GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 1: GLP regulations**
Subgroup	**L-1-1**
Theme	**GLP for drugs**

Continuing from the 11th Term (FY2012−2013), Subgroup 1, Study Group 1, GLP Division worked under the theme of "GLP regulations: GLP for drugs" on the basis of the GLP survey/inspection case reports provided by many members of the Japan Society of Quality Assurance (JSQA). We conducted search activities focusing on the classification of instructions and provisions for their rationales, and generated a collection of cases. The instructions were categorized into items corresponding to various articles of the GLP Ordinance for Drugs. We endeavored to create a collection of cases for ready use with a focus on searchability; for example, single instructions considered to be relevant to more than one provision were included in the respective items.

Concurrently with this activity, we investigated the two themes on GLP shown below. It should be noted that these results do not represent the only solution, but provide no more than one reasonable answer by Subgroup 1, Study Group 1, GLP Division. We hope that each facility will act according to its status of GLP operation, utilizing the information given here for the sake of reference only, rather than blindly following it.

1. Risks arising from habituation and experience of staff members—How should GLP training be implemented?—

Training systems for staff members newly allocated to GLP organizations have so far been a topic of many debates at JSQA, and are adequately organized at individual facilities. However, effective training for middle-standing GLP staff members who are fully familiar with GLP studies has been infrequently discussed to date, with no training systems beyond periodical classroom learning, etc. adequately organized. With this situation in mind, an Eastern Japan subgroup extensively worked this term to collect suggestions by QAU attributable to habituation and experiences (including suggestions concerning GLP studies, and some concerning non-GLP studies) and identify risks to clarify points of note regarding training and investigation for middle-standing GLP staff members provided by QAU.

2. Questionnaire-based survey on the application of SOPs

The GLP Ordinance includes provisions to prepare, amend, and provide SOPs (Article 11, Paragraphs 1 to 3), and to provide training (Article 6, Paragraph 1, Term 7), suggesting the necessity of inspections on SOPs for QAU from the viewpoint of that "studies and facilities should comply with the GLP Ordinance"; however, no rules are available on the application of SOPs, with each facility acting upon their own discretion. In recent years, increased diversity on how to apply SOPs at individual facilities has been seen, with an increasing

number of facilities utilizing computerized systems as a means of securely complying with the provisions of the GLP Ordinance. Against this background, many members of a Western Japan subgroup voiced wishes to know about the up-to-date situation regarding how to apply at each facility in the context of relationships among SOP preparation/amendments, training, electronic access, and QAU. Hence, a questionnaire-based survey composed of a collection of questions voiced by subgroup members was implemented for the members of the L-1-1 group to obtain basic information on discussing how to apply the SOP.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 1: GLP regulations**
Subgroup	**L-1-2**
Theme	**GLP for medical devices**

The concept of “GLP” was for the first time applied to safety studies of medical devices on October 1, 2003 (Notification on GLP for Medical Devices). Subgroup 2, Study Group 1, the GLP Division was organized soon after the application, in April 2004 (7th Term). In April 2005, “medical devices” was newly included in the GLP Ordinance for Drugs and Medical Devices. In June 2008, a major amendment was made to the GLP Ordinance. We discussed themes to cope with these systematic changes. In April 2010 (10th Term), the scope of investigational themes was expanded to include safety studies to which the medical devices GLP applied. Since then, we have been engaged in comparisons and differential analyses of Japanese and foreign safety study guidelines. The activities of five terms over the past 10 years discussed a set of major issues related to medical devices GLP. However, many subgroup members were facing a wide variety of issues in their daily activities. For this reason, we discussed such problems and issues at hand in the context of a “case study” in the previous term. In the current term, this “case study” was the main topic of our activities. A total of 17 cases were discussed during these two years, and results and conclusions were reported in the deliverable.

In addition, we worked on a subgroup workshop concerning a broad range of regulations on medical devices in order to understand the Japanese and foreign approval/authorization systems for medical devices in this term. The documents used in the subgroup workshops are provided in this deliverable.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
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 questions or problems that occurred while practicing the GLPs for agricultural chemicals, chemical substances, etc. With regard to the GLP for agricultural chemicals, the studies of residues in crops are subject to the GLP regulations and almost all the studies are carried out as “multi-site studies”, and so we took up the “multi-site studies” as the main theme of our discussion in this term.

