| **GLP Division, Activity Summary of the 14th Term (April 2018– March 2020)** | |
|---|---|
| **Study Group** | **Study Group 1: GLP regulations** |
| **Subgroup** | **L-1-1** |
| **Theme** | **GLP for drugs** |

In Study Group 1, we performed the following activities in this term.

1. Research on themes
2. Case report meeting of GLP inspection by PMDA
3. Planning and Practice of training courses for Auditor
4. Cooperation with affiliates for GLP syudy
5. Publication of activities for following themes

In the research on themes, we set five themes: Evaluate the case report of GLP inspection by PMDA, Practical use of electronic archives, Data Integrity, Risk-based approach, and OECD AD19. We examined the theme in each group, and prepared the deliverable. The titles of these activity are as follows.

- GLP surveys / inspection cases and their trends and the fact-finding survey following the release of OECD GLP document No. 19
- Guidance on the use of external electronic archive facilities (non-GLP)
- Identify gaps in GLP facilities in Japan for MHRA's GXP data integrity guidance and take countermeasures
- Examination of process-based inspection using a risk-based approach
- OECD GLP Advisory Document No. 19 Adivisory Document of the Working Group on Good Laboratory Practice on the Management, Characterization and Use of Test Items

We organized A GLP inspection case report meeting every December to share information on our industry. We also planned and practiced GLP Basic Training Course and GLP Advanced Training Course once a year. In addition, in collaboration with related organizations (Japan Pharmaceutical Manufacturers Association, Japan Safety Testing Commission, and the Japan Federation of Medical Device Industries), we lead discussions to resolve shared issues within the industry, and discussed with PMDA twice a year.

As a result of the activity this term, we published a tranlation of AD19 on the JSQA website, and presented by poster on the above three themes in five at 6th GQAC. We also planned and conducted the session on OECD GLP document AD19, "What has changed by issuing OECD Advisory Document No.19?", at 6th GQAC.

| **GLP Division, Activity Summary of the 14th Term (April 2018– March 2020)** | |
|---|---|
| **Study Group** | **Study Group 1: GLP regulations** |
| **Subgroup** | **L-1-1-1** |
| **Theme** | **Evaluate cases of GLP Inspection** |

During the 14th term, Review Case Working Group, Subgroup 1, Study Group 1, of the GLP Division worked according to the policy "the main activities are to collect, analyze, and evaluate cases of GLP inspections for drugs and to organize a GLP review/inspection case report meeting." Continuing from the 13th term (FY2016–2017), we used "GLP Compliance Review Case Reports" provided by members of the Japan Society of Quality Assurance to classify regulatory instructions, search provisions that support the classification and other information, and prepare a list of GLP compliance review cases. The regulatory instructions were categorized according to which article of the GLP Ministerial Ordinance for drugs the instruction corresponded to. Other information than regulatory instructions, including review details, main points, and feedbacks and requests from reviewers, were classified in line with the new format of case reports and were presented, so that the case list can be easily used as supporting information for the management of each GLP facility.

In the GLP review/inspection case report meeting in the 14th term, the results of a trend analysis of GLP review cases were presented, and a post-meeting questionnaire survey was conducted. With the consent of all reporting facilities, our group members conducted a trend analysis of GLP review cases and presented the results on the day of the meeting. In the FY2018 case report meeting, we had conducted a post-meeting questionnaire survey to improve future report meetings, investigated the responses, and then reflected the results in the FY2019 case report meeting.

For the sessions organized by Study Group 1 of the GLP Division at the 6th Global QA Conference, we determined to investigate the actual conditions associated with the issuance of the OECD GLP Advisory Document (AD) No. 19 and thus prepared a questionnaire used for the survey and collected and analyzed the responses from facilities. This questionnaire survey was conducted among Study Group 1 members of the GLP Division to investigate the interpretation of the OECD GLP AD No. 19, which was issued in April 2018, differences from the conventional operation, and points checked by authorities during the GLP inspections. All responses obtained in the survey were presented in the deliverable.

| GLP Division, Activity Summary of the 14th Term (April 2018– March 2020) | |
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| **Study Group** | **Study Group 1: GLP regulations** |
| **Subgroup** | **L-1-1-2** |
| **Theme** | **Practical use of electronic archives** |

We investigated the methods necessary for operating external servers used as electronic archives to store GLP electronic data.

The GLP Ministerial Ordinance for drugs requires that study-related records be appropriately stored in an archive. The OECD GLP (Advisory Document No.15) also requires that electronic data be stored in the same manner as paper records.

Electronic GLP data to be stored in CD-R, DVD-R, and other recording media should be stored in a GLP-compliant archive equivalent to that for storing paper records. When electronic data are stored in a server, the server should be controlled as a GLP-compliant archive. The potential need for using servers outside GLP laboratories is recently increasing to align with the management status of other GxP regulations, improve the efficiency of in-house work, reduce the expenses for IT devices and other equipment, and diversify the risk of disasters and other emergencies. Under these situations with regard to the archives, we considered it essential to examine the use of external non-GLP-compliant electronic archives. Our group thus determined that the theme of the 14th term was to investigate whether external non-GLP-compliant electronic archives can be used to store electronic GLP data and if it would be considered possible, to clarify the requirements and specific methods for operating the archives.

Given that the use of external electronic archives for storing electronic data varies widely, depending on the range of outsourcing and the method for storing electronic data, we first investigated the details of individual uses and classified the types of outsourcing range and the patterns of archiving.

