

National GLP programmes and implication of regulatory authorities for pharmaceuticals, pesticides and other chemicals

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Summary. There are various kinds of good laboratory practice (GLP) monitoring authorities (MAs) in the world. Some countries have only one MA, while others, including Japan, have more than one MA. In addition, each MA has its own relationship with regulatory authorities (RAs), receiving authorities (RcAs) and industry based on the internal regulatory systems. There are eight GLP MAs in Japan. This number is probably the largest in the world. Efforts have been made to establish a close link among MAs and to apply and implement GLP programmes in an efficient, effective and consistent way, namely: i) interministerial meeting on GLP. It is essential to establish a system for information exchange and decision making when there are a number of MAs such as in Japan. To this end, the interministerial meeting on GLP has been set up as a means for MAs, RAs, and RcAs to share information on Organization for Economic Co-operation and Development (OECD) and foreign countries and make national decisions as a whole country; ii) joint training programme. With the goal of training inspectors and minimizing differences in inspections among MAs, a joint training programme has been started including joint visits to test facilities (TFs) and participation in evaluation committees at other MAs. One of the purposes of this training programme is to get ready for the on-site evaluation visit (OEV) of the OECD by simulating it at MAs in Japan; iii) joint translation programme of the OECD documents. To avoid unnecessary confusion due to differences of interpretation and translation of OECD documents among MAs, these have been translated into Japanese in cooperation with industry. This has also other substantial merits such as cost reduction and time saving for all stakeholders in Japan. Some countries, both members and non-members of the OECD, have also established more than one GLP MA. It is hoped that the Japanese experience can be useful to them.

Key words: good laboratory practice, monitoring authorities, receiving authorities, regulatory authorities.

Riassunto (*Programmi nazionali per la BPL e coinvolgimento delle autorità regolatorie per i farmaci, antiparassitari e altre sostanze chimiche*). Esistono nel mondo diversi tipi di autorità di monitoraggio (AM) per la buona pratica di laboratorio (BPL). Alcuni paesi hanno solo una AM, mentre altri, Giappone incluso, ne hanno più di una. Inoltre, ciascuna AM tiene i suoi propri rapporti con le autorità regolatorie (AR), le autorità riceventi (ARs) e l'industria sulla base del sistema regolatorio nazionale. In Giappone vi sono otto AM. Questo è probabilmente il numero più elevato in assoluto. Viene fatto ogni sforzo per assicurare uno stretto collegamento tra le AM e per adottare ed applicare i programmi di BPL in maniera efficace, efficiente e coerente, e precisamente: i) l'assemblea interministeriale per la BPL. È essenziale disporre di un sistema per lo scambio di informazioni ed il processo decisionale quando ci sono più AM come in Giappone. A questo scopo è stata istituita l'assemblea interministeriale per la BPL quale strumento che permette alle AM, alle AR ed alle ARc di scambiarsi informazioni sull'Organizzazione per la Ricerca e lo Sviluppo Economico (OCSE) ed i paesi esteri ed arrivare a decisioni comuni a livello nazionale; ii) programmi comuni di addestramento. Si è dato inizio ad un programma congiunto di addestramento con l'obiettivo di formare gli ispettori e minimizzare le differenze nelle pratiche ispettive tra le AM, che tra l'altro comprende visite congiunte ai centri di saggio (CdS) e la partecipazione a commissioni di valutazioni presso altre AM. Una delle finalità di questo programma di addestramento è la preparazione alla visita di valutazione sul posto (VVP) dell'OCSE tramite simulazione presso le AM Giapponesi; iii) programmi comuni di traduzione dei documenti dell'OCSE. Per evitare inutile confusione causata dalle differenze di interpretazione e di traduzione dei documenti dell'OCSE da parte delle AM, questi sono stati tradotti in Giapponese con la cooperazione dell'industria. Ciò comporta altri notevoli vantaggi quali la riduzione dei costi ed il risparmio di tempo per tutte le controparti in Giappone. Anche altri paesi, membri e non-membri dell'OCSE, hanno istituito più di una AM per la BPL. È auspicabile che l'esperienza Giapponese possa loro essere utile.