The 1st training meeting on the GLP for agricultural chemicals was held in February 2015 in cooperation with Food and Agricultural Materials Inspection Center (FAMIC), Japan Crop Protection Association, and Japan Society of Quality Assurance (JSQA). In this meeting, one of themes was the “multi-site studies”, which was also the main theme of our discussion, and we could make use of this opportunity. The questions and answers about the GLP for agricultural chemicals were carried out in the meeting after an interval of 16 years from the first questions and answers carried out in 1999, and our group contributed to the preparation of the questions and answers. Through the preparation of the questions and answers, we came to better understand the GLP for agricultural chemicals. On the other hand, new questions or problems about the GLP for agricultural chemicals appeared, and those were taken up as the subjects of our discussion.

When the GLPs were considered from the global viewpoint, the MAD (Mutual Acceptance of Data) system was established by OECD (Organization for Economic Co-operation and Development). Under this system, the test results of non-clinical safety studies conducted by adhering to the OECD Test Guidelines and OECD Principles of GLP must be accepted mutually among the member countries of OECD and non-member but MAD participating countries. All GLPs in Japan, including the GLP for agricultural chemicals are under the MAD system. However, the MAD system has been applied incompletely among the GLPs in Japan. With regard to this matter, FAMIC had stated that the GLP for agricultural chemicals would accept test results prepared by means of other GLPs in Japan, and this statement was widely known in the 1st training meeting on the GLP for agricultural chemicals. Considering that the GLP regulations in Japan are showing a tendency to be divided, all GLPs in Japan are requested to coordinate with each other in the on-site evaluation of the GLP compliance monitoring programs by OECD. Consequently, joint inspections were attempted, but they were far from coordinated. Progress in the coordination of the GLPs in Japan is ongoing.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 1: GLP regulations**
Subgroup	**L-1-4**
Theme	**GLPs in overseas countries**

We feel that the requirements for practical GLP management by the Japanese Regulatory Authority is sometimes much higher than the required GLP standards. To examine this "excess requirements" issue related to three topics (Archive, Process-based inspections, and Deviation), we conducted questionnaire surveys in eight regions (the UK, France, Germany, Sweden, the US, China, Korea and Taiwan), whose societies of quality assurance have concluded a memorandum of understanding (MoU) with the Japan Society of Quality Assurance (JSQA). Here are the major points of the survey results.

1. Archive

Since study materials are essential for the re-construction of studies, the procedure for archiving study materials is extremely important. Although there are some minor differences, in all the eight regions, the study materials are maintained in a manner fundamentally similar to the procedures in Japan.

2. Process-based inspections

The Japanese Regulatory Authority requires that some of the procedures, such as dosing of the test article and some special study operations, should not be applied to process-based inspections. However, there are no similar requirements by the regulatory authority in other regions. We conclude therefore, that there would be "excess requirements" related to the procedure of the process-based inspections in Japan.

In fact, process-based inspections have not been introduced widely to the Test Facilities in Japan. We hope that the process-based inspections will be actively introduced to promote the effective quality assurance activities in Japan, too.

3. Deviation

The Japanese Regulatory Authority requires that all deviations need to be written in a defined paragraph in the final report, except those that don't clearly affect the reliability of the study. However, there are no such kinds of requirements by the regulatory authorities in other regions. We conclude that there would be "excess requirements" related to the procedure of the deviation in Japan.

The minimum requirement of the deviation shown in the questionnaire survey is that "the study director should evaluate the impact of the deviations on the reliability of the study. If there are any deviations that do have an affect on the reliability of the study, the deviations should be written somewhere in the final report."

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 1: GLP regulations**
Subgroup	**L-1-5**
Theme	**Overall GLP issues and training**

Following the last term, we have been working under the activity theme of "GLP Regulations -Considerations of Various GLP Issues and Training of GLP QA Personnel-".

As for GLP issues, this subgroup has worked on the following tasks in cooperation with the relevant industry societies and worked as the contact with the regulatory authorities;

- Preparation of Questions and draft Answers for the GLP Training Workshop
- Exchanges of views in regard to the revision of GLP inspection program with PMDA
- Collection of public comments to the draft OECD GLP guidance document (IT)

,etc.

A member of this subgroup gave a presentation about the revision of PMDA's GLP facility inspection program at the 2nd Asia QA Forum held in Seoul (November 2015).

With regard to the training of GLP QA personnel, this subgroup was in charge of planning and holding JSQA's two training seminars (i.e. GLP Basic Training Course and GLP Advanced Training Course), and each seminar was successfully held once a year.

In addition, there were two discussion teams in the subgroup. One team addressed the risk based approach to GLP QA inspections, and the other team discussed about GLP Archiving. The outcomes from both discussion teams were faithfully compiled and partly used for the above mentioned GLP training courses.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 2: Quality management of non-GLP studies**
Subgroup	**L-2-1**
Theme	**Quality of CMC studies**

At the start of activities in this term, a questionnaire-based survey on activities was implemented for subgroup members, revealing high demand for GMP for investigational medicinal products and for quality assurance (data, documents, testing). Hence, the members were divided into two groups to work on the respective themes: (1) consideration of issues concerning GMP for investigational medicinal products (team examining GMP for investigational medicinal products), and (2) consideration of quality assurance for CMC studies (CMC team).

