

Implementation of the OECD GLP principles at test facilities in Japan

Shinoi Sakata

Environmental Health Science Laboratory, Sumitomo Chemical, Osaka, Japan

Summary. For the implementation of the Organisation for Economic Co-operation and Development (OECD) principles of good laboratory practice (GLP) and performance of studies according to worldwide regulatory requirements, test facilities (TFs) in Japan have been making constant effort to promote better understanding of this matter and improve communication with monitoring authorities (MAs). Their activities to ensure the international acceptance of data in accordance with the OECD principles of GLP under the programme of mutual acceptance of data (MAD) are discussed with particular reference to the scope of Japan Society of Quality Assurance (JSQA), which comprises most of TFs in Japan, including international activities with EU, USA and Asian countries to establish global quality network.

Key words: good laboratory practice, OECD, Japan Society of Quality Assurance.

Riassunto (*Adozione dei principi di BPL dell'OCSE da parte dei centri di saggio del Giappone*). I centri di saggio (CdS) del Giappone hanno fatto e stanno facendo uno sforzo costante, nel contesto dell'adozione dei principi di buona pratica di laboratorio dell'Organizzazione per la Cooperazione e lo Sviluppo Economico (OCSE) e della conduzione degli studi secondo i requisiti regolatori internazionali, per agevolare una più ampia comprensione reciproca della materia e migliorare le relazioni con le autorità di monitoraggio (AM). Viene presentata, con particolare riferimento agli scopi della società giapponese per l'assicurazione di qualità (AQ), una rassegna delle attività dei CdS intese ad assicurare l'accettazione internazionale dei dati secondo quanto prescritto dai principi di BPL dell'OCSE nel quadro del programma di reciproca accettazione dei dati (RAD). A questo programma aderisce la gran parte dei CdS giapponesi anche per quanto riguarda le attività internazionali verso la UE, gli USA ed i paesi asiatici con l'intento di sviluppare una rete globale per la qualità.

Parole chiave: buona pratica di laboratorio, OCSE, società giapponese per l'assicurazione di qualità.

INTRODUCTION

Test facilities (TFs) in Japan conduct good laboratory practice (GLP) studies for not only domestic submission, but also for overseas submission under the mutual acceptance of data (MADs) system of the Organisation for Economic Co-operation and Development (OECD) [1, 2]. It is of critical importance for them to understand and comply with more than one set of GLP regulations in Japan, *i.e.* pharmaceutical GLP, chemical substances GLP, agricultural chemicals GLP [3]. Needless to say, they have to understand the OECD principles of GLP and the GLP programmes of each country where the study will be submitted. Communication with monitoring authorities (MAs) is also important to apply each GLP regulation properly and consistently. Meanwhile, TFs in Japan are connected with other OECD member countries through the OECD mutual acceptance of data (MAD) programme. Hence, it is important to establish network with overseas countries and related associations. The activities of the Japan Society of Quality Assurance (JSQA), which comprises most of the TFs in Japan, cover all these key issues and are illustrated in the following sections.

THE JAPAN SOCIETY OF QUALITY ASSURANCE

History and scope of JSQA

JSQA was established in 1992 as a nationwide organization encompassing all GLP parties in Japan such as pharmaceutical companies and contract research organizations (CROs). In 1995 it expanded its scope to cover also good clinical practice (GCP). Furthermore, in 2006, its coverage was extended to post marketing, *i.e.*, good vigilance practice/good quality practice/good post marketing study practice (GVP/GQP/GPSP). At present, these three divisions (GLP, GCP, and GVP/GQP/GPSP) are all operative.

At the time of establishment in 1992, it covered only GLP and comprised about 200 members. But as of 2007, it comprised about 1800 members of 476 companies in total. The breakdown was 600 members of GLP division, 1000 members of GCP division, and 200 members of GVP/GQP/GPSP division. Both size and activities of JSQA are growing year after year (Figure 1).

The purpose of JSQA is to raise and develop the knowledge and technical know-how of those involved

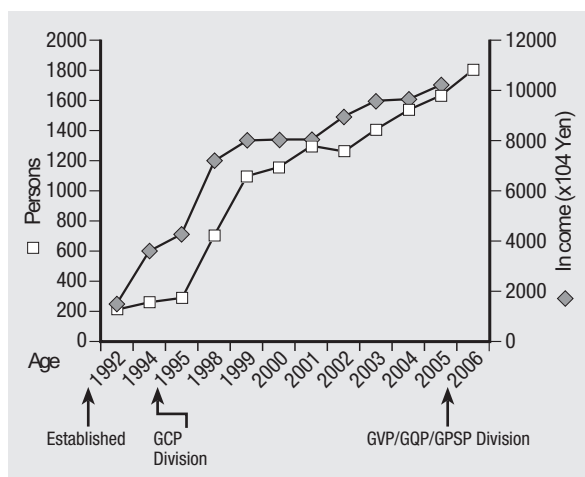


Fig. 1 | Historical Changes in Japan Society of Quality Assurance.