Focusing on the respective roles and responsibilities of GLP facilities and external electronic archives, we next investigated their roles assigned from archive selection to operation stopping to determine the GLP management systems that were considered necessary for all types of outsourcing range and all archiving patterns. The results concluded that external non-GLP-compliant electronic archives can be used to store electronic GLP data when the archives are properly managed, appropriate procedures are used, operators are adequately trained, security measures including access rights are exercised, and the agreement between the facility and the archive is appropriately concluded and adhered to. We summarized the results of this investigation as guidance for using external non-GLP-compliant electronic archives, by using the information obtained from discussions with the PMDA and Study Group 3 as needed.

| GLP Division, Activity Summary of the 14th Term (April 2018– March 2020) | |
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| **Study Group** | **Study Group 1: GLP regulations** |
| **Subgroup** | **L-1-1-3** |
| **Theme** | **Data Integrity** |

The OECD Working Group is planning the issuance of guidance on data integrity (DI) in the GLP area. The Working Group 3 (Data Integrity Working Group), Subgroup 1, Study Group 1, thus investigated gaps between the guidance on DI (DI Guidance) in the GXP area, which was issued by the Medicines & Healthcare products Regulatory Agency (MHRA) in March 2015 and the current status of GLP facilities in Japan.

To well understand DI, the following information was extracted: doubtful points that could not be clearly interpreted and gaps between the guidance and the current status. The extracted gaps were ranked according to three-level priorities for the investigation.

The investigation mainly focused on gaps with the first priority, and the results revealed that gaps with major impacts on Japanese GLP facilities were found in the following three categories: the governance system, the control of blank formats, and the management of computerized systems mainly for dynamic data.

These three gaps were further investigated. For the gap in requirements for the governance system, the impact would be reduced with flexible actions, depending on the situations of each GLP organization. To minimize the gaps in requirements for controlling blank formats and computerized systems, enormous costs and tasks would be inevitable, and thus, we investigated currently possible actions to reduce the gaps.

We explained the investigation results in the 6th and 8th discussion meetings with the Pharmaceuticals and Medical Devices Agency (PMDA) and industrial associations to share with the PMDA the concept of compliance with the DI Guidance and the course of action to be followed. At the 9th GLP Advanced Course, we presented the gaps between the DI Guidance and the current status of Japanese GLP facilities, in collaboration with Study Group 3.

| GLP Division, Activity Summary of the 14th Term (April 2018– March 2020) | |
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| **Study Group** | **Study Group 1: GLP regulations** |
| **Subgroup** | **L-1-1-4** |
| **Theme** | **Risk-based approach** |

GxP inspection/audit methods using the concept of risk-based approach (RBA) concentrate resources related to compliance assessments by regulatory authorities and quality assurance of pharmaceutical companies on higher-risk processes, which thereby may reduce costs for various regulations and in-house compliance and produce efficient and effective quality and reliability assurance. The RBA-based inspection/audit methods have also been established in the GLP area in the United States and Europe, but are not yet widely used in Japan.

In the 11th term, Subgroup 1 of Study Group 1 started to examine the RBA-based quality assurance (QA) inspections and elucidated their usefulness for facility and experimental procedure inspections. In the 14th term, we categorized experimental procedures for typical toxicity studies, extracted situations that can be problematic in conducting the studies (possible issues), and evaluated the risks to determine whether the process-based inspections are applicable. The following toxicity studies were selected: the 4-week repeated-dose toxicity study (hereinafter referred to as the "4-week repeated study") as an *in vivo* assessment system and the bacterial reverse mutation test (hereinafter referred to as the "Ames test") as an *in vitro* assessment system. As with in the 13th term, the risks were assessed using an analytical method based on the Healthcare Failure Modes and Effects Analysis (HFMEA). The degree of severity and occurrence of possible issues were assessed, and then the criticality was calculated by multiplying the severity by the occurrence to categorize the risk.

The results revealed that many possible issues were categorized as low risk in both toxicity studies. Most of the possible issues categorized as high risk were related to computerized systems (the 4-week repeated study) or records (the Ames test). We then investigated whether these high-risk cases can be detected at testing department. Most of the high-risk cases were considered detectable, which suggested that QA inspections are not necessarily required for experimental procedures. These results concluded that the process based-inspections are applicable to both studies.

In this investigation, facility-specific situations were not taken into consideration. Possible issues vary depending on the implementation systems, test articles, and used equipment and thus should be analyzed and assessed according to facility situations.

| GLP Division, Activity Summary of the 14th Term (April 2018– March 2020) | |
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| **Study Group** | **Study Group 1: GLP regulations** |
| **Subgroup** | **L-1-1-5** |
| **Theme** | **OECD AD19** |

The OECD GLP Advisory Document No. 19 (AD19) Draft Guidance was announced on May 4, 2017. As a result, PMDA began to grasp the situation and issue comments based on the contents of AD19 in the GLP compliance assessments. Since the official Guidance was issued on April 19, 2018, L-1-1 determined that quick understanding and response to the contents were necessary, and examination of AD19 was taken up as the study topic for L-1-1 group 5 (L-1-1-5).

First, we published the translated version of AD19 on the JSQA Homepage as an atypical product on September 20, 2018.

Then, for mainly the Japanese GLP of drugs, each section of AD19 was discussed by L-1-1-5 based on the indications and guidance of PMDA, and we compiled the interpretations and notes for the items where explanations were required.

In addition, at the 25th GLP workshop (October 2019), AD19 was clearly stated as “a basis for indications and guidance by PMDA”. Therefore, PMDA's commentary which should have been particularly taken into consideration at the GLP workshop was also described.

| GLP Division, Activity Summary of the 14th Term (April 2018– March 2020) | |
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| **Study Group** | **Study Group 1: GLP regulations** |
| **Subgroup** | **L-1-2** |
| **Theme** | **GLP for test articles other than drugs** |

During the 14th term, Subgroup 2 of Study Group 1 worked as a collaborative group with the Medical Devices/Regenerative Medicine Products GLP Working Group and the Agricultural Chemicals /Japanese Chemical Substances Control Act GLP Working Group.

