| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 1: GLP regulations |
| **Subgroup** | Subgroup 1: GLP for drugs |

(Summary)
Subgroup 1, Study Group 1, GLP Division performed activities such as classification of instructions and search for provisions serving as the rationale for the instructions, and prepared a collection of inspection cases, based on the GLP Monitoring/Inspection Case Reports provided by the members of JSQA. The instructions have been classified into items corresponding to each provision in the GLP Ordinance for Drugs.
In parallel to the above-mentioned activities, a great deal of consideration has been given to the following four themes on GLP.

1. Ideal QAU
Requirements for the QA personnel were considered from the following two perspectives: “knowledge” and “qualification/skill.” As for “knowledge,” each item of the requirements was classified into three levels, i.e., elementary to advanced levels, and training or practical experience required for step-up were examined and organized to show specific examples that serve as ideal QAU guidelines. As for “qualification/skill” requirements, although conflicting descriptions within an item are included, the subgroup believes that this led to the successful expression of some of the images of “ideal QAU.”

2. Handling of Deviations with No Indecision − How to Handle Deviations from Protocols/SOPs or Unforeseeable Situations
Regarding description of deviations from the Protocol, deviations from the SOP and situations that could not be foreseen in a GLP study (hereinafter referred to as “deviations, etc.”) in the final report, each test facility is often indecisive about what an appropriate action should be. Therefore, the subgroup examined how deviations, etc., should be handled according to the GLP principles.

3. Audit Sampling in QA Monitoring
The QA personnel must assure the quality of the documents by conducting monitoring to verify that the QC is properly performed. The subgroup examined to what extent the QA personnel should perform sampling for monitoring when these documents consist of a large amount of data. However, as there are differences among facilities in the amount or types of data generated, degree of computerization of data, etc., it was found difficult to define a guideline that could consistently apply to any facility. Therefore, consideration was given to investigating the current situation in each facility and providing information that would allow each QA staff to reaffirm or reconsider justification/appropriateness of the situation in his/her facility.

4. QAU's role in Proper Storage of Study-related Materials
Although Article 18 of the GLP Ordinance for P Drugs specifies “properly retain study-related materials in archives” and the Ordinance for Enforcement (PFSB Notification No. 0613007) provides explanations for “properly retain”, there are many unclear parts in terms of the details of the above description and how the QAU should be involved. Therefore, we examined the “proper storage of study-related materials” and “the way QAU ought to be in it”. A questionnaire survey for examination was conducted on the current situation of storage of materials at each facility and involvement of the QAU, and consideration was given based on the results of the survey.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 1: GLP regulations |
| **Subgroup** | Subgroup 2: GLP for medical devices |

(Summary)

"Comparison between the Japanese and foreign test methods for medical devices (2) − Comparison between the new Japanese guidelines (PFSB Notification No. 0301-20) and the ISO 10993 Series"

Although the international standard of biological evaluation test methods for medical devices is the ISO 10993 Series, there exists a Japanese version of "test method guidelines/guidance," in which the Japanese-specific way of thinking is incorporated on the basis of the ISO 10993 Series.

In its activities during the previous term (10th term), Subgroup 2, Study Group 1 compared the Japanese test method guidelines (hereinafter referred to as "the former guidelines") and the ISO 10993 Series and analyzed the differences, to extract issues on the conduct of biological evaluation tests for medical devices and viewpoints on QAU monitoring. However, a review of the Japanese test method guidelines was ongoing in parallel to the activities of Subgroup 2, Study Group 1, and a new guidance was issued concurrently with completion of the 10th term deliverables. The new guidelines are basically consistent with the current ISO 10993 Series, but the Japanese-specific way of thinking still remains in the details. Therefore, the subgroup compared the changes from the Japanese former to the new guidelines/guidance in this term (11th term) and examined what happened to the differences from the ISO 10993 Series extracted in the 10th term.

"Case Study for Examination of Issues at Hand"

Group members were asked to list any cases that they sensed as issues in their daily work or any questions that they have, and these cases were examined as a case study at group meetings. The members were also provided with an opportunity to send out questioning e-mails outside the meetings and receive responses from other members.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 1: GLP regulations |
| **Subgroup** | Subgroup 3: GLPs for agricultural chemicals etc. |

(Summary)
In Japan, there are eight GLPs per controlled substance (GLP for drugs, GLP for medical devices, GLP for agricultural chemicals, GLP for chemical substances, GLP for veterinary drugs, GLP for feed additives, GLP for the Industrial Safety and Health Act, and GLP for medical devices for animals), all of which comply with the OECD GLP. However, they are being operated/regulated in their own manners because of differing jurisdictional ministries and agencies/divisions among them. This is considered to be a contributing factor in the complexity of the GLPs in Japan and tangled GLP application by a facility having obtained multiple GLP compliance certifications.