At the team examining GMP for investigational medicinal products, we attempted to understand the ICH Guidelines Q11 “Guideline on Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)” issued on July 10, 2014, closely associated with the ICH Q7 and Q8 to 10 (the Q trio), and to deepen understanding of the required GMP management system, within the framework of activities to deepen our understanding of GMP for investigational medicinal products. Specifically, the contents of the ICH Q11 Guideline were checked by members, questions presented by individual members were discussed, and the findings were described in “Topics Discussed and Their Contents,” as a key issue for understanding the ICH Q11 Guideline to deepen our understanding with regard to differences between “traditional approaches” and “enhanced approaches,” and of their application to drug development.

At the CMC team, as in the previous term, matters for discussion were selected from among questions arising in daily work and issues encountered in routine duties to assure the quality of CMC studies. Members discussed and examined the selected matters, prepared draft responses, and documented them in a Q&A leaflet. The questions and issues presented included contents already discussed in past JSQA deliverables. With regard to such topics, we attempted to more organically link deliverables to each other by preparing Q&A while checking the contents of past deliverables, and presenting information on checked deliverables in this deliverable.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 2: Quality management of non-GLP studies**
Subgroup	**L-2-2**
Theme	**Discussion of the reliability of pharmacology and pharmacokinetic studies and CTDs** Discussion of problematic cases of M2/M4 in CTDs

A questionnaire-based survey on CTDs was implemented for all members of Subgroup 2 at the start of this term, and "problematic cases of Module 2 (M2) / Module 4 (M4)" were identified as issues to be discussed.

The identified "problematic cases of M2/M4 (25 cases)" were diverse, ranging from "integrity between M2 and M4" to "studies to be conducted at overseas licensees," all of which were problematic to respond to with regard to the method of ensuring reliability. Discussion findings were described in the separate sections of Background, Conclusion, and Opinion Exchange/Discussion for each case.

"Problematic cases of M2/M4" represent difficulties that were encountered, or may possibly be encountered, by members in daily CTD-related work, and that need to be overcome for task completion. For the 25 cases discussed in this term, the best countermeasures at the present time were identified following explanations about the content and background by case providers, presentation of actual responses by team members at their own facilities, and exchanges of opinions.

Although the conclusion concerning "problematic cases of M2/M4" reached through the opinion exchange represents the unified opinion of the drug approval dossiers team, it is not always the correct answer and does not need to be reflected in the policy/practice at each facility. It is believed, however, that a compilation of cases involving problems that can arise in CTD-related work, as well as countermeasures, would be useful in coping with future problems that could not easily be resolved by individual facilities and individual persons in charge.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 2: Quality management of non-GLP studies**
Subgroup	**L-2-2**
Theme	**Discussion of the reliability of pharmacology and pharmacokinetic studies and CTDs** Discussion of the reliability of overseas data and initial data from pharmacology studies

With regard to "primary pharmacodynamic studies," we examined the acceptability of overseas data and data from studies at the drug discovery/exploration stage (initial data) as dossiers at the start of clinical trials or at the time of drug approval, as well as how to assure their reliability.

In the examination, we implemented a questionnaire-based survey on the reliability of overseas data and initial data for the members of Subgroups 2 and 3, Study Group 2 with reference to an activity report from Subgroup 2, Study Group 3 for FY2006-2007 (Document No. 89). Based on the tabulated results, we attempted to understand the actual status at each company and examine methods for ensuring reliability.

As a result, it was revealed that the ability to reconstruct the study in some way is necessary when using overseas data and initial data as dossiers at the start of clinical trials or at the time of drug approval, including supplementation of the study content with supporting evidence. In addition, it appears important to establish requirements for acceptability of the use of overseas data and initial data, and to share awareness of ensuring reliability as part of the applicant's responsibility.

With regard to overseas data, 32 companies responded to the questionnaire, of which about 60% stated that they had used overseas data as evaluation documents for domestic drug approval. However, many facilities have irregularities in at least one of the following: protocols, test articles, key equipment, testing systems, implementation records, measurement records, and reports. In-licensed products having notably many irregularities compared with CRO contracted studies. A likely cause was the lack of awareness of "standards for the reliability," a regulation that is unique to Japan, and which is not specified in GLP. However, even with these irregularities, such data were considered to serve as evaluation documents, provided that they allow the contents of the study to be reconstructed with a reasonable explanation. In addition, regarding the applicant's responsibilities, we concluded that emphasis should be placed on the implementation of surveys as required to determine whether reliability could be assured, and on the establishment of requirements for data use as evaluation documents.