Parole chiave: buona pratica di laboratorio, autorità di monitoraggio, autorità riceventi, autorità regolatorie.

INTRODUCTION

There are various types of good laboratory practice (GLP) monitoring authorities (MAs) in the world. Some countries have only one MA, while others, including Japan, have more than one MA. Some MAs are in charge of only GLP inspections. Others have other monitoring functions, such as good clinical practice (GCP) and good manufacturing practice (GMP), in addition to GLP. Also, each MA has its own relationship with regulatory authorities (RAs), receiving authorities (RcAs), and industry based on the internal regulatory systems.

The revised guidance for the exchange of information concerning national programmes for monitoring of compliance with the principles of good laboratory practice [Annex III to C(89)87(Final), Revised in C(95)8(Final)], hereafter referred to as revised guidance, states that “To facilitate international liaison and the continuing exchange of information, the establishment of a single GLP monitoring authority covering all good laboratory practice activities within a member country has obvious advantages”[1]. Japan has six GLP programmes and eight GLP MAs as set forth in Table 1 [2]. The number is probably the largest in the world. GLP monitoring programmes for pharmaceuticals, medical devices and workplace chemicals are managed by the Ministry of Health, Labour and Welfare (MHLW). The Ministry of Agriculture, Forestry and Fisheries (MAFF) is in charge of three GLP programmes which cover pesticides, veterinary drugs, and feed additives. As regards industrial chemicals, three Ministries, *i.e.*, MHLW, Ministry of Economy, Trade and Industry (METI), and Ministry of Environment (ME) manage the programme from the toxicity, bioaccumulation/biodegradation, and ecotoxicity points of views, respectively. These ministries play a role as RAs that issue regulations and guidance for GLP. Almost all ministries have related organizations and transfer the functions of practical inspection to them. For example, the Pharmaceuticals and Medical Devices Agency (PMDA), an incorporated administrative agency responsible for the compliance with the pharmaceuticals affairs law, plays a role as an MA and inspects test facilities (TFs) which perform non-clinical studies for medical products.

The revised guidance also prescribes that “Where more than one authority exists, a member country should ensure that they operate in a consistent way and have similar GLP compliance programmes. The authority or authorities with responsibilities for international contacts should be identified”. GLP programmes and MAs in Japan are aligned with the revised guidance. For example, their GLP regulations are based on the OECD principles of GLP and GLP advisory and consensus documents. In addition, Japan has been making efforts to establish a close link among MAs to apply and implement GLP programmes effectively, efficiently, and consistently, as illustrated below.

Some countries, both members and non-members of the OECD, have also established more than one GLP MA. It is hoped that the Japanese experience can be useful to them.

ADVANTAGES AND DISADVANTAGES OF MULTI-GLP MAS

In the countries with multi-GLP MAs each MA is, in principle, responsible for specific groups of products within a given regulatory context. Moreover, the MAs can play dual or triple roles as RcAs and/or RAs in addition to function of MAs for each area. For example, PMDA takes part in the process from development to post-marketing use of pharmaceuticals and medical devices. As its role includes GLP inspections and review of new drug applications, information exchange between the MA (*i.e.*, the GLP Inspection division) and the RA (*i.e.*, the Review division) is quite smooth through close relationship by internal meetings and transparent procedures. For workplace chemicals, one division at the MHLW has several sections that play the roles of MA, RA, and RcA. In these examples, there is no hindrance to communication among them as they all belong to the same organization.

Efficient communication among authorities prevents them from asking more than once the same questions to industry. When an MA and RcA belong to the same organization, this is beneficial to industry. On the other hand, disadvantages for multi-GLP MAs have also been pointed out, namely.