With these situations in mind, Subgroup 3, Study Group 1 is engaging in activities focusing on discussions about questions/issues that members or members' facilities have. Having participants from facilities conducting tests under various GLPs, our activities will help us understand how to apply each GLP, differences in application among authorities or how each facility deals with those differences, and guide us in solving questions/issues we or our facilities have.

In addition, as part of building/strengthening relationships with the authorities, we created an opportunity for discussion with the Food and Agricultural Materials Inspection Center (FAMIC), an inspection authority for GLP for agricultural chemicals, and their honest opinions on our questions/issues were obtained. These are additional useful suggestions for us or our facilities to ensure the quality of tests.

Our future goal is to develop further discussions about the questions/issues and build relationships with the authorities, which would enable us to actively discuss our requests on GLP application, etc.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 1: GLP regulations |
| **Subgroup** | Subgroup 4: GLPs in overseas countries |

(Summary)
In this term, Subgroup 4, Study Group 1 focused on GLP interpretation in the Asian region, as part of examination of Japanese and foreign GLPs. Among Asian countries, GLPs are considered to be relatively established in South Korea and China, and therefore they were selected as countries to be compared with Japan in terms of interpretation of GLP for drugs. To efficiently collect information on actual GLP interpretation in South Korea and China, the Korean Society of Quality Assurance (KSQA) and the Chinese Society of Quality Assurance (CSQA) were asked for cooperation as the concerned bodies in their respective countries. Our investigation was carried out as follows: They were asked questions about several items picked up from GLP interpretation in Japan, and the responses obtained were summarized and compared with GLP interpretation in Japan. The responses obtained were tabulated by item, based on which materials were prepared to include the differences/similarities analyzed in terms of GLP interpretation in Japan, South Korea and China. The subgroup's comments were also added.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 1: GLP regulations |
| **Subgroup** | Subgroup 5: Overall GLP issues and training |

(Summary)
Under the theme of "GLP Regulations − Consideration of Various Issues Surrounding GLP and Training," Subgroup 5, Study Group 1, GLP Division has been engaging in activities for recognition of GLP-related issues and actions to be taken in relation to these issues, formulation of the JSQA GLP Division's points of view, GLP-related personnel training, etc., as the pillars of our activities.

As one of the pillars, in order to keep collecting and examining GLP-related information in Japan and foreign countries and dealing with various issues in this term, a great deal of consideration has been given, in cooperation with relevant industry groups and academic societies, to examination of draft OECD guidance documents (Pathology Peer Review), examination of test items that are subject to facility compliance monitoring, a questionnaire survey to grasp the situation of storage of materials after GLP facility closure, etc. In addition, the subgroup, as a superior GLP body, had been performing activities to respond to various situations, including negotiating with the regulatory authorities as the contact.

As for GLP-related personnel training, which was another pillar of our activities, basic and advanced GLP training sessions were planned and performed as a variety of JSQA-sponsored educational training programs.

As an overall summary for this term, reports on the following Subgroup's agendas were prepared: the results of consideration of the two themes of "Training Programs for QA Personnel" and "GLP Facility Inspections Using A Risk-based Approach," and the results of "A Questionnaire Survey to Grasp the Situation of Storage of Materials after GLP Facility Closure" conducted in May 2013 within the GLP Division.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 2: Quality Management of non-GLP Studies |
| **Subgroup** | Subgroup 1: Quality of CMC studies<br>Consideration of Quality Assurance of Studies Compliant with GMP for Investigational Medicinal Products and CMC Studies Conducted for New Drug Application, taking into account Globalization |

(Summary)
We selected the following four items related to CMC (Chemistry, Manufacturing and Controls) studies that are conducted during the phases of drug development, and summarized points for quality assurance and future tasks.