Thirty companies responded to the questions on initial data, of which 60% stated that they had used initial data as clinical trial dossiers or evaluation documents for drug approval, whereas the remaining 40% had not. We considered that it was necessary to implement a

survey emphasizing accuracy (particularly of raw data and reports) through QC etc. when using initial data as clinical trial dossiers. When using them as evaluation documents for drug approval, on the other hand, we considered that a survey complying with “standards for the reliability” would be required. For this reason, we concluded that when using initial data as evaluation documents for drug approval, emphasis should be placed on the prior sharing of awareness of ensuring reliability for the study through educational sessions etc., and that it is also important to establish requirements for the possible use of such data as clinical trial dossiers and/or evaluation documents for drug approval.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 2: Quality management of non-GLP studies**
Subgroup	**L-2-2**
Theme	**Discussion of the reliability of pharmacology and pharmacokinetic studies and CTDs** Discussion of various problems concerning pharmacokinetic studies to determine the reliability of exploratory/trial-and-error studies and points of note for the handling of electronic data

We chose the "reliability of exploratory/trials-and-errors studies" as an issue to be discussed with regard to pharmacokinetic studies. Specifically, points of note in assuring the reliability of studies to explore human metabolites or studies on structural predictions, for example, were examined on the basis of the "essence of reliability." In addition, since pharmacokinetic studies often involve the use of measuring instruments with computerized systems, such as LC-MS/MS, we also discussed the handling of electronic data from such instruments from the viewpoint of the benefits of using electronic data as raw data, its necessity, and points of note.

Questions arising from the pharmacokinetics team, i.e., 11 questions on exploratory/trial-and-error studies (studies to explore human metabolites / studies on structure prediction, integrity between raw data and reports) and 12 questions on the handling of electronic data (handling of measured data from LC-MS/MS, reliability of LC-MS/MS-related software, storage of electronic data), were discussed. The results were separately presented in the Background, Conclusion, and Opinion sections for each question, with comments, reference information, etc. presented in the Remarks section when required. Please note that although the contents described in the Conclusion section represent the pharmacokinetics team's unified opinion based on opinion exchange, they do not always need to be reflected in the policy/practice at each study facility since they are not based on information that has extensively been collected from facilities, both in and outside Japan, via questionnaire-based surveys etc.

The consideration of exploratory/trial-and-error studies identified many issues that raised problems with decision-making on how to respond, including study procedures, adoption of results, and content to be presented in reports. For this reason and since opinion exchange meetings identified a wide variety of countermeasures/viewpoints, the conclusions reached comprised example responses only. From a comprehensive standpoint, it was concluded that all records of implemented studies should be retained, since it is essential to be able to reconstruct the test as with other types of testing.

Consideration of the handling of electronic data revealed that paper output from measuring equipment was defined as raw data at all facilities belonging to the pharmacokinetics team. However, an opinion was voiced that such responses involve the risk of contradiction in that the definition of raw data is temporality changed to electronic data if re-analysis becomes

necessary. To prevent such situations, individual team members worked to collect and share various types of information, including regulations and overseas situations; and points of note (authenticity/integrity, visial readability, storability, etc.) in view of a shift to a new system of data, in which electronic data serves as raw data, were drawn as the conclusion.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 2: Quality management of non-GLP studies**
Subgroup	**L-2-3**
Theme	**Study of training programs for Reliability Criteria**

Training for personnel engaged in studies compliant with Reliability Criteria of Application Data had been studied in various ways in previous terms. The content is focused on professional background and occupational ability.

In this term, we discussed the overall vision of what training should entail for all personnel involved in studies applied to Reliability Criteria from the viewpoint of those who provide training at each facility, including ethical perspectives for scientists.

The result of study was tabulated in a list of items of training. We expected that essential items would be selected from this list according to the background and roles of each trainee when providing training at each facility.

Furthermore, the following three items were selected from the list, and training materials were prepared for direct use at each facility.

● Medicine and history: What is medicine (characteristics of medicine)? Japanese people and history of medicine, tightening of regulations and its background.

● Effective QC/QA: Present status of QC/QA, QC/QA explanation from ISO viewpoints

● Communication: Points of note for communication based on situation (audit results reporting/observations, queries/advice, inside the QC/QA department, etc.), and usual attitudes required for the QC/QA department.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 3: Computerized systems**
Subgroup	**L-3-1**
Theme	**Quality assurance procedures for computerized systems** The best practice for the promotion of computerization －Consideration of the management of electromagnetic records at the time of retirement－

Procedures for managing electromagnetic records were examined through the activities of the issue examining team up until the previous term. Highly useful findings can be obtained by referring to their deliverables.