with quality and reliability of pharmaceuticals, medical devices, agricultural chemicals, chemical substances, veterinary drugs, feed additives, etc. JSQA is fostering internationally recognizable quality assurance (QA) specialists and is also promoting the development of the said good practices (GXLP). JSQA is also putting substantial effort into interacting with governmental and other related agencies as well as overseas counterparts.

Organization of JSQA

The organization of JSQA is shown in Figure 2. JSQA has a President and a board of directors. It consists of committees and study groups within the GLP, GCP, and GVP/GQP/GPSP divisions. Activities of committees cover the items common to all divisions. Study groups are further subdivided into several groups. Members belong to at least one group and participate in the relevant study themes.

One term of activity is two years. In addition to this, joint study group and special projects are also formed when necessary.

Activities of JSQA

JSQA shall perform the following activities to accomplish its purposes: *i)* research related to QA; *ii)* preparation of documents based on collected information and research results; *iii)* organisation of conferences, seminars, and the like; *iv)* association with the relevant government authorities and interested organizations; *v)* collection of information from concerned government agencies and supply of information to JSQA members; *vi)* association with concerned overseas organization, collection of overseas information, and supply of information to JSQA members; *vii)* any other matter necessary for JSQA to achieve its objectives.

ACTIVITIES OF JSQA ON GLP

The GLP division of JSQA is focusing on timely topics and issues to improve and upgrade knowledge and technological levels of personnel. The division has four major themes for the period 2006-2008. One study group is assigned to each theme, as follows: *i)* GLP regulations: study group 1. GLP regulations in Japan and foreign countries including the OECD principles of GLP are studied. Information on GLP and inspection cases are collected from members of the GLP Division and shared with all members. Inspection observations and guidance issued by MAs are also studied; *ii)* study on integrity and quality of application data: study group 2. For consistent scientifically-based QA from drug development to drug application in the medicine development cycle, QA of application information, QA of GXLP, and QA examination of electric data are dealt with; *iii)* studies under

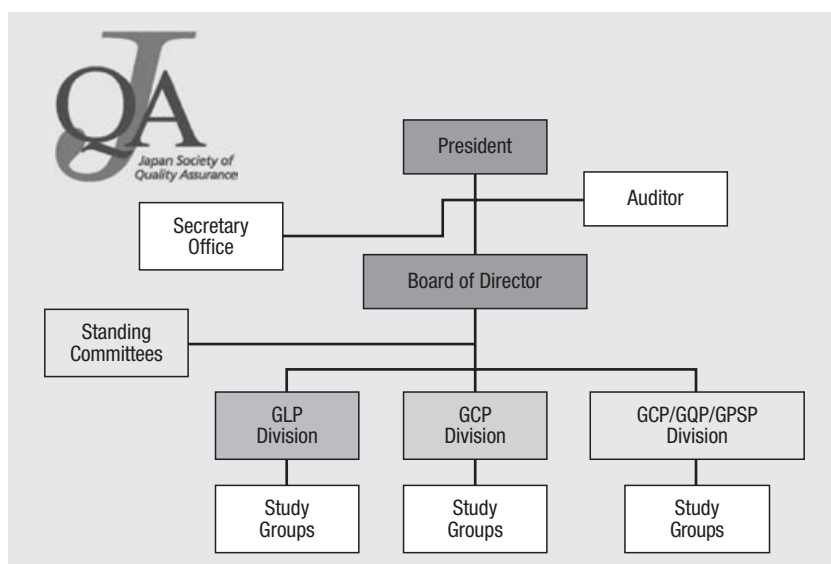


Fig. 2 | Organization of Japan Society of Quality Assurance (JSQA).

reliability standard: study group 3. QA of analytical tests including drug development and QA of pharmacological efficacy and pharmacokinetic tests are considered. Specific cases of documentary investigation of compatibility are collected from members of the division and examined; *iv*) GLP supporting system: study group 4. Supporting systems for non-clinical studies, computerized systems, QA, and personnel education are studied.

In addition to the above, the GLP division has further study groups that deal with other issues related to regional specificity in eastern and western Japan. The theme of the two regional groups is quality assurance of non-clinical studies, of general interest.

Progress in the activities of each group is reported at the annual meeting of JSQA and the results are published every other year to share information among JSQA members.