- Studies during the phases of clinical trials (studies compliant with GMP for investigational medicinal products)
- CMC studies to obtain data to be used for new drug application
- Dealing with the globalization of GMP for investigational medicinal products (compatible with PIC/S GMP guidance)
- Implementation of ICH Q9 and Q10 in the development phases

There are a wide range of CMC-related guidelines and notices, and their requirements are complicated. Therefore, it is a common task for each company to work on quality assurance of CMC studies, while looking at the whole picture of drug development.

In order to deal with this task, we discussed the above four items after accurately understanding the CMC-related guidelines and notices, and prepared a dossier as an outcome of our activity in which key points related to the CMC testing were described referring to the CMC-related guidelines and other requirements. The dossier may help you understand the above points in the phases of drug development. It also can be used as a reference when planning to deal with PIC/S GMP and ICH Q9 and Q10 during the development phases.

The following future tasks emerged from this consideration:

- Dealing with the new ICH guidelines M7 and Q3D that are expected to be released in the near future
- Dealing with the studies conducted under the GMP for investigational medicinal products to comply with PIC/S GMP
- Dealing with ICH Q9 and Q10 during the development phases

In order to deal with the new tasks, it is necessary to collect information on trends of the regulatory authorities and to further properly understand the guidelines. Subsequently, proceeding to the collection of case examples from each company may be an effective way for dealing with the tasks.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 2: Quality Management of non-GLP Studies |
| **Subgroup** | Subgroup 1: Quality of CMC studies<br>The Way QC/QA Associated with Quality Assurance Ought to be during the Development Phases |

(Summary)
The Quality Guideline Deliberation Team established as its activity goal "to prepare a collection of Q&A items associated with the roles of QA during the development phases based on the questions raised in a daily business activity or the cases encountered."

The deliberation theme was classified into the following seven categories: 1) quality assurance of the drug formulation design data, 2) validation, 3) equipment control, 4) study plans/reports, 5) quality assurance of the studies, 6) general activities for quality assurance, and 7) others.

As for a collection of Q&A items, a table consisting of the following five items was prepared: "questions," "backgrounds," "answers," "discussions," and "rationales." In this table, the questioner filled in the "questions" and "backgrounds" fields, and then the summarized results of discussions at regular meetings were entered into the "answers" and "discussions" fields. Supporting information, etc., if any, were entered into the "rationales" field.

The total number of questions was 61. Of these, 11 questions were related to "validation," 11 related to documents such as "study plans/reports," 7 related to "device management," 7 related to "quality assurance of the studies," 5 related to "quality assurance of the drug formulation design data," 12 related to "general activities for quality assurance," and 8 related to "others."
The following points were considered as backgrounds on which these questions were raised: (1) inquiries about "concrete" actions in relation to individual cases due to "abstract" requirements by the regulatory authorities for the quality of application dossiers
(2) increasing awareness about harmonization between the global development of corporate activities in recent years and conventional domestic corporate activities,
(3) reduced labor spent on quality assurance at study sites and quality assurance units in relation to resources of the applicants, etc.

The answers are based only on the members' opinions. Any comments on or criticism, etc. in relation to the answers will be accepted with sincerity for further consideration.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 2: Quality Management of non-GLP Studies |
| **Subgroup** | Subgroup 2: Quality of Pharmacology and ADME studies |

(Summary)
A questionnaire survey on Pharmacology and Drug Metabolism and Pharmacokinetics (DMPK) studies conducted at foreign facilities was performed in terms of the quality management system, study plan, conduct, report, and storage of each study to ensure quality, and compared with those in Japan. Studies included in the survey were studies on primary pharmacodynamics for pharmacology and non-clinical PK studies and metabolism-related studies for DMPK.

In this questionnaire survey, responses were obtained from each institution of SQA (the United States), RQA (the United Kingdom), SoFAQ (France), and DGGF (Germany) and from institutions of Study Group 2 of JSQA GLP Group (Japan). The total number of institutions responding to the survey was 70 for pharmacology and 123 for DMPK in US/EU, and 36 and 35, respectively, in Japan. The most common country/region of the responding foreign facilities was the United States, accounting for approximately half of the total for both pharmacology and DMPK studies. The majority of the institutions were pharmaceutical companies or CROs, while the number of responses from CROs was greater for pharmacology studies.

Regarding pharmacology studies, comparison was made primarily between the quality management system in US/EU and in Japan. It was shown that, in US/EU, many facilities conduct studies according to GLP, and in cases where no guideline was used, 70% or more conduct studies at GLP facilities. This may suggest that a certain level of quality is maintained for pharmacology studies in US/EU even without global guidelines and/or regulations. Therefore, each item was compared by seeing how much the quality level is different from that in Japan. The result showed that differences were observed in some items when examined in detail. Overall, however, it was suggested that there was no difference in the quality level of pharmacology studies between US/EU and Japan.