No definite guidelines are available to assure the properties and stability of medical devices and regenerative medicine products as test articles, unlike drugs. Therefor the Medical Devices/Regenerative Medicine Products GLP Working Group investigated the results of cases collected in a questionnaire survey conducted by Study Group 1, the OECD Advisory Document (AD) No. 19, which was issued in April 2018, and other information to propose the guidelines for assuring the properties and stability of medical devices and regenerative medicine products as test articles, with the member of Japanese Society for Regenerative Medicine as a liaison. Establishing definite guidelines was difficult because medical devices and regenerative medicine products vary widely, and there are various concepts and opinions on the assurance of the properties and stability. However, the questionnaire survey results, individual responses, and opinions expressed in working group discussions were considered very useful for each facility. We would like to take this opportunity to thank all facilities that answered the questionnaire. In parallel with these activities, the group members collected questions and difficult cases for the quality assurance unit (QAU) in routine reviews and discussed them in a “case study.” After discussing many cases, we selected five cases in which a conclusion was drawn in the group and summarized them in the deliverable, with the results on investigations of property/stability assurance explained above. These results will allow us to not only improve individual and organization levels but also enhance the commonality of understanding across the industry.

The Agricultural Chemicals /Japanese Chemical Substances Control Act GLP Working Group investigated the issues on the Agricultural Chemicals GLP, Chemical Substances GLP, and other regulations. In the “Investigation of common questions and problems,” participating members brought their questions and problems to the group meeting and exchanged their opinions. The questions included whether shared use of a test system in different studies should be documented in the study plan and how raw data should be obtained from the shared test system. For these questions, the current status of each facility was presented, and member’s advices were used to improve the efficiency of studies. In the “email consultation,” after questions were asked by group members *via* email, reports of the present situations and comments were given by each facility, and the answers were put together by the member who asked the question. For example, the members presented the criteria for determining the actions for GLP deviations at each facility: how GLP deviation are recorded, whether exceptions are specified, and whether GLP deviations are documented in the final report. Continuing from the previous term, we held the 3rd Agricultural

Chemicals GLP Training Workshop on November 29, 2018, in collaboration with the Food and Agricultural Materials Inspection Center (FAMIC), the Japan Crop Protection Association (JCPA), and the Japan Society of Quality Assurance (JSQA). For questions that had been asked from the JSQA and JCPA members to the FAMIC before the workshop, group members handling agricultural chemicals played a central role in preparing response ideas and provided them for the FAMIC for preparing the responses. Majority of the prior questions were about the inspection methods and process inspections for multi-site studies, which was an issue to be addressed by our working group in the present term. For these questions, the FAMIC clearly stated their opinions at the workshop. The Agricultural Chemicals Regulation Law was partially revised on June 15, 2018, and the first step came into effect on December 1, 2018. The Agricultural Chemicals GLP standards were raised in status from a director-general notification to a ministerial ordinance, with partial modification of texts and reconsideration or addition of study areas and items. We also discussed new questions resulting from these changes and asked the FAMIC about part of the questions to elucidate how they should be interpreted. Furthermore, we supported the Agricultural Chemicals GLP Seminar, which was held for JSQA members on January 14, 2020, upon the request of the Agricultural Chemicals Office in the Ministry of Agriculture, Forestry and Fisheries. We will continue to improve the quality of GLP operation at each facility while maintaining a good relationship with regulatory authorities and other external institutions.

| GLP Division, Activity Summary of the 14th Term (April 2018– March 2020) | |
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| **Study Group** | **Study Group 2: Quality management of non-GLP studies** |
| **Subgroup** | **L-2-1** |
| **Theme** | **Quality of CMC studies** |

Study Group 2 of the GLP Division in this period has examined the reliability of various non-clinical studies in accordance with the goals of the GLP Division as a whole, which aims to further improve self-study by members, select topics of interest, and actively publish research results. Subgroup L-2-1 has been examining two topics, CMC studies and GMPs for investigational products, to review the reliability of quality studies.

The theme for examination of the reliability of CMC studies was "Data integrity in studies pursuant to the Standards for Reliability of Application Data" in order to discuss how data integrity as proposed by GMPs, GLPs, GCPs, etc. should be addressed when examining the application of reliability standards. The data integrity required during the preparation of test records, the creation and storage of raw data from analytical instruments, and the auditing trail of retrieved data, which were of particular interest to members, were examined from the perspective of Standards for Reliability of Application Data. In addition, the recommendation on the necessity was offered in view of the future for each.

Cooperating facilities were surveyed on the problem examination regarding GMPs for investigational products in order to ascertain the role of the QA in GMPs for investigational products at each facility and the implementation of GMPs for investigational products at each facility, which were not apparent from past subcommittee activities and results. The facilities were also surveyed on the response as GMP for investigational products to the planned revision of the GMP ordinance. All these findings were analyzed and examined. Survey results confirmed that the QA was heavily involved in the implementation of GMPs for investigational products in a wide variety of ways. It was also recognized that efforts were unique to GMPs for investigational products, and efforts adeptly responded in accordance with the manufacturing frequency of the investigational product and the stage of development. Survey results in response to revision of the GMP ordinance indicated that few facilities had acted before the revision, but facilities that were considering their response had already met some of the GMP requirements not described in the notification regarding GMPs for investigational products.

| GLP Division, Activity Summary of the 14th Term (April 2018 – March 2020) | |
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| **Study Group** | **Study Group 2: Quality management of non-GLP studies** |
| **Subgroup** | **L-2-2** |
| **Theme** | **Use of electronic laboratory notebooks in pharmacology and pharmacokinetic studies** |

Study materials should be stored for a long period because they are used as evidence of patent application and drug marketing approval application. Paper-based materials require enormous costs for their storage and for securing their space, which are a heavy burden on each facility. Poor accessibility and searchability of paper-based materials causes limited use of information, which does not justify the costs.

In recent pharmacology and pharmacokinetic studies, electronic data, such as measurement results generated from equipment, are increasingly used as study materials, and thus, electronic data should be stored for a long period in a safe and secure manner, which is also a big issue. Electronic laboratory notebooks (ELN) are expected to solve these issues, the facilities that use them for drug discovery research (e.g., exploratory studies) are increasing.