COMMUNICATION WITH MAs

Communication with MAs is encouraged by JSQA through the activities described above. JSQA has communicated and cooperated with MAs in promoting the development of quality test data. For example, the Pharmaceutical medical devices agency (PMDA), the MA for Pharmaceutical GLP, and JSQA are keeping well in touch with each other since many JSQA members belong to pharmaceutical companies and have a great interest in Pharmaceutical GLP. JSQA regularly collects questions from its members about interpretation of GLP regulations and inspection observations, puts them together and addresses questions to PMDA. Then, PMDA answers questions and explains in details at annual GLP training seminars held by PMDA. Questions, answers, and inspection observations presented in the training seminars are published by PMDA in the GLP guide book every year and are shared with all parties concerned. Furthermore, JSQA peruses inspection observations and answers from PMDA and discusses with PMDA to promote development of quality test data. As an example of this, two cases of bilateral communication with PMDA illustrated below.

Case 1. Use of digital camera in GLP studies

At the annual GLP training seminar in 2000, answering a question from JSQA on the use of digital cameras in GLP studies, PMDA expressed their views as follows: "At present, it is difficult to define image taken by digital camera as raw data". That is, digital image cannot be used to prepare final reports of GLP studies on topics such as irritation, sensitization, etc. But in recent years, camera market is rapidly shifting to digital camera from film camera also in the case of cameras for medical use such as funduscopy. In the near future, the use of film camera will decrease or come to end and there will be no choice but to use digital cameras. This being the current state, JSQA set forth the key points to be considered when using digital cameras in GLP studies. Two major phases

can be identified as regards the storage process, *i.e.*: i) from taking photographs by digital camera to transferring the digital image to electronic media for storage; ii) storage of digital image in electronic media. Phase 1 concerns specific aspects of the digital camera which are related to the process of editing and deleting images in the device itself and have obvious consequences from the viewpoint of authenticity and storage stability. On the other hand, Phase 2 is not specific to the digital camera and rules already existing on the proper storage of electronic information can be applied.

The JSQA took into account, in particular, how to assure the quality of digital images in Phase 1. A questionnaire survey on use of digital cameras in GLP studies was circulated in the GLP division members in 2006. 117 companies responded (about 67% of the total). The high response rate demonstrated that a lot of companies were interested in the use of digital cameras in GLP studies. JSQA put together and analyzed the results obtained through the questionnaire, and prepared a document entitled "An approach to the use of digital cameras in GLP studies". The key problem is that it is easy to modify or delete images obtained by digital cameras, while on the other hand, it is difficult to make sure whether the image was processed or not. Though it is desirable that functions meeting GLP requirements be added to digital cameras, this is not completely feasible at present as the development of new digital cameras and peripheral devices is necessary.

In consideration of the above, JSQA discussed with PMDA the document mentioned above and concluded that reliability of images of digital cameras could be assured by very rigorous procedures, record keeping and training of study personnel. In other words, to assure that images taken by digital cameras cannot be falsified while taking photographs and transferring images to electronic media, the various steps should be described in standard operating procedures (SOP) and recorded properly, and process suitability should be confirmed. The major points to consider in the SOPs are the actual operation of taking photographs, the method of recording, the storage of data, the method of generating paper printouts, the definition of raw data, etc. Since each step should be documented by records, dated signature of operator, date and signature of photographs, identification number of raw data, and signature on printouts are of key importance.

As an outcome of communication with JSQA, at the annual GLP training seminar in 2007, guidance for the use of digital cameras in GLP studies was presented by PMDA as follows: "Digital images are usually used as supplementary data in pathology, funduscopy, irritation study, etc. In GLP studies, however, it is necessary to assure reliability and absence of falsification. Well trained personnel should conduct operations and take records as fully described the relevant SOPs. Audit trail and process suitability of a series of operations are also critical".

The GLP division of JSQA believes that the reliability of digital camera in GLP studies can be assured if appropriate measures are taken at every TF based on the latest guidance of PMDA and the document of JSQA entitled "An approach to the use of digital cameras in GLP studies".

Case 2. Procedures and records of general clinical observations using a computerised system

At the annual GLP training seminar in 2005, PMDA presented inspection findings on general clinical observations. The findings were summarized as follows: "General clinical observations should be conducted properly based on SOPs. Though various items of general clinical observation were described in SOPs, whether observation was conducted according to SOP or not could not be verified by records". Although operations of general clinical observations are quite usual the risk of overlooking something important still exist. JSQA started investigating why inspection observations of this kind were raised by PMDA and how the situation could be improved.