Regarding DMPK studies, it was shown that the number of responses was similar between pharmaceutical companies and CROs, and many facilities conduct studies according to GLP in US/EU. In Japan, most of the responses were obtained from pharmaceutical companies, which follow the Standards for the Reliability of Application Data (Article 43 of the Ordinance for Enforcement of the Pharmaceutical Affairs Act). Therefore, the comparison was made on the items regarded as essential requirements to ensure the quality of studies discussed by our group before, paying attention to three divisions based on the guidelines used (US/EU facilities with the GLP guideline, US/EU facilities with other guidelines, and Japanese facilities with other guidelines). The results showed no major difference among the three categories in terms of whether or not the essential requirements are considered as an item for study conduct, suggesting that there is no difference in the concept of the quality assurance of studies between US/EU and Japan.

In summary, a survey was conducted on the quality management of pharmacology and DMPK studies in US/EU. For both types of studies, it was suggested that there is no major difference in the quality of studies, and the study enforcement environment is similar between US/EU and Japan.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 2: Quality Management of non-GLP Studies |
| **Subgroup** | Subgroup 3: Training |

(Summary)

In this term, Study Group 2, GLP Division continued to consider "Quality Management of non-GLP Studies, which are conducted under the 'Standards for Reliability of Application Data (Article 43 of the Ordinance for Enforcement of the Pharmaceutical Affairs Act, Ordinance of Ministry of Health and Welfare No.1 of 1961". In particular, Subgroup 3 worked on the theme, "Consideration of Training on this Quality Guideline."

It is an important task for each facility to train personnel to acquire abilities/skills required for proper conduct of studies under the quality guideline.

For that purpose, as "Agenda I: Consideration of Actual Training Methods", all group members acquired planning/management abilities for personnel training, and skills required of an instructor through training seminars.

As "Agenda II: Consideration of Training System," responsibilities and abilities (knowledge and skills) required of the Study Director and the Study Personnel were identified, and a deliverable entitled "Consideration of Training Programs on the Quality Guideline: Step-by-step Training System" was prepared as a reference material that can be used to design training programs and curriculums at each facility, by considering the timing of training, training materials, and methods to train personnel efficiently to reach the suitable level.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 2: Quality Management of non-GLP Studies |
| **Subgroup** | Subgroup 4: Quality of application dossiers |

(Summary)
Continuing from the previous term (10th term), Subgroup 4, Study Group 2, GLP Division performed its activities under the group theme of "Consideration of Quality of Application Dossiers." Consideration on the quality of application dossiers had been made from two broadly-divided perspectives, i.e., the quality of "electronic Common Technical Document (eCTD)" and "contents of application dossiers." Taking over this flow, consideration was given to two agendas, i.e., "consideration on the results of the factual survey on eCTD conducted in the previous term" and "consideration on specific cases associated with the quality of application dossiers" as specific activities for this term (11th term).

The factual survey on eCTD conducted in the previous term was a questionnaire survey primarily on leaf files of non-clinical studies in the eCTD, including their creation and QC/QA structure. From the results of the survey, items with potential high risk or items of interest were selected, and discussion was made on what methodology can be used for each item to ensure quality. During this process, a typical eCTD preparation flow was prepared, and consideration was given to potentially problematic points found in the flow and check points for leaf files, etc. Although check points for leaf files have already been identified in the deliverable prepared by Common Special Project 2 in the 8th term (No.07 K02), a factual questionnaire survey on check points was conducted within the group, and regulatory notices and relevant information were reviewed to improve the members' understanding.

In addition, from the collection of case examples used as the basis for the 10th term deliverable prepared by the Team B, Subgroup 4, Study Group 2 (No.119), "Quality Assurance of Application Dossiers - A Case-based Consideration of Quality Assurance of Application Dossiers and Relevant Documents," cases that had not been included in the deliverable were re-selected, and they were examined, together with new cases collected, as familiar questions about application dossiers.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 2: Quality Management of non-GLP Studies |
| **Subgroup** | Subgroup 5: Cases from document-based conformity inspections |

(Summary)
We have been investigating the actual practice of document-based conformity inspections by PMDA since 2000.