ELN are a system enabling to record or retain study information and materials and are known to have advantages in terms of searchability and accessibility, audit trails, space saving, and coordination with equipment. Based on these characteristics, ELN are expected to serve for effective use and reliability assurance of study materials.

Based on these situations, we selected the theme on the use of ELN in pharmacology and pharmacokinetic studies. We first conducted a questionnaire survey on ELN among the group members to extract points to be considered and questions. To deepen the understanding of ELN, we invited the venders to hold a lecture meeting. Because of differences in points to be considered between exploratory studies and studies compliant with the reliability standards, we discussed in regular meetings the points to be considered when ELN are used mainly in exploratory studies and also in studies compliant with the reliability standards, if any.

As a result of the discussions, the specifications, functions, and management (including operation of QC/QA) of ELN were summarized, and the discussions in meetings were summarized in a Q&A format in an attachment.

The results suggested that ELN are a useful system for a long period storage of electronic data in a safe and secure manner. On the other hand, depending on how to use ELN, contemporaneousness of data recording might be inferior to paper-based materials. Taking these points into consideration, the currently practical method is a hybrid use—a combination of ELN and paper-based materials. The recommended management is firstly to use both systems in a hybrid manner, and gradually increase and shift to the use of ELN.

Introduction of ELN requires computerized system validation (CSV) of ELN and related software applications, arrangement of the operating procedures, and training of the users. Each facility

should prepare suitable procedures, from data generation to archiving in ELN, and should be prepared in advance and recruit/keep human personnel with IT skills. Please keep in mind the need to build a good relationship with vendors, ensure data authenticity and legibility in the case of system replacement in order to prevent data fabrication, falsification, and loss.

We concluded that ELN can be used for not only exploratory studies but also studies compliant with the reliability standards by conducting appropriate CSV, establishing a system with secured reliability of studies, and developing appropriate management procedures. We hope that this deliverable can be useful to facilities that have introduced and are considering introduction of ELN.

| GLP Division, Activity Summary of the 14th Term (April 2018–March 2020) | |
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| **Study Group** | **Study Group 2: Quality management of non-GLP studies** |
| **Subgroup** | **L-2-3** |
| **Theme** | **Discussion on training programs regarding studies compliant with Japanese regulations: "Reliability Standards"** |

In this term (FY2018–2019), we in Subgroup 3 of Study Group 2 in GLP Division have discussed the following topic: "Training programs regarding studies compliant with Japanese regulations (Reliability Standards) — For controlling the quality of studies for regulatory submissions."

To control the quality of studies, i.e., preserve the reliability of studies and report accurate data, it is crucial to ensure that study materials, including raw data and records, are appropriately maintained. Personnel who are engaged in maintaining study materials—study directors, staff who conduct the studies, and third-party staff who verify study materials—may tend to think of inspecting study materials as simply ensuring consistency between the materials. However, there are many cases in which an event that affects the quality of a study has arisen caused by late timing of confirmation or lack of awareness for potential issues, even the consistency of study materials was ensured carefully. Such cases indicate that checking for consistency between study materials is not enough to preserve their reliability.

Based on such situations, we have created training materials for personnel who are conducting the verification of study materials. These training materials are designed to help personnel realize the essence and importance of carefully inspecting study materials to preserve the quality of the studies. The training is intended to improve personnel's understanding of the following points: (a) how the inspection of study materials can be conducted appropriately and effectively, and (b) what details should be focused on while checking study materials.

The training materials are composed of two parts, "Overview" and "Case Studies."

In the Overview unit, the results of a discussion on the following elements of study material inspection are described: the details to be checked in the study materials, when to perform the check, and who should conduct the check. Regarding the last point, personnel adequate for conducting checks for each type of study material are classified in two categories: personnel who can just check for accuracy and consistency of study materials and personnel who have additional professional experience in conducting checks or knowledge about the studies that they can apply in a comprehensive check of study materials.

In the Case Studies unit, training materials have been created as presentation slides to be used for classroom training sessions in each facility. The presentation slides are intended to raise personnel's awareness of the importance of thorough checks through examples of negative incidents and explanations of their causes.

The presentation is composed of a set of slides for the overview and sets of slides for individual cases. Each slide has a manuscript for trainers that explain the slides' contents; therefore, sets of slides can be selected by each facility according to the purpose of training sessions and personnel to be trained.

We hope that both the overview and the case studies are useful and helpful for training personnel in each facility.

| GLP Division, Activity Summary of the 14th Term (April 2018– March 2020) | |
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| **Study Group** | **Study Group 3: Computerized systems** |
| **Subgroup** | **L-3-1** |
| **Theme** | **The future of GLP brought about by new IT technology** |

The computerized systems have led to increases in efficiency and reliability at GLP facilities. That said, digitized data and records have produced new problems in quality assurance such as difficulties in detecting signs of falsification, distinguishing between originals and duplicates, and an insufficient duration of electronic recording media; however, such problems have been solved by proper CSV implementation and operational procedure setting. The computer system, which allows more objective and stringent management of data and records than paper, has become a central component of GLP quality assurance.

Today's innovative IT technologies have made remarkable progress and have been creating products and services we could not have previously imagined. New IT technologies have permeated our daily lives as common services within a short period, and they are also expected to make GLP facilities more efficient. However, the introduction of innovative IT technologies at GLP facilities has been slow, and those technologies are hardly widespread. This is likely due to the difficulty of establishing new methods for quality assurance because those IT technologies are not easily applied to conventional CSV approaches. In order to remedy this situation, it is important that industry and regulatory authorities need to have a shared vision of GLPs in the future where problems are identified and addressed using innovative IT technologies.

