International GLP: a critical reflection on the harmonized global GLP standard from a test facility viewpoint

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Summary. The implementation of the Organisation for Economic Co-operation and Development (OECD) principles of good laboratory practice (GLP) on an international level is well advanced. However, the OECD GLP guidelines as well as the corresponding national GLP regulations leave room for interpretation. As a consequence, working in parallel in GLP environments in several countries represents a challenge. Some experiences highlighting key issues are presented in order to create awareness of the international impact of national differences.

Key words: good laboratory practice multisite studies, import tolerance, mutual acceptance of data, archiving.

Riassunto *(La buona pratica di laboratorio a livello internazionale: riflessioni critiche sulle norme BPL globali dal punto di vista di un centro di saggio).* L'adozione dei principi di buona pratica di laboratorio (BPL) dell'Organizzazione per la Cooperazione e lo Sviluppo Economico (OCSE) è ampiamente realizzata sul piano internazionale. D'altra parte, le linee guida dell'OCSE per la BPL, nonché le corrispondenti norme nazionali sulla BPL, mostrano un certo margine interpretativo. Ne consegue che la conduzione in parallelo di attività in BPL in paesi diversi può dar luogo a problemi. Allo scopo di creare consapevolezza in merito alle conseguenze a livello internazionale delle differenze nazionali, vengono illustrate alcune esperienze in questo contesto relativamente ad alcuni aspetti critici.

Parole chiave: buona pratica di laboratorio, studi multisito, tolleranza nell'importazione, accettazione reciproca dei dati, archiviazione.

INTRODUCTION

The principles of good laboratory practice (GLP) have been developed to promote the quality and validity of test data used for determining the safety of chemicals and chemical products. Based on this, the Organisation for Economic Co-operation and Development (OECD) introduced the OECD principles of GLP, which were formally recommended for use in member countries by the OECD Council in 1981 [1]. One integral element of the OECD GLP approach is the mutual acceptance of data (MAD) on an international level, *i.e.*, "the GLP data generated in the testing of chemicals in an OECD member country in accordance with OECD test guidelines and OECD principles of good laboratory practice shall be accepted in other member countries for purposes of assessment and other uses relating to the protection of man and the environment [C(81)30(Final)]" [1].

Since then, the OECD principles of GLP have gone through several revisions, supplemental guidance and advisory documents addressing special GLP areas have been set up, and the MAD concept has been extended beyond the scope of OECD member countries [C(97)114/FINAL] [2].

For the implementation of GLP on national level, the OECD principles of GLP have in most cases been transposed into national GLP laws or regulations, such as the German Chemicals Act ("Chemikaliengesetz") in Germany for all kinds of chemicals and chemical products, or the decree number 2006-1523 in France for pesticides [3, 4]. These national GLP guidelines in most cases already include some deviations from the basic OECD principles of GLP *(Figure 1)*.

An integral part of the implementation of the GLP principles is the installation of a national monitoring system (MS) to control the GLP compliance of the local test facilities (TF). In many countries, more than one monitoring authority (MA) have been set up to monitor GLP compliance. For instance, in the USA the Food and Drug Administration (FDA) is in charge of monitoring GLP TF which work in the pharmaceutical area, while the Environmental Protection Agency (EPA) is in charge of monitoring those working in the environmental field. In Germany, on the other hand, the MS has not been organized along areas of expertise, but along the federal system, *i.e.*, each federal state has implemented its own GLP MA, resulting in 16 German GLP MAs overall.

Keeping in mind that the OECD principles of GLP leave room for interpretation, that the national

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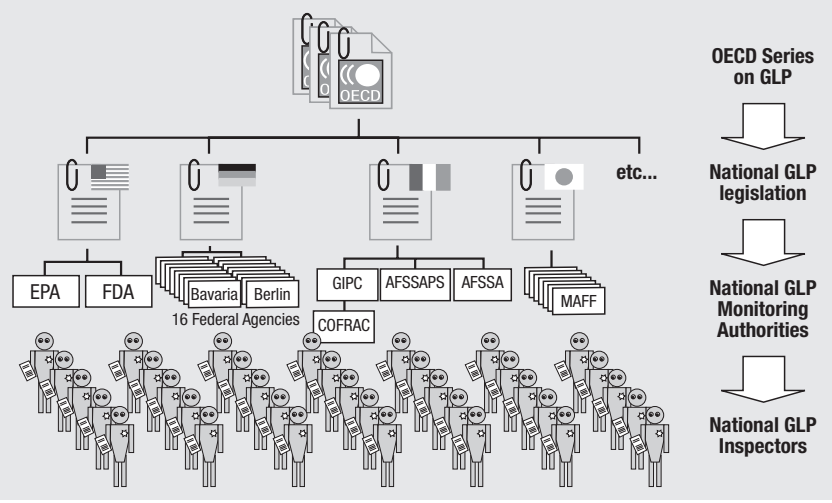