A document-based conformity inspection is an inspection performed by PMDA to see whether the approval application materials are prepared properly and accurately according to the "Standards for Reliability of Application Data" (Article 43 of the Ordinance for Enforcement of the Pharmaceutical Affairs Act) by verifying/validating them against the source data.

Using questionnaires targeted at the member companies of JSQA, we collected information on CTD M3 and M4 in terms of what type of documents had been submitted to and inspected by PMDA, what had been communicated with PMDA during inspection, what type of written inquiries had been received from PMDA after inspection, etc. The information collected was examined from various angles. The results obtained were reported at a debriefing meeting to provide information and to contribute to improving the quality of studies and application materials.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 3: Computer systems |
| **Subgroup** | Subgroup 1: Quality assurance of electronic data<br>Activity Summary |

(Summary)
Information and communication technology evolves from moment to moment. There are new technologies that have already been used up front in foreign regions, especially in Europe and the United States, while there are other technologies that have been used continuously. QA-related industry groups in Japan and foreign regions are in the process of consideration to ensure the quality of these technologies. Also during the period between April 2012 and February 2014 (11th term of JSQA), there were many key words/phrases related to electronic data management and computerized system validation (CSV). These key words/phrases were “archiving of electronic records,” “use of cloud computing,” “inspection of data centers,” “consideration of audit guidelines related to software validation,” “consideration of Standard for Exchange of Data (SEND),” and so on, extending to a wide range.

As a research group on the quality of non-clinical electronic data management/CSV in Japan, Subgroup 1, Study Group 3, GLP Division worked toward the goal of “following technological advances to ensure the quality required for information and communication technology at any given time.” Our activities can be divided into two; the first is “consideration for ensuring the quality of GLP-compliant systems” and the second is “consideration for upgrading the skills of QA personnel to maintain compliance.”

As for “consideration for ensuring the quality of GLP-compliant systems” the following topics were covered: “Case Review for Promotion of Computerization - Familiar Questions/Utilization of Technologies,” “Operational Issues throughout the Life Cycle of Computerized System Validation,” and “The Status of “Archiving of the Electronic Records in external Contract Archiving Facilities” and “Use of Cloud Computing” in Non-clinical Areas in Japan.”

As for “consideration for upgrading the skills of QA personnel to maintain compliance,” the following topics were covered: “Roles of QA in Ensuring the Quality of Computerized Systems,” “Regulation Review - Electronic Raw Data Archiving,” and “Current Topics on Computerized Systems in the Pharmaceutical Industry - Based on Information Exchanges with Related Organizations.”

More than 60 members gathered for Subgroup 1, Study Group 3 for the 11th term, making it the biggest subgroup in the GLP Division. The participating members are “software suppliers,” “system experts of pharmaceutical-related companies,” “QA personnel of pharmaceutical-related companies,” etc., who are concerned with different roles in their own facilities. In the activities of the issue examining group, deliverables were prepared while the members exerted their own strong points to provide useful information. Additional activities performed to supplement the activities of the issue examining group, such as “collection of regulatory authority inspection cases at each facility,” “collection of inspection cases by foreign pharmaceutical-related manufacturers,” and “group workshops” also contributed to the productive outcome.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 3: Computer systems |
| **Subgroup** | Subgroup 1: Quality assurance of electronic data<br>Case Review for Promotion of Computerization - Familiar Questions/Utilisation of Technologies |

(Summary)
Currently, IT is widespread and used for business operations in many industries. Similarly in the pharmaceutical industry, IT is used for document preparation to make work more efficient. Electronic data were adopted as raw data to increase efficiency in research work, and regulations on computerized system validation and electronic records/electronic signatures were released to assure the quality of electronic data. Thus, there are regulations/guidelines to be followed when utilizing IT, suggesting that information technology is making progress in terms of Information and Communication Technology (ICT). In Japan, however, the reality is that electronic data in computers are printed on paper and used as raw data at many facilities.

In Japan, use of electronic data as raw data tends to be avoided. As a result of examining the reason for this tendency in the 10th term, it was found that there exists “skepticism toward the long-term quality and availability of electronic data” and it is considered that “using paper as raw data is safer.” To eliminate the concerns about electronic data and promote computerization of raw data, items required for computerization were further identified based on an interrelationship between the life cycle of the system and the life cycle of electronic data, and methods of long-term storage of electronic raw data were examined.