Based on these useful findings uncovered, the activities of our team commenced proposing the best practice for the management of electromagnetic records. When first starting our examination of electromagnetic records to be appropriately managed, we considered that we would be able to identify electromagnetic record items to be managed appropriately and propose efforts to be made at the computer system concept phase, project phase, and operation phase, by considering the appropriate method for managing electromagnetic records at the time of computer system retirement. We therefore decided to implement a survey and discussions on the best practice regarding the retirement of computer systems as a scaffold for making proposals.

Although how to appropriately manage electromagnetic records at the time of system retirement had been examined through the past activities up until the previous term, the content consisted of no more than the overall handling of electromagnetic records as a whole. We considered that examination of more extensive data needed to comply with GLP requirements, such as raw data and raw data change history, or the way to manage the audit trails generated at the time of system retirement, would be useful in configuring the best practice for the management of electromagnetic records.

Strangely, this term (FY2014-2015) coincided with noteworthy events—the termination of customer support for Windows XP in April 2014, and for Windows Server 2003 in July 2015. The term also came at a time when we had to consider countermeasures against the deterioration of computer systems hardware that rapidly spread with the growth of the IT industry and were introduced in the 2000s. Accordingly, we presumed that we would be blessed with opportunities to collect information from the viewpoint of both software and hardware, which were expected to provide us with materials for considering the best practice when implementing system retirement.

We conducted surveys and examinations on the following items.

1. Questionnaire-based survey on system retirement

A questionnaire-based survey on retirement implemented at various companies, and the way to implement system retirement assumed for computer systems in operation was performed

2. Holding group workshop meetings on system retirement

Group workshop meetings were held to collect information concerning the ideas of system supllier on system retirement, and on the type of retirement that they expect to be implemented.

3. Consideration regarding efforts for the best practice concerning the management of electromagnetic records

On the basis of questionnaire-based survey results, we examined items to consider at the time of retirement and the management of electromagnetic records defined as raw data, incorporated the results into the system lifecycle, and studied various efforts taking into account retirement in system concept, project, and operation.

In addition to the results of the surveys and examinations, citations from various guidelines on the retirement of computer systems and the documents published by the aforementioned group workshop are also attached for reference purposes.

We hope that this deliverable will serve as a reference for considering the best practice, and assist with computer system retirement at each company as well as the management of electromagnetic records in computer systems in operation or to be introduced in the future.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 3: Computerized systems**
Subgroup	**L-3-1**
Theme	**Quality assurance procedures for computerized systems** The best practice for the promotion of electronization － Hop! Step! SEND! －Present status of SEND compliance and workflow sample－ －

On December 17, 2014, the FDA launched an official version of guidance for the electronic submission of application data entitled “Providing Regulatory Submissions in Electronic Format—Standardized Study Data.” This guidance will obligate investigational data from nonclinical studies that will commence after December 18, 2016 to be submitted to the FDA in accordance with the Standard for Exchange of Nonclinical Data (SEND) formulated by the Clinical Data Interchange Standards Consortium (CDISC). In addition, in Japan, electronic submission of clinical study data to the PMDA will commence on October 1, 2016; it is likely that electronic submission will become mandatory for nonclinical study data as well, as required by the FDA. As of the time this article was written, no notifications, etc. concerning the electronic submission of nonclinical study data have been issued by the PMDA; however, the PMDA has adopted the CDISC Standard for clinical study data, and is therefore likely to adopt the SEND, which complies with the CDISC Standard, for nonclinical study data as well. Europe appears to monitor the FDA’s actions, and Asian countries are ready to follow the actions taken by the FDA and PMDA.

Against this background, it appears highly useful not only for companies that submit applications to the FDA and contract research organizations, but also for domestic pharmaceutical companies that do not submit applications to the FDA, to commence early examination, taking into account electronic data submission.

Hence, the issue examining team conducted the following activities to consider our responses to SEND:

1. Collection of information on responses to SEND

A subgroup workshop was held to collect basic information on SEND. A SEND examination member from the CDISC Japan User Group (CJUG), which is working to disseminate the CDISC in Japan, cooperated to deliver a lecture, introducing basic knowledge on SEND, presenting FDA requirements, and answering questions from study group members.

The findings compiled through this subgroup workshop were included in a formalized deliverable.

2. Understanding of the present status of responses to SEND at domestic companies in Japan

To clarify the current status of SEND compliance at domestic companies in Japan, a

questionnaire-based survey was implemented for members of Study Group 3. Results showed that some companies had already commenced with SEND compliance, while others had not. Many companies were found to have no definite policy on SEND compliance, stating that they did not know what to do specifically.