Fig. 1 | *The international GLP cascade: translation of the basic principles into local regulations and monitoring systems.*

guidelines derived from them already create some diversity, and that each MA and each individual GLP inspector will naturally have their own way of interpreting the basic principles, it becomes obvious that the actual application of GLP features a very high degree of variation.

From the viewpoint of a national MA – or from the point of view of a TF working in a rather isolated way, this does not create an issue. However, as a consequence of the increasing globalization of regulatory requirements – *e.g.*, in the field of registration of pharmaceuticals or plant protection compounds – GLP TF act more and more in an international environment, reaching far beyond their "own" GLP home base.

CONDUCTING INTERNATIONAL MULTISITE STUDIES. A PRACTICAL EXAMPLE

Here the difficulties resulting from the variations in the application of the GLP principles are illustrated by means of an international multisite GLP study in which the leading TF and the study director (SD) are located in Germany.

Study plan, amendments and deviations

According to the OECD principles of GLP [1] and the German Chemicals Act [3], the study plan needs to be approved by the SD, TF management and principal investigators (PIs). Amendments of the study plan need to be approved by the SD – in special cases, the approval of the TF management may be required in addition (*e.g.*, if the SD is changed, a study is cancelled etc.).

If one of the involved test sites (TSs) is located in Belgium, however, the Belgian GLP compliance monitoring programme manual also requires, that the study plan and each amendment must be signed additionally by the sponsor and the TS management of each TS involved in the multisite study [5].

Deviations from the study plan, *i.e.*, unplanned departures from the study plan after the study initiation date, should be documented. In accordance with the OECD GLP principles these deviations need to be retained with the raw data.

However, if one TS is located in Brazil, the current draft GLP guideline requires that both, amendments and deviations, should be maintained with the study plan [6].

If one of the TSs is located in Japan, this TS can actually refrain from documenting some deviations, as laid out in the MAFF guideline on GLP, which states that deviations which have no impact on the quality of the study do not need to be described at all [7].

Assignment of QA responsibility

In accordance with the OECD consensus document on multisite studies, "test facility management should designate a *lead quality assurance* that has the overall responsibility for quality assurance of the entire study" [8]. In the German version of the document OECD No. 13, the phrase "Die Leitung der Prüfeinrichtung hat eine *Federführende Qualitätssicherung* zu bestimmen, welche die Gesamtverantwortung für die Qualitätssicherung der gesamten Prüfung erhält" is used, which is a literal translation of the English text. Both phrases clearly refer to a unit or group of people, and in compliance with this, a quality assurance (QA) unit is assigned as lead QA.

However, in the French version of the document OECD No. 13, the same paragraph requires that la direction de l'installation d'essai doit désigner *un coordonnateur chargé de l'assurance qualité* pour l'ensemble de l'étude" (test facility management must designate a coordinator who has the responsibility for the quality assurance of the entire study). The French version specifically requires that an individual QA person is assigned as lead QA for each multisite study. As a consequence setting up the GLP and QA structure for an international multisite

study with a TS in France may turn out to be rather difficult, if all parties refer to the same guideline, but miss out on the fact that the content is different in different language versions.

Characterization of the test item

According to the OECD GLP guidelines, the test item used in a GLP study must be characterized, but there is no requirement that this characterization has to be prepared under GLP.

If one of the TSs is located in the USA, for instance, the EPA requirements have to be taken into consideration, which require that the test item characterization data must be prepared either under GLP or good manufacturing practice (GMP) [9].

The requirements to be followed at TSs in Japan are even stricter, as GLP is considered as the only acceptable standard which has to be applied to the certification of the test item [7].