Based on the activity of the team examining computerization of raw data up to the previous term, the policy for the activities in the this term (11th term) was determined to be “to eliminate familiar concerns, more specifically, collecting questions and issues that team members have in their daily work and considering responses to them. To collect cases to be reviewed, it is necessary to limit themes. For the team examining computerization of raw data, appropriate themes should include issues associated with use of electronic records, points to be noted when computerizing paper-based raw data, etc. In the 10th term, however, cost-effectiveness was listed as one of the contributing factors for the delay in computerization of raw data. For this reason, electronic data including electronic files such as electronic documents (e.g., plans/reports, SOPs), rather than electronic data as electronically (electromagnetically) recorded test results, was selected as a theme. We examined how each facility is dealing with the situation and what solutions would be possible, and explored how IT should be utilized for each case (ICT).

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 3: Computer systems |
| **Subgroup** | Subgroup 1: Quality assurance of electronic data<br>Current Topics on Computerised Systems in the Pharmaceutical Industry - Based on Information Exchanges with Related Organisations |

(Summary)
There are a number of research or industry groups examining various issues on computerized system validation.

As the laws and regulations to be complied with and backgrounds are different among GxP specific areas (GLP, GCP, GPSP), there may be difference about the prioritization/interpretation of CSV issues, and the actions to be taken on the same issue may be different in each group.

In addition, finding out answers to these questions may lead to identification of issues that we have never been aware of. On the other hand, we share the same fundamental philosophy and therefore there may be many points that are useful to one another.

In this context, we as an issue examining team set the purpose of our activities as “to collect information on any issues to be considered regarding quality assurance of computerized systems and electronic data in these groups and their opinions on such issues, and examine the activities of Subgroup 1, Study Group 3.”

Specific achievements of our activity are:
(1) Collection of information from JSQA’s annual reports and deliverables
(2) Participation in meetings, holding of joint meetings, etc.
Continuous exchange of opinions/sharing of information with the relevant organizations are expected to be useful for activities on both sides.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 3: Computer systems |
| **Subgroup** | Subgroup 1: Quality assurance of electronic data<br>Operational Issues throughout the Life Cycle of Computerised System Validation |

(Summary)
There is no longer any doubt that computer systems play an important role in the practice of research, development, manufacture, and application for approval of drugs. These computer systems need to be operated properly in a form complying with the regulations. In fact, it seems that regulation-compliant methods for operation of computer systems are being established, given that 1) it has been several years since GAMP 5, the practical guideline for CSV, was released, 2) the "Guideline on Appropriate Management of Computerized Systems" has been released in Japan, and 3) Subgroup 1, Study Group 3, GLP Division, JSQA also has examined the operational management methods for computer systems throughout the life cycle from various perspectives and summarized the results as a deliverable.

Nevertheless, there seem to remain questions, issues, and challenges associated with operational management of computer systems.

A possible cause of this may be that IT technology is constantly and rapidly advancing, and it can be a trial-and-error process when actually trying to use such state-of-the-art technology because regulations lag behind or there are no prior cases. An example of such cases is utilization of data centers or cloud computing.

Another cause of the trouble experienced by those who are involved in computer system management or quality assurance tasks may lie in the fact that there is a need to establish computer system operation methods suitable for each site. In other words, different computer systems are used in different ways at each facility, and it is necessary to establish an operation method customized for each facility. Therefore, an operation method shown in a textbook manner would fail to fit into that specific framework; instead, each facility may need to actively seek a regulation-compliant operation method for themselves.

With this as a background, we decided to engage in the activities, in this term, with the purpose of clarifying what problems or issues exist at each facility in terms of operational management of computer systems and considering solutions to them more specifically. Although it is a theme that fills in the gaps in what we, Subgroup 1, Study Group 3, GLP Division, JSQA, had previously considered, problems or issues that a facility has may be an event of interest for other facilities and therefore solving individual questions is considered useful when considering methods for operational management of computer systems.

In the deliverable, issues submitted by each facility and answers to them are provided in a Q&A format. We hope that the facilities will consult questions and answers of interest in the deliverable and make effective use of them to improve their methods for operational management of computer systems.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 3: Computer systems |
| **Subgroup** | Subgroup 1: Quality assurance of electronic data<br>Regulation Review - Electronic Raw Data Archiving |

(Summary)
Under the theme of "Electronic Data Archiving," the team examining electronic data-related regulations, etc., selected the "Guidelines for the Archiving of Electronic Raw Data in a GLP Environment" by AGIT (Arbeitsgruppe Informationstechnologie) as a subject material for this term, and started to work on understanding the guidelines.