3. Examination of work model for SEND compliance

The results of the questionnaire-based survey suggested that demand for information exists that will serve as a specific guide for SEND compliance at many companies.

When a filing company responds to SEND, it is necessary to determine “how to generate a SEND dataset” and “who/which organization is engaged in the generation of the SEND dataset,” as well as to clarify other issues.

Accordingly, we decided to visualize workflows for SEND compliance expected from the FDA guidance. Workflow charts were generated for three model cases and assumed the following: “SEND data are generated by the user company,” “the generation of SEND data is outsourced,” and “data from outsourced studies are internally converted to SEND data.”

We hope that this article will serve as a good tentative plan to determine countermeasures, formulate operating procedures, establish a work system, and assign risk assessments at each company that complies with SEND.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 3: Computerized systems**
Subgroup	**L-3-2**
Theme	**Upgrade of the skills of QA staff members who handle CSV and electronic data** The best practice for the promotion of computerization －Hop! Step! SEND!: Present status of SEND compliance and workflow sample - SEND compliance - －

SEND is a “standard” for electronic data from non-clinical toxicology studies used for IND, NDA, and BLA submissions to the FDA. To increase examination efficiency, the FDA requires the submission of standardized study data compliant with the SEND format intended for IND, NDA, and BLA submissions. If the submitted data are not standardized properly, the application will not be accepted. Therefore, the submission in SEND format involves risks including developmental schedule delays and increased cost for re-application.

At this subgroup, we assumed that many companies would choose to outsource the creation of SEND data because specialty skills and knowledge are needed to ensure the creation of SEND data in the limited time frame. Hence, we focused on matters considered to be important to ensure the quality of SEND data generated by outsourcing in this term. The following describes details of the examination and an outline of the deliverable:

1. Selection of CROs

When outsourcing the creation of SEND data, the sponsor should provide the CRO with an explanation about the requirements for generating the data, manage progress, and also confirm the quality of the SEND data. In addition, the sponsor must be ready to respond to queries from the FDA after filing the application. Therefore, the scope of outsourcing (whether only the creation of SEND data or both toxicology study and creation of SEND data) has a major impact on the selection of the CRO.

2. Quality assurance

Even when outsourcing the creation of SEND data, some operations should be still performed internally. Because SEND data constitutes a part of the application dossiers, the applicant should be responsible for the SEND data. Although studies subject to SEND requirements are performed in compliance with GLP, SEND data are not subject to GLP regulations. However, the regulatory authority asks for that the quality of SEND data is required to be at the GLP level. One of the risks regarding the process of creating SEND data is that the analytical results from SEND data are inconsistent with statements in the final report. To ensure the quality of SEND data, the status of the process for creating SEND data at the CRO (expertise of the person who prepares the data, software used to create the data, documentation of the

preparation procedures, etc.) must be assessed. In addition, it is also necessary to directly check SEND data against the final report.

3. Collection of information

Controlled terminology used to create SEND data and SEND specifications are updated whenever necessary. The FDA requires that the acceptable versions of SEND and controlled terminology are used. Therefore, applications cannot be successful without collecting up-to-date information on SEND. The deliverable presents information that is considered to be important to check the quality of SEND data and its source. It also includes “FDA Data Standards Catalog,” which specifies the version numbers of SEND and controlled terminology that are acceptable to the FDA and “Study Data Technical Conformance Guide,” which explains about the technical recommendations/specifications concerning for standardization of study data, and other information published by the FDA, as well as the Study Data Reviewer’s Guide templates published by the PhUSE (a non-profit organization for biostatistics and clinical information technology) and other information.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 3: Computerized systems**
Subgroup	**L-3-2**
Theme	**Upgrade of the skills of QA staff members who handle CSV and electronic data** The best practice for the promotion of computerization －The Roles of QA personnel in quality assurance of computerized system－

We have investigated the following two issues to clarify the roles of QA personnel in quality assurance of computerized system:

- Quality assurance of the computerized system in CRO
- Competency and personnel training of QA personnel in CSV documents (hereafter "CSV-QA staff")

To specify an industry standard in Japanese pharmaceutical laboratories of QA investigation of the computerized system in CRO, we conducted a questionnaire survey. The questionnaire items are below:

- Breakdown of respondents
- Whether your company investigates computerized systems in CRO or not?
- Who investigates computerized systems in CRO?
- When does your company investigate computerized systems in CRO?
- Confirmation items about management system of computerized systems in CRO
- Confirmation items about operational status of computerized systems in CRO

We created a checklist for QA investigation of computerized systems in CRO based on the industry standard specified by the questionnaire survey.