Table 1 | Overview of the GLP programmes in Japan

GLP Programme	Ministry	Related Organization
1. Pharmaceuticals and Medical Devices	MHLW	Pharmaceuticals and Medical Devices Agency
2. Workplace Chemicals	MHLW	National Institute of Occupational Safety and Health
3. Pesticides	MAFF	Food and Agricultural Materials Inspection Centre
4. Veterinary Drugs	MAFF	National Veterinary Assay Laboratory
5. Feed Additives	MAFF	Fertilizer and Feed Inspection Services
6. Industrial Chemicals		
i) Toxicity	i) MHLW	National Institute of Health Sciences
ii) Bioacc./Biodegr.	ii) METI	National Institute of Technology and Evaluation
iii) Ecotoxicity	iii) ME	National Institute for Environmental Studies
MHLW: Ministry of Health, Labour and Welfare; MAFF: Ministry of Agriculture, Forestry and Fisheries; METI: Ministry of Economy, Trade and Industry; ME: Ministry of Environment.		

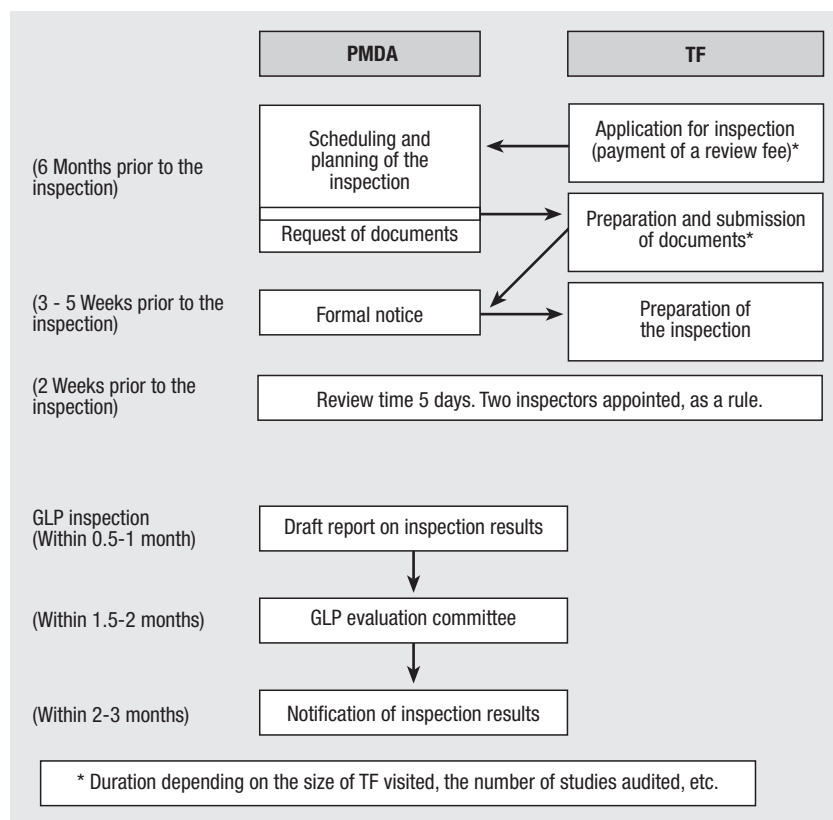


Fig. 1 | Example of the scheme of a GLP inspection (PMDA).
PMDA: Pharmaceuticals and Medical Devices Agency

Complexity of information flow

Appropriate sharing of information is necessary to properly manage the programme. On the other hand, confidentiality of information must be preserved. The large number of stakeholders ensuing to the multi-GLP MAs approach has as a consequence complexity and difficulty of information management.

Difference in policies and decision-making processes

Each MA has its own relationship with RAs, RcAs, and industry, this leading inevitably to differences of in policies and decision-making processes among MAs. Needless to say, however, it is important to better harmonize the various approaches because of the participation in international meetings including the OECD meetings and to facilitate the work of Contract Research Organizations (CROs) which in general cover various GLP areas. Hence, the mechanism of policy arrangement and decision-making is self-evident.

Difference in translation and interpretation

In order to comply with the requirements of the OECD Principles of GLP, each MA translated those principles and other OECD documents and interpreted them. This process led to differences among MAs. In other words, for the same OECD documents there were different translations arranged by different MAs and industry organizations. This caused confusion and difficulties to industry, especially to CROs which have to comply with multiple national GLP

programmes, e.g. the choice of language they should use for their standard operating procedures (SOPs).