The final report

As laid out in the OECD guidance on GLP, the final report needs to include a statement of GLP compliance (SOC), which declares that the study has been carried out in accordance with the OECD Series on GLP [1]. In accordance with the MAD agreement, the reference to the OECD GLP guidance is sufficient and no national GLP regulations need to be referenced in addition.

However, national GLP MAs in many cases require in their national GLP inspections that the relevant local GLP regulation from the country in which the TF or a TS is located also should be cited in the SOC.

According to the OECD document No. 1, the SOC only needs to be signed by the SD [1].

On the other hand, the GLP regulations of some countries again require deviations from the OECD, even regarding the preparation of the SOC. The US EPA GLP and submission guidelines require that the SOC also needs to be signed by the sponsor and by the applicant submitting the study [9]. The latter requires a change of an already completed GLP report, often without involvement of the SD. In most cases, regulatory managers from the local US organization simply add their signature to the SOC page. This procedure is seen as critical with respect to the strict GLP rules applicable for the alteration of completed GLP reports by other national GLP authorities. If TFs adapt the SOC and add the additional signatures required for a submission in the US, this can lead to acceptance problems with other GLP authorities. For instance, it was criticised in the inspection report of a TF in Belgium that "it is not acceptable that the SOC is also signed by the sponsor".

In addition, several receiving authorities (RAs) have disputed the acceptability of GLP reports if the SOC did not mention the compliance of their local GLP guidelines, *e.g.*, the US EPA GLP guidelines or the Japanese GLP, thus overriding the OECD MAD agreement.

Deputies in the GLP world

The OECD GLP principles do not require the appointment of deputies for the key roles in a GLP TF.

On the other hand, many national GLP MAs, *e.g.*, in Germany, require that there is a clear description of how the responsibilities of the key GLP roles are assigned in case of absence of, for example, the head of TF or the SD. In Germany a common approach to address this issue is to appoint a deputy SD in the study plan.

However, this does not only lead to discussions with other national GLP authorities, which do not support the system of deputies for GLP responsibilities; it also leads to discussions with GLP inspectors regarding the actual responsibilities of this deputy SD – to the effect that the deputy must not sign the final report, as he/she was not involved in detail in the study. Nevertheless, a basic procedure in GLP is to assign a new SD for a study in an amendment to the study plan. This amendment can be prepared by the new SD, who is then authorised to sign the final report.

Additions to a completed study

The OECD principles of GLP clearly describe how to modify final reports of completed studies. However, there is no guidance whether the actual preparation of new raw data resulting in an amendment of a completed study is acceptable.

Basically, the general interpretation by most European GLP authorities is that it is not acceptable to add new raw data to completed studies. On the other hand, the interpretation of the GLP requirements in the USA clearly allows reopening a completed study, preparing new raw data and reporting these in an amendment to the final report.

Archive issues

The new OECD advisory document on archiving under GLP addresses many of the issues on GLP archiving requirements which had led to discussions and misunderstandings in the past [10]. However, some rather critical issues still have not been resolved, namely:

i) archiving periods

No global standard has been defined for the archiving period required for GLP raw data. The archiving periods are defined (if at all) in national regulations set up either by the GLP authorities (*e.g.*, in the Chemikaliengesetz in Germany [3]) or by the receiving submission authorities (for instance, in the US by the EPA [11] or the FDA [12]). As a consequence, the archive periods vary from 10 years in France [13] and Italy [14], to 15 years in Germany [3] – or flexible requirements such as "as long as a marketing-permit is held" are in place [11].

Dealing and complying with these diverse requirements is difficult because: there are mixtures of GLP requirements and requirements based on commercial laws. A clear distinction is often not possible. In many cases data are archived according to GLP conditions for periods defined by commercial law;

- it is not clear whether the archiving periods defined on a national level apply for the GLP data produced in the TFs in this country and/or for the GLP data submitted in this country (regardless in which country the data were produced) – although the first interpretation seems to be the most prevalent one;
- it has not been defined which archiving period has to be applied for raw data which are transferred from one country to another. Do the raw data inherit the archiving period of their country of origin - or does the archiving period change if the data are transferred to a GLP archive in another country?
- in multisite studies, different portions of raw data may be archived at different locations (TF, TS). Which archiving period has to be applied in this case – the one relevant for TF, or the different local requirements of the TSs?