As a first step in investigating competencies and personnel training of CSV-QA staff, we placed competency into the following three categories:

- Knowledge: the information necessary to carry out his/her tasks. The information can be acquired through lectures.
- Skill: work-related abilities which can be acquired through practical training and experience
- Attitude: psychosocial features which help to carry out his/her tasks

Next, we investigated the competencies for CSV-QA staff and supplier auditors by means of a case study in the following three scenarios:

- A QA staff member who has no experience to review CSV documents is assigned to a CSV-QA staff.
- A staff member who has enough experience to create CSV documents but has no experience of quality assurance is assigned to the CSV staff.
- A CSV-QA staff member's first time to conduct a supplier audit.

Finally, we proposed training programs for each competency specified by the case study.
The outline of the training program is below:

- Classroom leaning: in-house seminar, outside seminar and self-schooling
- Practical training: on-the-job training with coaching by an experienced CSV-QA staff member
- Others: participation in the industry group such as Japan Society of Quality Assurance

We believe that the training program is effective, because the training program is proposed based on competencies required for CSV staff.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 3: Computerized systems**
Subgroup	**L-3-2**
Theme	**Upgrade of the skills of QA staff members who handle CSV and electronic data** The best practice for the promotion of computerization －CSV for spread sheets－

1 Purpose of activities

The team examining electronic data-related regulations had been working to translate overseas notifications and guidelines into Japanese to deepen the understanding of the reliability of electronic data. In this term, we decided to translate the "GUIDELINES FOR THE DEVELOPMENT AND VALIDATION OF SPREADSHEETS (Version 01, August 2011)" issued by the Working Group on Information Technology (Arbeitsgruppe Informationstechnologie, AGIT) into Japanese.

This publication was selected to enhance understanding of the following two matters:

● Computerized System Validation (CSV) method for spread sheets (Microsoft Excel)

● Requirements for spread sheet management even when paper outputs are defined as raw data (calculated results).

2 Achievements of activities

The following are achievements identified through the Japanese translation of the Guidelines:

2-1 General

● The spread sheet should be managed in consideration of the OECD's GLP Principles, i.e., data lifecycle, if it concerns GLP study data.

2-2 Development

● Should be documented in accordance with the V model used in the Guidelines for CSV.

● User requirements should include matters concerning security and compliance with relevant laws (GLP).

2-3 Verification

● Verify that the spreadsheet generated functions under different settings (OS, application version).

● The dataset used for OQ should allow not only accurate calculations, but also identification of conditional program branches (e.g., if any numeral that includes a decimal point is input in a calculation formula to be completed using an integer, the program will no longer accept the subsequent operation).

● The data used for PQ should include not only actual measured values, but also a data set that is far removed from anticipated results.

2-4 Change management

● Any change in the spread sheet should be made in accordance with the change management

procedures, irrespective of whether or not it influences the study results.

● Specific needs will include user requirements, risk assessments, specifications, planning, testing, and reporting.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Study Group 4: Quality assurance for non-clinical studies (Eastern Japan)**
Subgroup	**L-4-1**
Theme	**All aspects of reliability assurance for GLP and reliability standards**

Study Group 4, as an Eastern Japan regional study group, performed activities with the main theme of consideration of topics on overall aspects of reliability assurance. Free discussion style was adopted, and the "frequent questions/issues in the work" that the members encounter in their daily work were considered in this Study Group 4 activities.

In the first half of the term (FY2014), we discussed the "frequent questions/issues in the work" as the whole study group, and in the second half of the term (FY2015), we discussed as the three separate subgroups of "GLP", "Pharmacology / Pharmacokinetics", and "Quality". 41 issues in all were discussed with a focus on ensuring reliability of daily work.

In addition, we held various seminars and lecture meetings in order to improve the reliability assurance skills of the members of the study group and to broaden their viewpoints. At the seminars, the members of the study group reported the compliance assessments cases by regulatory authorities in each country, so as to deepen understanding of response cases and recent trends of those regulatory authorities. On the other hand, at the lecture meetings, we invited outside speakers and asked them to speak about entitled "Basics of LCMS - Outline of Instrumentation and Analyses - ", "CSV Guidelines and PIC/S GMP", "Points of Note in Preparing Application Dossiers and Keys to Successful Preparation of Responses to PMDA Queries", and "Anger Management - How to Correctly Cook Anger - ".

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

As stated above, Study Group 4 worked on a wide variety of topics concerning reliability assurance. In the activities, we could improve our skills for reliability assurance, and create opportunities for learning about thinkings and attitudes to ensure reliability of daily work through the exchange of opinions among all members.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
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 in 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

In this 12th term, we discussed 12 "familiar or frequent questions/issues" submitted by members and examined 5 opinions collected using the mailing list.