Therefore, our group started the investigation by envisioning GLP facilities of the near future that are introducing the latest IT technologies, which include operating support with blockchain technology, AR technology, biometrics and image recognition with AI technology, and a room access system with an indoor positioning system. As part of this vision, we outlined "Prospects for innovation in GLP data storage based on blockchain technology" and "An examination of quality assurance methodologies involving AI technology."

| GLP Division, Activity Summary of the 14th Term (April 2018– March 2020) | |
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| **Study Group** | **Study Group 3: Computerized systems** |
| **Subgroup** | **L-3-1** |
| **Theme** | **Promotion of computerization of raw data - Will electronic data contribute to the improvements in non-clinical studies? -** |

During the 14th term, we investigated the reason for slow computerization of raw data in GLP/non-GLP studies and the reason for promoting the computerization of raw data.

As part of efforts to promote data computerization, we conducted a questionnaire survey in the working group and a “Questionnaire on computerization promotion” in Study Group 3 to understand the current status and prospects of data computerization. The results revealed the current status of slow computerization and some problems at each facility. We also confirmed that paper-based materials are still highly reliable for data management because they have been a familiar tool so far and are easy to handle.

To overcome such difficult situations and understand important points for developing a computerization strategy, we conducted a SWOT (strengths, weaknesses, opportunities, and threats) analysis. The results of the SWOT analysis revealed that data computerization could be an effective measure to overcome the weaknesses of papers, <<storage space,>> <<security,>> <<data utilization,>> and <<information processing performance,>> and the threat of papers, <<loss of original documents>>. Although electronic data also have specific weaknesses and threats, these problems except costs can be overcome technically, and electronic data can be used effectively and efficiently once the operating procedures have been established. High costs are a big obstacle for computerization, which is expected to become mandatory in the near future, and are a problem that should be resolved by each facility.

Although data are being managed mainly using papers in GLP/non-GLP studies, no occasions favoring papers were found with external factors, as demonstrated in the SWOT analysis. In the recent pharmaceutical industry, opportunities to use important external factors, big data analysis and AI technology, are expected to increase in GLP/non-GLP studies. In studies using these external factors, it is difficult to use the conventional paper-based method and essential to use electronic data. In Japanese GLP studies, the Pharmaceuticals and Medical Devices Agency (PMDA) currently permits the use of papers as raw data, but maintaining electronic data is almost obligatory. To ensure data integrity, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) also require the maintenance of electronic data in GLP studies, and the PMDA will also impose the same requirement in the near future. To use electronic data, various actions should be prepared before data computerization becomes mandatory.

There are several obstacles in promoting computerization, but all of those can or must be overcome. In the “Questionnaire on computerization promotion,” two facilities answered that “electronic data are defined as raw data for all devices” and “data are controlled using the Scientific Data Management System (SDMS),” demonstrating that complete computerization would be practical. We strongly recommend data computerization, which should be achieved for reliability assurance.

| GLP Division, Activity Summary of the 14th Term (April 2018– March 2020) | |
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| **Study Group** | **Study Group 3: Computerized systems** |
| **Subgroup** | **L-3-1** |
| **Theme** | **Best practice for the operation of equipment that does not meet the regulatory requirements for data integrity<br>A stand-alone HPLC as an example** |

The GLP-compliant operation and management of equipment in Japan is in a transitional period for complying with data integrity (DI). DI compliance is being considered by the OECD and will also be regulated in Japan, and thus, we should prepare for the compliance of DI on the basis of OECD's actions.

However, many facilities are using measuring equipment or system of Category 3 that generates electronic data and does not have necessary functions for complying with the regulatory requirements for DI. It is obvious that using equipment that meets the regulatory requirements for DI will be required. If impossible, "what actions should we take using equipment or system that does not meet the regulatory requirements for DI?" To answer this question, we used a stand-alone high-performance liquid chromatograph (HPLC) as an example and investigated the best practice for operation during the 14th term.

The results indicated that "access control," "audit trail," and "raw data (backup)" would be important points to comply with DI when an HPLC that does not have functions meeting the regulatory requirements for DI must be used. We concluded that if any functions related to these three important points for DI compliance cannot be added to the equipment or system, the best practice would be "using the HPLC with operating procedures for the mechanism and processes" until the DI guidance is issued and enforced in Japan. Based on the situations in the GMP area in the United States, we investigated the following matters to comply with the DI regulatory requirements that will be established in the GLP area in Japan:

- What issues about DI are arising? (investigated using the Warning Letters [WLs])
- Regarding the operating methods for ensuring DI and the management methods that are required globally, what actions should we take after the DI regulations are issued? (investigated using research papers published outside Japan)
  We also examined the data collection system model using a network, the Laboratory Information Management System (LIMS), which is recommended to enhance software functions.

Although new equipment and system will be continuously developed with technical advances, equipment and system are still used by humans, and how we use them is still the most important. Of primary importance are human aspects; equipment and system are only tools to achieve goals. It is thus strongly desired to continuously investigate operating methods that comply with regulations and to aim at ensuring reliability.

We hope that the best practice included in this deliverable will be used to improve the system operating methods, with appropriate understanding of the latest guidance.

This working group will continue to investigate the system operating methods that comply with the latest regulations and guidelines to resolve various questions and issues and will widely contribute to the pharmaceutical industry.

| **GLP Division, Activity Summary of the 14th Term (April 2018– March 2020)** | |
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| **Study Group** | **Study Group 3: Computerized systems** |
| **Subgroup** | **L-3-2 (Examination of regulations and guidelines)** |
| **Theme** | **Upgrade of the skills of QA staff members who handle CSV and electronic data<br>"Consideration of appropriate management of the GLP computerized system for data integrity"** |

Many GLP guidelines on computerized systems have been issued globally, and companies must respond to comply with their requirements. In addition, the OECD GLP Working Group has agreed to create a GLP-specific document based on the MHRA GXP Data Integrity Definitions and Guidance for Industry. Requirements for data integrity are expected to increase and facilities need to be prepared for the future. Therefore, we adopted the following approaches to consider appropriate management of GLP-related computerized systems with a focus on data integrity.