ii) archive location

The easiest approach to avoid the latter predicament is to archive all raw data of a multisite study at the TF, which is in full compliance with the OECD requirements [1, 10]. However, some countries still require that the local TSs retain either a copy of the raw data, or even the originals (*e.g.*, Greece);

iii) archive media

Finally, archiving paper raw data under GLP is expensive, requires large space, makes quick access to the data at different sites difficult and involves many risks which are difficult to mitigate (*e.g.*, fire protection). As a consequence, many TFs have set up systems to transfer the raw data status from the original paper to different media which are easier to store, backup and access, *e.g.*, microfiches or electronic files (tiff, pdf). This approach is in full compliance with the requirements of OECD GLP if certain provisions are considered (validation of "new" raw data, readability, no loss of information etc.) [1, 10, 15]. After acceptance of the "new" raw data as true copies, the original raw data can be destroyed.

In the US this approach is questionable because of a mixture of GLP and commercial law requirements. According to EPA advisory 44, the true copy provisions under GLP do not extend to 40 CFR 169 2(k) – the original notebooks need to be retained [16]. If this rule is applied in full consequence to the GLP world, this means that it is also not acceptable to change the medium (*i.e.*, file format or storage location) of electronic raw data, which actually challenges the whole concept of electronic GLP raw data.

iv) archiving at contract research organizations

If GLP studies or phases of GLP studies are conducted by contract research organizations (CROs), the issue of archiving is impacted by conflicting GLP interests.

CROs often insist on archiving the GLP raw data in their own archives, at least until they have passed the next GLP inspection, which may be up to 4 years. National GLP authorities require to review the raw data of studies during an inspection. If a CRO handed over all raw data to the sponsor immediately after study finalization, there might be no raw data available or calling back the raw data for inspection might be difficult.

On the other hand, the sponsors depend on the GLP status of the studies which were conducted at CROs and this again depends on the fact that the raw data are archived according to GLP. As a consequence of globalization, sponsors often use different CROs in many different countries, which makes tracking the off-site raw data increasingly difficult. In addition, there is no international warning system if a CRO closes down its business and there is no international systematic approach for dealing with GLP archives in such a case. There have already been cases in which CROs went out of business and the raw data from their archives were lost.

GLP AND INFORMATION TECHNOLOGY

The gap between GLP and information technology (IT) is constantly widening. While technical development in the area of IT is very fast, GLP develops at a moderate speed. Therefore the use of new IT technologies such as virtual machines in the GLP environment is very challenging.

In addition, there is a tendency towards global IT strategies and systems, as TFs want to make optimum use of expensive laboratory information systems, to be able to work efficiently on a global level and capture maximum synergies. Such global IT systems have to be validated according to several national GLP requirements if they are used in several countries. Different individual (national) interpretations make these validations very complicated and further constrain the use of modern IT systems in the GLP environment.

CONDUCTING GLP STUDIES IN NON-GLP COUNTRIES

In spite of the advanced global implementation of GLP, there are still many countries across the world without OECD MAD status and/or a national GLP program, so-called "non-GLP" countries.

On the other hand, TFs located in GLP countries specifically have to conduct GLP studies in "non GLP" countries, *e.g.*, import tolerance studies for plant protection compounds. If a plant protection product is not registered in the USA or the EU, but used, *e.g.*, in Costa Rica, the Philippines or India, treated crops can only be imported to the USA and/or Europe if an import tolerance study has been conducted according to GLP in the respective country of origin.

There are limited options for working under GLP in these countries. Some national GLP MAs from OECD GLP countries are prepared to certify individual TFs in "non-GLP" countries. For instance, the German authority has certified as GLP compliant TFs in India, and Switzerland has GLP certified TFs in Brazil. However, there is no guarantee that the GLP status and the data from these TFs will be accepted in other GLP countries. Strictly speaking, these foreign TFs are not covered by the OECD MAD agreement or bilateral agreements between individual countries.

The only remaining option is to "import" GLP knowledge on a study-by-study basis by a certified TF into the "non-GLP" country in question. This involves enormous effort, time and cost. In addition, depending on the use of the data (*e.g.*, for EU and NAFTA) several GLP requirements have to be considered at the same time. This study-by-study approach does not contribute to build a sustainable GLP basis in these "non-GLP" countries.