JSQA conducted a fact-finding inquiry on procedures and records of general clinical observations from the GLP division members of JSQA by means of questionnaires with the aim of enhancing study reliability. 125 companies responded (about 71% of all those contacted). Hence, information obtained through the questionnaire reflected pretty well the situation of TFs in Japan.

Currently, computerized systems are used for general clinical observations at many TFs. In some cases, however, SOPs for general clinical observations, especially at TFs where computerized systems are used, might not cover all key aspects. Sometimes SOPs are just a manual for operation for computerized systems. For example, when there were no abnormal signs, though various observation items were described in the SOP, results of observation were entered all together. As a consequence, the records might interpreted as if all observations had been conducted at the same time. Though observations were conducted in a proper fashion, it seemed as if it would take a very short time to conduct general clinical observations for a number of animals and for various observation items.

JSQA summarized the results obtained through the questionnaires and prepared a document entitled "Results of fact-finding inquiry on general clinical observations". The document was discussed with PMDA. It is of the greatest importance that procedures and methods of observation be prescribed in SOPs with a very practical approach and that the results of observations be recorded according to the applicable SOPs. JSQA proposed JSQA members to check current SOPs at their TFs. Observation items and method of recording of results for each observation should be also detailed in the SOPs. In addition, when computerized systems are used, the study director (SD) and the study personnel should clearly understand how data are processed and recorded by the computer.

ESTABLISHMENT OF A GLOBAL QUALITY NETWORK

In order to better cooperate, JSQA, the US Society of quality assurance (SQA), and the UK British association of research quality assurance (BARQA) signed a memorandum of understanding in 2000 (revised in 2005). One of the major activities jointly performed by SQA and BARQA is the global quality assurance conference (GQAC) which is held every third year with the purpose of sharing and developing views, knowledge and experiences in the field of QA. The first GQAC was held in Florida in 2005 and was hosted by US SQA, while the second GQAC was held in Edinburgh in October 2008, hosted by BARQA, and then, in 2011, the third GQAC will be held in Kyoto (Japan) hosted by JSQA. JSQA also joined the international project entitled "Comparison of the practical GLP interpretation among tripartite countries". In the project, inspection observations were studied in the said three countries along with differences in the practical interpretation of the GLP principles by MAs in USA, UK, and Japan, in particular as regards their application in the pharmaceutical sector. The results of the project was reported at the second GQAC.

Regarding the activities of JSQA in Asian countries, as an example of activities in 2007, a GLP workshop in Chinese Taipei is worth mentioning. The GLP workshop was sponsored by the Toxicology society of Taiwan and cosponsored by JSQA. JSQA gave lectures on GLP regulations in Japan, GLP inspection system in Japan, and critical issues in the QA activities and GLP implementation and had lively discussion on the said topics.

Moreover, GLP team from Korea visited JSQA in 2007. In 2008 and beyond, JSQA will further expand its activities in Asian countries such as China and Southeast Asian countries.

OTHER ACTIVITIES OF JSQA

As regards educational and training programmes, the following training courses are held every year for JSQA members and GLP personnel such as SD and study personnel: *i)* basic training courses; *ii)* advanced training courses; *iii)* seminars, lectures, and panel discussions (for GLP personnel).

In basic training courses, the role and responsibilities of the QA Unit are presented and procedures for inspecting protocols, study conduct, records and final report are illustrated. In advanced training courses, with the aim of using and applying knowledge and techniques in practice, examples, role playing, and brainstorming are dealt with. Various types of seminars, lectures, and panel discussions are also planned throughout the year.

JSQA has also a qualification system named GLP-Quality assurance professional (QAP) registration system. It started in 2002 and qualifying examinations have been conducted once a year. As of 2007, 205 persons have been registered.

Finally, as an activity in cooperation with MAs, JSQA is participating in joint translation programmes and is responsible for the translation of the OECD GLP documents. Recently, the translation of all 15 OECD GLP consensus, guidance, and advisory documents into Japanese has been completed and is now accessible on the web site of JSQA (<http://www.jsqa.com/>).

FUTURE GOAL OF JSQA

Through the aforementioned steady and continuous activities, TFs in Japan are more and more in compliance with international GLP regulations and conduct studies of high quality not only from the viewpoint

of GLP, but also of science. In recent years, assessment of safety of various materials to human health and environment are becoming ever more important. Hence, it is inescapable that safety studies be more accurate, more detailed, and, in the first place, more reliable. To fulfil these requirements, future goals of JSQA are the reinforcement of its structure, operations and communications. The competence and technological level of JSQA members will thus be further enhanced and updated so that they will be recognized at home and abroad as a professional group for QA.

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