1) Compilation and analysis of case studies
Compilation and analysis of FDA Warning Letters of data integrity issues related to computer systems.

2) Considerations from an inspector's point of view
Trends in FDA Warning Letters

3) Considerations from the viewpoint of a facility
Focal points to improve data integrity

We collected FDA Warning Letters issued from April 2016 to September 2019 and categorized them into the 5 phases of the data life cycle. Most data integrity issues found in FDA warning letters fell into the early phases of the data lifecycle (generation and processing). The main findings during the generation and processing phases included inadequate control of the computer clock or audit trail, and reprocessing or deletion of data without justification. In each case, the data were falsified or deleted in violation of ALCOA principles. It is considered that the priority for GLP facilities is to improve their response to data integrity based on ALCOA principles and to focus on the generation and processing phases of the data lifecycle.

| GLP Division, Activity Summary of the 14th Term (April 2018– March 2020) | |
|---|---|
| **Study Group** | **Study Group 3: Computerized systems** |
| **Subgroup** | **L-3-2 QA Role Working Group** |
| **Theme** | **Upgrade of the skills of QA staff members who handle CSV and electronic data**<br>**QA's roles in reliability assurance of computerized systems** |

We started the 14th term with new members, who were in majority in the group. Due to the many new members joining the QA Role Working Group, the group members were divided into the following three subworking groups according to which theme each member was interested in:

- Implementation status of computerized system validation (CSV) compliant with the reliability standards
- Understanding of digitalization
- Education of CSV-QA staff

The "Implementation status of CSV compliant with the reliability standards" Sub working Group reanalyzed the results of the "questionnaire survey on CSV of Category 3 systems," which was conducted in the preceding term, to elucidate the implementation status of CSV for measuring instruments in compliance with the reliability standards. The rationale of this reanalysis was the possibility of different actions among companies because of unclear CSV requirements for measuring instruments in compliance with the reliability standards.

The results of the reanalysis revealed that among facilities that had independent CSV procedures compliant with the reliability standards, less than half of the facilities prepared CSV documents, and many facilities did not conduct CSV audits. As originally expected, CSV methods varied by company.

The "Understanding of digitalization" Subworking Group reviewed the past deliverables of the Japan Society of Quality Assurance (JSQA) and compared them with the regulations used at that time to deeply understand the digitalization history.

One of the JSQA deliverables that were first published in the 1992–1993 term already included the description about computer inspections. At that time, the Food and Drug Administration (FDA) also started to conduct computer inspections, and we realized that the JSQA responded to the industrial trend in a timely manner. We then sorted computer-related JSQA deliverables that have been published until now and the regulations issued in each country in a chronological order, checked their relationship, and read the deliverables again. By comparing the regulations with the deliverables rather than just reading the regulations alone, we better understood the background to the issuance of the regulations and the actions taken. The deliverables developed through JSQA's activities were a kind of explanatory manuals to interpret the regulations and supported deep understanding of digitalization.

The "Education of CSV-QA staff" sub working Group discussed how CSV-QA staff should be educated, continuing from the preceding term. Based on the educational requirements for CSV-QA staff that had been elucidated in the preceding term, we developed education materials that can be used by QA staff who are not well familiar with CSV.

We selected the guidance used for educating CSV-QA staff and summarized points to be assessed

for each phase (concept phase, introductory phase, operation phase, and retirement phase) in the system lifecycle and the assessment timings. Given that many facilities have difficulties in educating CSV-QA staff as demonstrated in a previous questionnaire survey, this education material contains very useful information, and we hope this will help you educate CSV-QA staff.

| GLP Division, Activity Summary of the 14th Term (April 2018 – March 2020) | |
|---|---|
| **Study Group** | **Study Group 3: Computerized systems** |
| **Subgroup** | **L-3-2** |
| **Theme** | **Impact on quality assurance with the introduction of new ICT** |

1. Purpose of activity

We discussed the following two themes during the current term.

・ Quality Assurance when introducing New Information Communication Technology

As new Information and Communication Technologies (ICTs) have made significant progress in recent years, they are expected to be used for GLP studies. First, we clarified the systems using Robotic Process Automation (RPA), Artificial Intelligence (AI), Internet of Things (IoT), and Computer Vision that are expected to be used in GLP studies and their usage status. Next, we examined how to validate the systems using new ICTs including RPA and AI and how to assure the validation. Finally, we compared the validation method and the points to be checked by QA for the systems using new ICTs with those for the systems using conventional technology, and discussed the differences.

・ Tips for Quality Assurance of Huge Cloud Services

Cloud services have been employed by a lot of users around the world because of their technical expertise and the potential for reducing management costs.

In the pharmaceutical industry, cloud services are already widely used in the clinical division, but are not widely used in Japanese GLP facilities.

When using cloud services in GLP facilities, it is necessary to audit or assess suppliers. However, huge cloud services don’t accept on-site audits by customers, primarily for security reasons. Therefore, we examined how to audit a huge cloud service provider

2. Activity reports

As a result of studies, we concluded as follows:

・ Quality Assurance when introducing New Information Communication Technology

We examined the applicability of the new ICTs to the GLP studies and the expected validation method. It was concluded, that in principle, even a system using new ICTs would be validated by the conventional method.

However, there are some differences:

In systems using RPA and AI, QA personnel should be involved in the change control process more than systems using conventional technology, in cooperation with suppliers and other experts.

Since it is necessary for a person to make a final decision on the results obtained using AI, it is necessary to ensure the qualification of that person.