Basic handling of data archiving should not be different between electronic data and paper-based raw data archived at archiving facilities. However, special consideration is necessary because the material to be archived is electronic data. Therefore, understanding of electronic data is essential to understand the guidelines, and each member reviewed various reference books and guidelines to restudy electronic data. In addition, all participants gained deeper understanding of electronic data and their archiving by listing questions related to electronic data archiving and examining and discussing answers to these questions.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 3: Computer systems |
| **Subgroup** | Subgroup 1: Quality assurance of electronic data<br>Roles of QA in Ensuring the Quality of Computerised Systems |

(Summary)
Along with increased opportunities for electronic data management and advancing IT technology, the importance of considering the way QA activities ought to be is increasing. We investigated the current situation of the way QA monitoring is involved with computerized system validation (CSV) and management of electronic records/electronic signatures (ER/ES) at each company, and further examined the way QA monitoring ought to be in the future.

Before initiating our activities, the personnel involved in QA monitoring on CSV were classified into the following three categories in terms of specialties and task categories of the QA personnel.

- Study QA personnel: Perform monitoring on study plans/final reports, monitoring on the process of study conduct, and facility monitoring from the perspectives of GxP and guidelines on the quality of application materials.
- CVQA personnel: Full-time personnel designated to monitor the operating process related to CSV and ER/ES from the perspectives of CSV/ER/ES-related regulations and industry standards.
- CSV-QA personnel: Perform QA monitoring on CSV, regardless of whether they are CVQA or study QA personnel.

We conducted a questionnaire survey from various perspectives such as the framework of QA monitoring on CSV, qualification requirements for CSV-QA personnel, and ideal and reality of QA activities on CSV, and obtained the following results.

- It is rare that experts like CVQA personnel are designated, and study QA personnel often perform monitoring on CSV.
- CSV-QA personnel are required to have the following three factors; knowledge about rules on CSV/ER/ES-related regulations/ company rules, general skills required for QA personnel, skills specifically required for CSV-QA personnel.
- We examined and compared the reality and ideal of the roles of QA by the life cycle of computerized systems. It was found that the gap was small for the process associated with introduction of the systems, while the gap was big for the process associated with operation or retirement of the systems.
- Study QA personnel do not give their signatures on CSV documents when they perform monitoring on the documents, while CVQA personnel may give their signatures on the CSV documents when they perform monitoring on the documents.

Although currently a few facilities are staffed with experts like CVQA personnel, there are advantages of having these experts; e.g., they can offer advice to personnel involved in CSV based on their experience with or knowledge of CSV from a preventive perspective, and they can prevent problems from spreading by reviewing CSV documents in a timely manner. If it is impossible to have experts like CVQA personnel, the roles played by other personnel (e.g., users, IT personnel, suppliers) would be important. It is recommend that facilities have experts like CVQA personnel when they are adequately-staffed and a sufficient amount of relevant work is generated.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 3: Computer systems |
| **Subgroup** | Subgroup 1: Quality assurance of electronic data<br>The Status of "Archiving of the Electronic Records in External Contract Archiving Facilities" and "Use of Cloud Computing" in Non-clinical Areas in Japan |

(Summary)
Along with the change of environment surrounding the pharmaceutical industry and IT technology advances in recent years, different types of suppliers are beginning to provide services/technologies that are thought to be useful for non-clinical research.

It can be imagined that for non-clinical studies, there are many advantages of retaining electronic records at sites other than research laboratories (e.g., data centers, external contract archiving facilities). However, use of these sites in non-clinical studies is regarded as highly challenging in Japan.

We, Study Group 3, GLP Division, JSQA (hereinafter referred to as "the Group"), has been examining specific procedures for the efficient adoption of the above-mentioned services and technologies into the non-clinical research areas according to GLP since the previous term (10th term/2010-2011).

In this term (11th term/2012-2013), we performed examination focusing on the following two points; "use of cloud computing" and "archiving of electronic records at external contract archiving facilities" at pharmaceutical-related companies in Japan. The flow of examination is shown below.