CONCLUSIONS

The international GLP community needs a more harmonized approach to facilitate working under GLP on a global level. In order to promote this, the following approaches are proposed:

- install a regular exchange forum of experts from industry and authorities to address conflicting GLP issues on an international level;
- provide an international list of all GLP TFs and implement an international warning system for closures of GLP TFs;
- foster mutual acceptance of different (national) GLP-validation approaches and mutual acceptance (at least partially) of validations from other quality systems, *e.g.*, GMP, GLP, good clinical practice (GCP) etc.;
- set up a system to certify GLP TFs in "non-GLP" countries by a group of OECD MAD countries, including acceptance of the GLP status on an international level.

The focus must be on the core objective of the GLP principles: promoting the development of quality test data as a basis for the mutual acceptance of data on an international level. Therefore, the diverging local GLP interpretations should be addressed and harmonized. Furthermore, broader implementation and acceptance of GLP should be fostered worldwide.

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References

1. Organisation for Economic Co-operation and Development. *OECD principles on good laboratory practice (as revised in 1997).* Paris: OECD; 1998. (OECD Series on Principles of GLP and Compliance Monitoring, No. 1, ENV/MC/CHEM(98)17). Available from: http://www.olis.oecd.org/olis/1998doc.nsf/LinkTo/env-mc-chem(98)17.
2. Council Decision Concerning the Adherence of Non-Member Countries to the Council Acts related to the mutual acceptance of data in the assessment of chemicals [C(81)30(Final) and C(89)87(Final)], C(97)114/FINAL, January 23, 1998.
3. Neufassung des Chemikaliengesetzes vom 20. Juni 2002, Bundesgesetzblatt Jahrgang 2002 Teil I Nr. 40, June 27, 2002.
4. France. Décret n° 2006-1523 du 4 Décembre 2006. *Journal Officiel de la République Française* December 4, 2006.
5. Belgian GLP Compliance Monitoring Programme Manual, Scientific Institute of Public Health, Bureau of Quality Assurance, DOC 03/GLP Manual/E, Edition 2, December 31, 2006.
6. *Requisitos Gerais Para Laboratórios Segundo os Princípios das Boas Práticas de Laboratório – BPL*. INMETRO, Norma NIT-DICLA-035, Revision 00 (Draft), December 2007.
7. The good laboratory practice standards for agricultural chemicals. JMAFF, 11 Nousan 6283, notified October 1, 1999.
8. Organisation for Economic Co-operation and Development. *Consensus document of the Working Group on GLP: the application of the OECD principles of GLP to the organisation and management of multi-site studies.* Paris: OECD; June 25, 2002. (OECD Series on Principles of GLP and Compliance Monitoring, No. 13, ENV/JM/MONO(2002)9).
9. Environmental Protection Agency, Code of Federal Regulations Title 40, Protection of the Environment, Part 160, EPA 40 CFR 160 – Good Laboratory Practice Standards, November 1983.
10. Organisation for Economic Co-operation and Development. *Advisory Document of the Working Group on GLP: Establishment and Control of Archives that Operate in Compliance with the Principles of GLP.* Paris: OECD; June 11, 2007 (OECD Series on Principles of GLP and Compliance Monitoring, No. 15, ENV/JM/MONO(2007)10).
11. Environmental Protection Agency, Code of Federal Regulations Title 40, Protection of the Environment, Part 160, EPA 40 CFR 160.195 – Retention of records, November 1983.
12. Food and Drug Administration, Code of Federal Regulations Title 21, Food and Drugs, Part 58, FDA 21 CFR Part 58 – Good laboratory practice for nonclinical laboratory studies.
13. France. Décret n° 2006-1523 du 4 Décembre 2006. *Journal Officiel de la République Française* December 4, 2006.
14. Italia. Decreto Legislativo 2 marzo 2007, n. 50. Annesso I, Capitolo 10: Archiviazione e conservazione di dati e materiali. *Gazzetta Ufficiale della Repubblica Italiana* n. 86 del 13 aprile 2007, p. 22.
15. Organisation for Economic Co-operation and Development. *GLP Consensus document: the application of the principles of GLP to computerized systems.* Paris: OECD; 1995. (OECD Series on Principles of GLP and Compliance Monitoring, No. 10, Environment Monograph no. 116, OCDE/GD(95)115, 1995).
16. Environmental Protection Agency. *EPA GLP Regulations advisory* No. 44, May 5, 1990.