・ Tips for Quality Assurance of Huge Cloud Services

Huge cloud services providers supply users with SOC2 reports obtained by highly specialized third-party audits. SOC2 reports are so detailed and professional that users can employ them to audit or assess the suppliers.

| GLP Division, Activity Summary of the 14th Term (April 2018– March 2020) | |
|---|---|
| **Study Group** | **Study Group 4: Quality assurance for non-clinical studies (Eastern Japan)** |
| **Subgroup** | **L-4-1** |
| **Theme** | **Examination of frequent questions/work issues GLP, Reliability Standards, and other general matters** |

Study Group 4 mainly works in Eastern Japan. We examine topics related to quality assurance of non-clinical studies and frequent questions/work issues that members may routinely encounter. Members belong to not only to quality assurance departments, QC departments, and research laboratories. The theme of our activities is to examine all topics concerning quality assurance. In the 14th term, discussions and presentations for the 6th GQAC took place in addition to the conventional “frequent questions/work issues” and “conduct of educational courses.”

In the first half of the term (FY2018), the whole study group was randomly divided into three subgroups to discuss “frequent questions/work issues.” In the second half of the term (FY2019), we discussed frequent questions/issues in three subgroups: “Consignors” (2 groups) and “Contractors.” During the 14th term, we discussed a total of 31 issues with a focus on the viewpoint of reliability.

In addition, we held various seminars and lectures in order to improve the quality assurance skills of the study group’s members and to broaden their viewpoints.

At the study session, members presented examples related to conformity inspections received from each regulatory authority and they gained a better understanding of the latest regulatory trends and examples of responses to audits. At the lecture, a workshop was held in which participants learned "QA knowledge" and external lecturers invited them to practice "listening and questioning skills," which are important for business.

In addition, we were in charge of conducting the GLP Division Educational Course "The 7th QA / QC Personnel Introductory Course (Entry Course)." Volunteers met seven times to create study sessions and educational lecture slides before regular meetings in order to improve the skills of the subcommittee members and foster future instructors.

For the 6th GQAC section, the members of the group worked together to draft a questionnaire on the presentation theme, to survey corporate members in the GLP division, to consider the contents of the presentation including the compilation and analysis of survey results, to create slides, and to make presentations.

Through these activities, Study Group 4 discussed various issues related to reliability assurance and exchanged opinions with members from various backgrounds to help members of the group think and prepare in order to ensure the reliability of non-clinical studies. We created a place to learn and developed activities to improve reliability assurance skills.

| **GLP Division, Activity Summary of the 14th Term (April 2018– March 2020)** | |
|---|---|
| **Study Group** | **Study Group 5: Quality assurance for non-clinical studies (Western Japan)** |
| **Subgroup** | **L-5-1** |
| **Theme** | **Quality assurance for GLP studies** |

Study Subgroup 5-1 has been working for 2 years on “Quality Assurance for GLP studies” as part of “Quality assurance for non-clinical studies (mainly in the western Japan).”

Our main activities were to broaden members’ horizons, to share information, and to interact personally, and we worked on:

1) Examination of specific examples of familiar questions/issues
2) Timely exchange of opinions using a mailing list
3) Educational lectures and topical lectures
4) Presentation at the 6th GQAC session

In this term, we discussed 23 “specific examples of familiar questions/issues” submitted by members and examined 5 opinions collected from the mailing list.

As an educational initiative, an educational lecture on OECD GLP AD No. 17 was held with the cooperation of advisors from Study Group 3.

In addition, we hosted a JSQA GLP Division educational session: the 5th training course entitled "An Explanation of the Ministerial Ordinance on GLPs for Pharmaceuticals" in collaboration with Study Group 4, which has addressed the same theme in eastern Japan.

Since the 6th GQAC was scheduled to be held in Sendai in February 2020, we worked with the Second Group of Study Group 5 to prepare for a presentation.

GQAC is held in Japan only once every nine years.

We named the session theme "SAMURAI" and "Quality Assurance" in order to use this valuable opportunity to attract participants from overseas.

While thinking about GLP and the “Standards for the Reliability of Application Data (e.g. Article 43)” which is a regulation unique to Japan, we applied the spirit of "Bushido" from the samurai era to QA efforts.

From the viewpoint of the seven most important virtues, namely, "Rectitude, Courage, Benevolence, Politeness, Veracity, Honor, and Loyalty," we described incidents that might occur during routine QA efforts.

We then considered the "nature required for QA" and the "principle of QA activities".

Finally, we attempted to obtain clues to improve reliability.

| **GLP Division, Activity Summary of the 14th Term (April 2018– March 2020)** | |
|---|---|
| **Study Group** | **Study Group 5: Quality assurance for non-clinical studies (Western Japan)** |
| **Subgroup** | **L-5-2** |
| **Theme** | **Quality assurance for non-GLP studies** |

As a Study Subgroup based in western Japan, L-5-2 has been acting under the theme of “Familiar Questions/Issues on Ensuring Quality for Non-clinical Studies− Studies Compliant with Standards for Reliability of Application Data.” In addition, we looked at items related to the work of group members and GLP studies.

We categorized "familiar questions/issues" into eight categories including “study results,” “maintenance of equipment,” “study reports,” and “QC checks and QA monitoring,” Tacking a new tack, we also discussed some familiar questions/issues from the point of view of CAPA.

We held a lecture meeting on a Risk-based Approach with a lecture by Study Group 1.

In addition, we hosted a JSQA GLP Division educational session: the 5th training course entitled "An Explanation of the Ministerial Ordinance on GLP for Pharmaceuticals" in collaboration with Study Group 4, which has addressed the same theme in eastern Japan.

Since the 6th GQAC was scheduled to be held in Sendai in February 2020, we were working with the First Group of Study Group 5 to prepare for a presentation. We described a regulation unique to Japan, the "Standards for Reliability of Application Data," with specific examples as a role of L-5-2.

| **GLP Division, Activity Summary of the 14th Term (April 2018– March 2020)** | |
|---|---|
| **Study Group** | **Special Project Group A** |
| **Subgroup** | **L-T-A** |
| **Theme** | **Reliability studies of the Scientific Research and Reports** |

Activities

* Examination of the reliability of scientific research (attending lectures and discussion)
* Study on the use of lab notebook system for the reliability of scientific research
* Survey of the education level of research integrity for new employees
* Investigation of research integrity education at universities.