1. Surveillance of the Use in the Non-clinical Research Areas
   We examined the "use of cloud computing" and "archiving of electronic records at external contract archiving facilities" in the non-clinical areas at the facilities that the members of the Group belong to.
2. Surveillance of the Use in Areas Other Than Non-clinical Research
   We examined the "use of cloud computing" and "archiving of electronic records at external contract archiving facilities" in GCP, GVP, or GMP areas at the companies that the members of the Group belong to.
3. Examination and Analysis of the Surveillance Results
   We analyzed the differences in the "use of cloud computing" and "archiving of electronic records at external contract archiving facilities" between non-clinical research areas and other areas, and examined causes and measures.
4. Examination of Specific Procedures for Introducing New Technologies Efficiently According to GLP
5. We organized the requirements of Japanese and foreign laws and regulations/guidelines on new technologies, and provided specific examples of the procedures for introduction according to GLP.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 4: Quality assurance for non-clinical studies (Eastern Japan) |
| **Subgroup** | Subgroup 1: Overall quality assurance |

(Summary)

Study Group 4, as an Eastern Japan regional study group, performed activities with the main theme of consideration of topics on overall quality assurance. Free discussion style was adopted, and the "frequent questions/issues in the work" that the members have in the daily work were considered in this Study Group 4 activities. In the first half of the term (fiscal 2012), we discussed 23 of the "frequent questions/issues in the work" as the whole study group, and in the second half of the term (fiscal 2013), we discussed 25 of them as three separate subgroups of "GLP" "Pharmacology/Pharmacokinetics" and "Quality" to ensure the reliability of daily work.

In addition, we held seminars/lectures aimed at improving quality assurance skills of the members of the study group and broadening the members' perspectives.

At the seminars, the members of the study group reported GLP compliance inspections cases, and the other members in JSQA talked about various topics related to quality assurance. On the other hand, at the lectures, we invited outside speakers and asked them to speak about "From the CITI Japan Project" and "GLP Studies and Well-being of Laboratory Animals" to attempt to acquire deep knowledge related to daily work. In addition, as part of the GLP Division's educating activities for this term, we held an English conversation course entitled "Performing a Successful QA Audit at an Overseas Site" aimed at acquiring language skills required for QA activities at foreign facilities.

As stated above, Study Group 4 focused on learning the way of thinking and attitude toward ensuring the reliability of daily work, and performed activities for improving quality assurance skills by addressing various topics related to quality assurance and exchanging opinions among all members.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 5: Quality assurance for non-clinical studies (Western Japan) |
| **Subgroup** | Subgroup 1: Quality assurance for GLP studies |

(Summary)
The research agenda of Study Group 5 is "Quality assurance for non-clinical studies (Western Japan)." As Subgroup 1, we have 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 work for information sharing and human exchange, and we worked on:
1) Examination of specific cases of familiar questions/issues
2) Timely exchange of opinions using a mailing list
3) Training lectures and subject offering lectures
4) "Content-rich" information exchange gatherings after meetings

In this term, we discussed 39 "specific cases of familiar questions/issues" submitted by members and examined 9 opinions collected from the mailing list.
We held 5 training lectures and subject offering lectures including 7 titles. In addition, we held "content-rich" information exchange gatherings after every meeting, and they played a great role as a lubricant among members.

| Activity Summary of the 11th Term (April 2012 – March 2014) | |
|---|---|
| **Study Group** | Study Group 5: Quality assurance for non-clinical studies (Western Japan) |
| **Subgroup** | Subgroup 2: Quality assurance for non-GLP studies |

(Summary)
As a Western Japan study group, we performed activities under the theme of "Familiar Questions/Issues on Quality Ensuring for Non-clinical Studies− Studies Compliant with Standards for the reliability of application data." However, it should be emphasized that we targeted items related to work of the members of the group and our examination included not only studies compliant with quality guidelines but also GLP studies, GMP, etc. Along with our main activity of examining familiar questions/issues, we had exchange of opinions by e-mail, training lectures, and free theme discussions.

The base for our activities is Shin-Osaka, and we held a total of 14 group meetings including those held once a year in Kyoto and Kobe, examined a total of 29 questions/issues, and summarized them in a deliverable. In the deliverable, the 29 questions/issues are classified into 11 items consisting of "study plans/amendments" , "study procedures" , "study results" , "study reports" , "SOPs" , "QC check and QA monitoring" , etc., and the background, conclusion, and opinions exchanged 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 of the former, and we had an occasion for presenting the outcomes of the latter following four examinations.