Difference in application forms and explanatory documents

When a TF plans to submit an application for the inspection of GLP compliance, MAs in Japan require them to fill in an application form. Furthermore, MAs in Japan request that TFs provide preliminary information before an inspection can take place. Differences in the forms adopted by the various MAs force them to make additional efforts to prepare the inspections.

Differences in the conduct of inspections

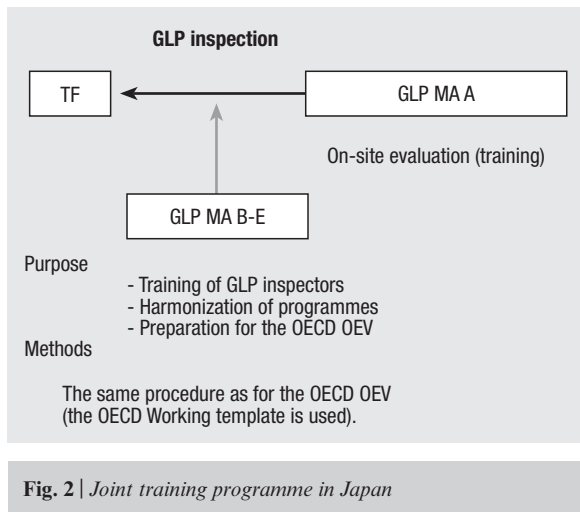
Even though each MA respects the OECD principles of GLP, the system of multi-GLP MAs leads to differences in the inspection patterns. In order to get rid of differences and harmonize as much as possible the inspecting modes adopted by the various MAs, detailed information on the inspection and assessment approaches of each MA plays a key role.

COOPERATION AMONG MAS

In order to cope with the above problems, various countermeasures were adopted, as follows.

Interministerial meeting on GLP

It is essential to establish a system for information exchange and decision making when there are a number of GLP MAs such as in Japan. To this



end, the interministerial meeting on GLP (hereafter referred to as the meeting) was established to ensure the exchange of information among MAs, RAs, and RcAs on OECD GLP activities of MAs and make national decisions with the consent of all parties involved. More detailed information on the activities of the meeting is given in following sections below. The meeting is regularly held approximately once a year, normally before the annual meeting of the OECD working group on GLP as well as on an ad hoc basis, whenever necessary.

Application forms for GLP inspections and documents for obtaining the certification of GLP compliance

Each MA sets up its own inspection procedures and make them available to the public as appropriate (Figure 1). In response to requests from industry, the MAs have harmonized the application forms for the GLP inspection and the forms for obtaining the certificate of GLP compliance. These documents should be carefully read and checked by the inspectors before the inspection takes place.

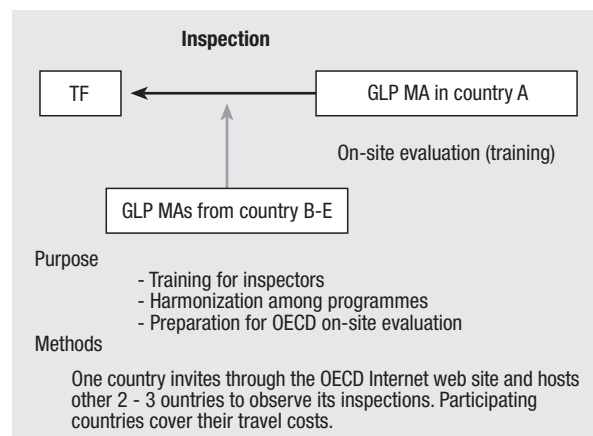
Joint training programmes

With the purpose of training inspectors and minimizing inspection differences among MAs, a joint training programme has been undertaken which also includes joint visit to TFs and participation in the evaluation committees of other programmes (Figure 2). When one MA inspects a TF and/or holds an evaluation committee, it invites inspectors of other MAs as observers. Observers can gain information on the methods of inspection and evaluation from the hosting MA. The observers, in their turn, provide information of the procedures and methods is use at their MAs so that the hosting MA can also obtain important information on the conduct of inspections and the problems encountered by the other MAs. One of the purposes of this training programme is to prepare for the OECD on-site evaluation visit (OEV) by simulating it at MAs in Japan. This being the scenario, PMDA and MHLW

are now conducting joint inspections. These two MAs have also decided to accept jointly the OECD GLP OEV performed in September 2008.