We held 5 instructive lectures and seminars for a total of 6 titles.

In addition, we cooperated mutually and built a human network with Study Group 4 addressing the same study theme, for example, by planning and providing the training course for "Ministerial Ordinance on GLP of Drugs" on October 30, 2015.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
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 Western Japan study group, L-5-2 has been performing activities 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, GMP, etc.

Along with our main activity of examining familiar questions/issues (26 cases), we had timely exchange of opinions using a mailing list (11 cases), instructive lectures and presenting topics of interest (8 titles), and free-theme discussions. In the deliverable, the 28 questions/issues, including 2 cases of exchanging opinions by e-mail are summarized, categorized into 10 items consisting of "study plans/amendments", "test articles", "study results", "study reports", "archives", and "QC check and QA monitoring", etc., and the background, conclusion, and exchanged opinions are provided for each question. Although the opinions exchanged by e-mail and free theme discussions were not included in the deliverable, we had an occasion for reporting the results and further discussion about the former, and had an occasion for presentation of the outcomes of the latter.

In addition, we had been collaborating with Study Group 4, addressing the same study theme, on the hosting of the beginner's course entitled "QC/QA introductory course".

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Special Project Group 1**
Subgroup	**L-T-1**
Theme	**References re-compile for the book of "What Is GLP?"**

In publishing the achievement in a book entitled "What Is GLP?" (published by Yakuji Nippo Ltd. on March 30, 2015), many historical records were referred to by L-T-1 member in overviewing Japan's GLP history. However, these valuable references, except special references, were not included in the published book due to the limited number of pages. We attempted to collate and re-compil these references, and store them in an electronic format to the maximum extent possible. In this project, past important references were collected, the references listed in the chapters of the "What Is GLP?" publication were reviewed, and the results were arranged in order. The goal was set to prepare searchable collected references to allow the next generation of JSQA member to have quick access for reference materials when conducting GLP research (not to be disclosed in the case of copyright violations). Only currently accessible websites were referenced. This project accomplished the collection of historical references allowing a broad range of references for referral, from the date of introduction of GLP to the present.

GLP Division, Activity Summary of the 12th Term (April 2014 – March 2016)	
Study Group	**Special Project Group 2**
Subgroup	**L-T-2**
Theme	**Cases in Study Outsourcings and Site Audits to Overseas Contract Research Organizations (CROs)**

Purpose; The mission of L-T-2 is to suggest better audit methods that can promote mutual understanding and avoid troubles in study outsourcings and site audits to overseas CROs. In this term, the questionnaire survey to member companies was carried out to collect trouble cases. It was aimed at grasping the cases which had made it difficult to negotiate with them due to conflicts derived from different cultures and customs. The results are shared through this presentation and deliverables.

Method; The questionnaire survey was conducted to study (archive) outsourcing management sections and quality assurance units. The scope of the survey was set to cases caused in not only GLP studies for drugs, medical devices and agricultural chemicals, but also studies for pharmacology, ADME, clinical PK and CMC. Collected cases and their backgrounds were summarized in tables based on the country of the location of CROs and the type of entrusted study and case. Furthermore, they were classified in accordance with the following indices: the presence/absence of countermeasures, the occurrence phase and cause. If the countermeasure for each case was not taken, the reason, settlement process and judgment of acceptance as sponsor were also asked for in the questionnaire.

Result; As a result of having distributed questionnaires to 160 facilities, answers were received from 71. But about two-thirds of the 71 facilities had no experience of outsourcing to overseas CROs. From a viewpoint of the type of entrusted studies, the number of answers on GLP study was the most common, followed by pharmacology, ADME and clinical PK studies with almost the same in number. However, there were less precise answers on ADME than on the other study types. From a viewpoint of the breakdown of the locations of CROs by country, it was common in every study type that the United States was top and the U.K. was the second in the number of answers. It was regarded as a result in proportion to the number of entrusted studies. In contrast with the GLP studies, the Non-GLP studies in pharmacology, ADME and CMC tended to be entrusted to various other countries. From a viewpoint of the presence/absence of countermeasures, the ratio of cases which had the countermeasures taken for the observations was the highest in the GLP study followed by the Non-GLP and the clinical PK study, while the cases that had failed to request the CROs to make improvements showed a tendency to increase. As a result of the classification of trouble and nonconformance cases according to the occurrence phase, it was shown that the most number of the cases occurred in a group of the phases of operation/assay/test system in the GLP study contracted out to CROs in the English language regions. Although they showed

characteristic distributions in each study type, the cases related to the phases of agreement/study preparation/contact system occurred in any category. This result supports the difficulty and importance of communications.