars, members presented cases of compliance assessment by regulatory authorities so as to deepen understanding of cases targeted for assessment and recent trends of those authorities. As for the lecture meetings, those led by visiting lecturer covered the topics of "human error: mechanisms and countermeasures" and "gamification: learning strategies for enhance training effects." Lecture meetings led by speakers of the Japan Society of Quality Assurance covered "learning from the fundamentals of auditing studies: an auditor training course based on risk-based auditing" and a lecture meeting on research data quality based on *GLP to wa: Shinraisei Kakuho no Kiseki* (what is GLP?: tracing quality assurance), a book for which JSQA served as supervising editor. We held a total of six lunch meetings that participants voluntarily attended during their lunchtimes.

Furthermore, we held GLP Division educational sessions entitled "The 6th Introductory Lecture Session for Persons in Charge of QA/QC Duties (Entry Course)" and "4th Training Course for Explanation of the GLP Ordinance for Drugs" in collaboration with Study Group 5.

As stated above, we worked on a wide variety of topics concerning quality assurance. In our activities, we improved our skills for quality assurance and created opportunities for learning about ways of thinking and attitudes to ensure quality in daily work through exchanges of opinions among all members.

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 5: Quality assurance for non-clinical studies (Western Japan)**
Subgroup	**L-5-1**
Theme	**Quality assurance for GLP studies**

Subgroup 1 of Study Group 5, as a Western Japan regional study group for “Quality assurance for non-clinical studies”, has been performing activities under the theme of “Quality assurance for GLP studies” for 2 years during this term.

Our main activities were to broaden the members’ perspectives and to develop networking among the members, and we worked on the following tasks:

1) Collection and examination of “specific cases of familiar or frequent questions/issues in the daily operations”
2) Timely exchange of opinions using a mailing list
3) Instructive lectures and seminars presenting topics of interest

We discussed 23 “familiar or frequent questions/issues” submitted by members and examined 6 opinions collected using the mailing list.

We held 7 instructive lectures and seminars covering a total of 8 titles.

In addition, we hosted the JSQA GLP Division educational sessions: the 6th entry course entitled "Introductory lecture to the person responsible for QA/QC" and the 4th training course entitled "Explanation for Ministerial Ordinance on GLP of Drugs", in collaboration with Study Group 4 addressing the same theme in eastern Japan. Furthermore, we joined in the cooperative effort to revise and publish "The practical textbook for the person responsible for Quality Assurance".

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Study Group 5: Quality assurance for non-clinical studies (Western Japan)**
Subgroup	**L-5-2**
Theme	**Quality assurance for non-GLP studies**

As a study group based in western Japan, L-5-2 has been acting under the theme of “Familiar Questions/Issues on Ensuring Quality for Non-clinical Studies− Studies Compliant with Standards for the reliability of application data.” Additionally, we targeted items related to the work of the members of the group and our examination also included GLP studies, etc.

Along with our main activity of examining familiar questions/issues (19 cases), we had timely exchange of opinions using a mailing list (1case), instructive lectures and presenting topics of interest (6 titles). In the deliverable, the 19 cases of familiar qestions/issues and the one case of exchanging opinions by e-mail are summarized, and the background, conclusion and exchanged-opinions are provided. Additionally, the familiar questions/issues are categorized into 8 items consisting of “study plans/amendments”, “test articles”, “study results”, “study reports”, and “QC check and QA monitoring”, etc.

In addition, we hosted the JSQA GLP Division educational sessions: the 6th entry course entitled "Introductory lecture to the person responsible for QA/QC" and the 4th training course entitled "Explanation for Ministerial Ordinance on GLP of Drugs", in collaboration with Study Group 4 addressing the same theme in eastern Japan. Furthermore, we joined in the cooperative effort to revise and publish "The practical textbook for the person responsible for Quality Assurance".

GLP Division, Activity Summary of the 13th Term (April 2016– March 2018)	
Study Group	**Special Project Group 1**
Subgroup	**L-T-1**
Theme	**Cases in Study Outsourcings and Site Audits to Overseas Contract Research Organizations (CROs)**

Purpose: The mission of Special Project Group 1 is to examine and suggest better audit methods that can promote mutual understanding and avoid troubles in outsourcings and site audits to overseas CROs. In this term, we had as our objective the sharing of anticipated problems and methods for avoiding them among all member companies and the clarification of viewpoints in outsourcings and facility audits to overseas CROs by examining methods for assessing high-risk cases using the risk-based approach (RBA) and gathering and considering problem cases supplied by overseas CROs.

Method: We applied Failure Mode and Effect Analysis (FMEA), which is one method for risk analysis, to approximately 120 problem cases that were collected through a questionnaire survey conducted by Special Project Group 2 in the 12th Term. We classified high-risk cases and difficult-to-detect cases using four indicators—severity, occurrence, detection (prior to occurrence), and detection (after occurrence)—and then considered ways of mitigating them.

To gather problem cases from overseas CROs, we conducted a questionnaire survey targeting RQA members using a web service. We classified the gathered cases and their backgrounds using country of respondent, study type, category (occurrence phase), cause of occurrence, and presence or absence of improvement measures as indicators.

Result: Of the approximately 120 cases that were targeted in our evaluation, 13 were selected as difficult-to-detect cases using FMEA, and of them seven were thought to be the result of deficient abilities among employees. The category with the highest percentage of difficult-to-detect cases was “operation/assay/test system,” followed by “records/data.” This result suggested that risk increases after actual study operations begin. Moreover, from a score analysis of each criterion, we found that it is difficult for the sponsor to immediately grasp that a problem has occurred in overseas outsourcing, and therefore it is important to have CROs provide accurate information. Effective means of avoiding problems with overseas CROs include having the sponsor grasp points where problems tend to occur beforehand and then take preventative measures through preliminary negotiations, site audits, and letter audits, etc., prior to the study, and requiring regular progress reports.

Although we successfully developed a method for conducting a questionnaire survey targeting RQA members with the cooperation of an internet questionnaire service and the RQA office, it was not sufficient for analysis due to the small number of responses Although there was no bias in the study types and categories of the cases, it was found that insufficient communication and differences in business customs/conventional thinking were a common cause in multiple cases. In addition, there were cases in which excessive demands by the sponsor appeared to be the cause. The results reconfirmed that the characteristic thinking, culture, and customs of the Japanese people are viewed favorably in some cases and unfavorably in others. Thus, understanding and considering regulatory requirements and cultural aspects in partner countries, rather than unilaterally pushing demands from Japan, can be said to be a key point in avoiding trouble.