The joint visit to TFs carried out to simulate an OECD OEV turned out to be extremely useful to train inspectors, thus decreasing the differences in inspecting among the various MAs and preparing for the planned OECD OEV in September 2008. This programme lends itself to be permanently run to promote international harmonization among MAs (Figure 3). In practice, one MA invites inspectors from MAs in other countries to its inspection as observers and hosting and hosted MAs can mutually exchange information on procedures and techniques. This system will produce valuable opportunities for MAs to observe actual inspections performed by other MAs. Moreover, if observers use the OECD template for their visits, they can gain some experience as assessors for the OEVs before they participate in a real one. Assessors of the OECD GLP OEVs use this template to summarize the results of their visits and report them to the OECD working group on GLP. The template also includes a check list to describe the approach adopted by the visited MA. As the OECD does not operate a training system for assessors, it is crucial to exploit such opportunities. The assessor ability is directly connected to reliability of the OECD on-site evaluation programme. The availability of english-speaking interpreters to assist the observers would be also greatly beneficial.

In this context, it is worth mentioning that currently each member of the OECD working group on GLP assists non-member countries to improve their ability to participate in the OECD mutual acceptance of data (MAD) programme. Members prepare for presentation at conferences and meetings in non-member countries. Moreover, each member country sets up training documents for the national GLP inspectors. Furthermore, speakers at OECD training courses for GLP inspectors prepare and make available training materials. If member countries would accept to jointly make common training documents for non-MAD



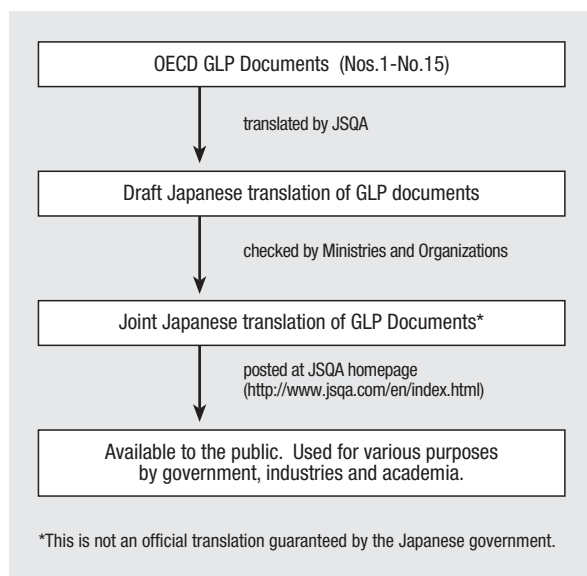


Fig. 4 | Joint translation programme in Japan

member countries as well as for GLP inspectors from member countries, this would ensue in substantial advantages such as cost reduction and time saving for all interested parties. The use of jointly prepared documents for information and training of inspectors would in the ultimate lead to further harmonization of inspections among countries.

Joint translation programme of the OECD documents

To minimize confusion caused by differences in translation and interpretation of OECD documents among the various MAs, a translation programme of the OECD documents has been launched in cooperation with industry (Figure 4). This programme has substantial merits such as cost reduction and time saving for all stakeholders in Japan.

As a first step, the Japan Society of Quality Assurance (JSQA) translated the whole set of OECD documents on GLP (No.1 through 15). All MAs checked and revised the translation as necessary, thus arriving at a Japanese translation accepted by all parties (this is not yet the official translation guaranteed by the Japanese government and MAs). It can be found on the publicly available JSQA homepage (www.jsqa.com). All stakeholders agreed to use this translation for the various needs of government, industry, and academia and follow the same procedure for future OECD GLP guidance and documents.