Activity contents

* Examination of the reliability of scientific research:
  We collected 17 cases related to research misconduct and analyzed the factors.
* We examined the use of Lab Notebook System to prevent research misconduct.
* Dr. Stani's lecture "Current status and countermeasures of research misconduct at IQB (Quantitative Biological Sciences Laboratory) at the University of Tokyo" was held on November 25, 2019. The outline of the lecture was published in JSQA Bulletin No.63 (p.41-).
* A questionnaire survey was planned and a pilot survey was conducted to confirm the degree of education completion regarding research integrity of new employees.

| GLP Division, Activity Summary of the 14th Term (April 2018– March 2020) | |
|---|---|
| **Study Group** | **Special Project Group D** |
| **Subgroup** | **L-T-D** |
| **Theme** | **QA involvement at test facilities in case of disasters and emergencies - Relationship between disasters and damages and QA's actions -** |

1. Objective of activities

After the Great East Japan Earthquake in 2011, we conducted a questionnaire survey in FY2013 to follow up the "Results of the questionnaire survey on anti-disaster measures in test facilities," which were included in Deliverable No. 144 presented in the 4th Global QA Conference (GQAC). The results of the questionnaire revealed that as low as "approximately 32% of facilities had a quality assurance unit (QAU) involved in recovery activities and planning from the occurrence of a disaster through the resumption of studies" and as low as "approximately 11% of facilities had standard operating procedures (SOPs) for investigation of recovery activities and planning." To examine the subsequent situations, we conducted a questionnaire survey among members of the GLP Division.

2. Results of investigation

1) Relationship between disasters and expected damage to test facilities (investigation)

We checked possible disasters and phenomena in Japan and predicted the damage caused by each disaster to the entire facility, animal care, test articles, data storage, and experiments.

2) Disasters, actual damages sustained by test facilities, and QA's actions (questionnaire survey)

A web-based anonymous questionnaire survey was conducted among 154 companies belonging to the GLP Division of the Japan Society of Quality Assurance (JSQA) (survey period: July 8 to 22, 2019).

Responses were received from 86 facilities.

2)-1. QA involvement

Approximately 59% of the surveyed facilities used the QA when a disaster occurred. The other facilities also recognized the need for contacting the QA. When a disaster caused any damage to the test facility, the QA was used in some way in many facilities. The results revealed that the system for using the QA has been increasingly established since the Great East Japan Earthquake. Some facilities, however, answered that notifying the QA of the occurrence of damages was not required, contacting the QA was considered unnecessary, or the QA should not be involved in disasters.

2)-2. Disaster-related damages and anti-disaster measures

The main disasters that occurred after the Great East Japan Earthquake and affected facilities and ongoing studies were "earthquake," "typhoon/torrential rain," and "lightning strike."

Most of the damages reported in this survey had been originally expected, including facility destruction, equipment failure, and electricity supply interruption. However, some unexpected disasters occurred, including difficulty in additional orders of heavy oil used for self-power generation due to a massive blackout. Based on the information and experiences of the Great East Japan Earthquake and the subsequent disasters, many facilities took effective anti-disaster measures: anchoring shelves, locating backup server facilities on an upper floor of the building, installing self-power generators, and stockpiling a sufficient quantity of water and fuel.

3. Actions for the 6th GQAC

We organized Session L-07 (Role of QA at the test facility in the event of disaster), Invited Lectures and Public Lectures of the conference. We also made a poster presentation on the results of investigation explained in Section 2 above.

| **GLP Division, Activity Summary of the 14th Term (April 2018– March 2020)** | |
|---|---|
| **Study Group** | **Special Project Group S** |
| **Subgroup** | **L-T-S** |
| **Theme** | **Quality assurance procedures for computerized systems**<br>**Examination of reliability assurance for SEND** |

We began examination activities concerning SEND (Standard for Exchange of Nonclinical Data), which is a data standard for non-clinical toxicology studies, in the previous term (FY2016-FY2017) of L-3-1 (SEND examination). In the previous term's deliverable (Material No. 17L12), we concluded that it is necessary to formulate quality certification standards for SEND data as a point to remember in SEND-related reliability assurance. Because SEND is not subject to GLP regulations, GLP-compliant reliability assurance is considered unnecessary. However, examination of standards for compliance in ensuring quality of a certain standard and certifying quality for electronic data in applications to authorities is needed. The QMS of ISO 9001 is an example of a means for that. Reasons for this include the fact that SEND requires quality certification that is specialized for production and the need to also consider data integrity with final reports and raw data. We intend to make research that enables us to propose best practices for SEND-related reliability assurance by understanding SEND's characteristics and clarifying the scopes that can be covered by GLP and by ISO 9001 a topic for this term. We have been examining understand the characteristics of SEND, clarify the range that can be covered by GLP and the range that can be covered by ISO9001, and consider the research that proposes the best practice of SEND reliability assurance as an issue.

The main issues for this term were the following three.

- Compare the requirements of GLP and ISO9001, and examine the advantages of applying ISO9001
- Issues seen by the quality assurance staff at the contract facility
- Issues from the point of view of the quality assurance staff at the contracted (created) facility

External presentations (3)

July 2018: 45th Annual Meeting of the Japanese Society of Toxicology

At an industry-government-academia collaborative symposium on SEND "Non-clinical safety assessment using CDISC", an oral presentation entitled "Issues from the perspective of reliability in SEND data" was presented.

June 2019: The 46th Annual Meeting of the Japanese Society of Toxicology

A poster entitled "SEND Issues and Proposals from the Viewpoint of Reliability Assurance" was presented.

February 2020: 6th GQAC (Global Quality Assurance Conference)

A Poster entitled "Issues and proposal for SEND from the perspective by quality assurance" was presented.