RELATIONSHIP WITH INDUSTRY AND OTHER COUNTRIES

Relationship with industry colleagues

To manage the GLP programme in an effective way, it is very important to collaborate with industry representatives. Each MA has its own relationships with the relevant industrial representatives. In the case of medi-

cal products, PMDA regularly exchanges information and views with the Japan Pharmaceutical Manufacturers Association (JPMA), the Japan Federation Association of Medical Devices (JEMDA), the Japan Association of Contract Laboratories for Safety and Evaluation (JACL), and JSQA. Major activities in 2007 were: i) training programmes for industry representatives; ii) publication of the guide book of the year 2007. The themes of these two activities were as follows: a) non-clinical testing guidelines and GLP for medical devices; b) Procedures of GLP inspections; c) recent problems regarding GLP implementation for medical products

The PMDA homepage includes key information for the public including industry representatives (www.pmda.go.jp/operations/shonin/outline/shinrai/glp.html).

Relationship with other countries

Currently, pharmaceuticals and medical devices are internationally developed and marketed. In this context, the OECD MAD and the activities of the OECD working group on GLP have gained paramount importance for both industry and governments [3]. This system is definitely efficient because thirty member countries and three non-member countries can attain a higher level of compliance through international GLP-related agreements. In this context, MAs in Japan actively supports these activities. For example, PMDA posts staff members to the OECD as consultants to assist the Secretariat and promote the OECD MAD system.

Bilateral cooperation with other countries is also an important component of the foreign policy in Japan. For example, in the area of medicines, Japan concluded the mutual recognition agreement (MRA) with the European Commission and the memorandum of understanding (MoU) with Switzerland. PMDA has further fostered the bilateral cooperation with non-member countries. The followings are additional examples of PMDA bilateral cooperations.

Example 1. China. Sino-Japan technical cooperation project for establishing of the National Centre for Safety Evaluation of Drug under Japan International Cooperation Agency (JICA) projects (2000-2005).

Example 2. Thailand. PMDA supported the two GLP symposia organized by the Ministry of Medical Science and the Ministry of Public Health of Thailand (2007).

FURTHER HARMONIZATION

The Japan's approach to GLP with its system of multi-GLP MAs requires further harmonization among the MAs themselves. It is believed, however, that Japan's experience can be useful to other GLP MAs abroad. More in general, it is hoped that future activities for the global harmonization of GLP issues at the international level can benefit from the experience gained by managing the GLP programmes in Japan. To this end it should be recalled that the first OECD event with industry (Frascati, Italy, 10-11 April 2008) was a successful opportunity both for authorities and industry. This may be the

first step for an open dialogue on GLP issues at the international level between the public and private sector. Planning of a second OECD GLP event with industry would further promote harmonization of GLP programmes and enhance mutual confidence.

Acknowledgement

Appreciation is expressed to Prof. Sergio Caroli (Istituto Superiore di Sanità, Rome, Italy) and his colleagues who arranged this Special Issue of the *Annali* and promoted and organized the first OECD GLP event.

The following ministries, organizations and industry groups are also acknowledged for their supports to the preparation of this paper and the Author's presentation at the OECD Industry event.

Ministries

- Ministry of Health, Labour and Welfare, Tokyo, Japan
- Ministry of Economy, Trade and Industry, Tokyo, Japan
- Ministry of Environment, Tokyo, Japan
- Ministry of Agriculture, Forestry and Fisheries, Tokyo, Japan

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Other organizations

- Pharmaceuticals and Medical Devices Agency, Tokyo, Japan
- National Institute of Occupational Safety and Health, Tokyo, Japan
- Food and Agricultural Materials Inspection Centre, Tokyo, Japan
- National Veterinary Assay Laboratory, Tokyo, Japan
- Fertilizer and Feed Inspection Services, Tokyo, Japan
- National Institute of Health Sciences, Tokyo, Japan
- National Institute of Technology and Evaluation, Tokyo, Japan
- National Institute for Environmental Studies, Tokyo, Japan

Industry groups

- Japan Society of Quality Assurance
- Japan Pharmaceutical Manufacturers Association
- Japan Federation Association of Medical Devices

Submitted on invitation.

Accepted on 22 September 2008.