

OECD and USA GLP applications

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Summary. Since the inception of the FDA good laboratory practice (GLP) regulations in 1979, the Organisation for Economic Co-operation and Development (OECD) principles of GLP in 1981 and the finalization of the EPA GLP programme in 1983 there have been recognizable differences among the three compliance programmes. All have been revised since their initial publication, but still there remain differences in verbiage, and in some cases content, among the FDA, EPA and OECD GLP principles, but the end result for each is the assurance that the experimental information generated under each programme is of sufficient quality and integrity to support the reports for the various studies. These differences, while not affecting the data quality, can result in issues when submitting studies globally. An overview is offered of some of the differences that exist between the USA and OECD GLP principles and the challenges global companies face when making regulatory submissions.

Key words: good laboratory practice, test facilities, study submission, inspections.

Riassunto (*Applicazione dei principi di buona pratica di laboratorio in ambito OCSE e negli USA*). Sin dalla prima formulazione dei criteri di buona pratica di laboratorio (BPL) dell'FDA nel 1979, i principi di BPL dell'Organizzazione per la Cooperazione e lo Sviluppo Economico (OCSE) nel 1981 e la realizzazione del programma BPL dell'EPA nel 1983 è stata evidente la presenza di differenze tra i tre programmi di verifica della conformità. Successivamente alla loro iniziale adozione, questi programmi sono stati sottoposti a revisione, ma vi sono ancora differenze nei termini e, in alcuni casi, nei contenuti tra i principi di BPL dell'FDA, dell'EPA e dell'OCSE. Il risultato finale per ciascuno di essi è comunque l'assicurazione che i dati sperimentali contenuti nei rapporti finali degli studi siano di sufficiente qualità ed integrità. Queste differenze, ancorché non abbiano conseguenze per la qualità dei dati, possono però dar luogo a problemi quando gli studi sono presentati per la registrazione su scala globale. Viene fatta una disamina delle differenze che esistono tra i principi di BPL statunitensi e quelli dell'OCSE, nonché delle sfide che le aziende globali devono affrontare quando si presentano studi alle autorità regolatorie.

Parole chiave: buona pratica di laboratorio, centri di saggio, registrazione degli studi, ispezioni.

INTRODUCTION

Since the inception of the FDA good laboratory practice (GLP) in 1979, the Organisation for Economic Co-operation and Development (OECD) principles of GLP in 1981 and the finalization of the EPA GLP in 1983 there have been recognizable differences among the compliance programmes [1-4]. All have been revised since their initial publication. Nonetheless, there remain differences in verbiage, and in some cases content, among the FDA, EPA and OECD GLP principles. The end result for each is the assurance that the experimental information generated under each programme is of sufficient quality and integrity to support the reports for the various studies. These differences, while not affecting the data quality, can result in issues when submitting studies globally.

The USA GLP programmes, in general, tend to be more prescriptive than the OECD principles. In some cases they are more stringent, e.g.; as regards animal care requirements, or requiring the reporting of all circumstances that may have affected the quality or integrity of the data be included in the final report. Another

notable difference is in the USA test facilities (TF) required to submit an application to the monitoring authorities (MA) and receive GLP certification prior to generating or submitting GLP data to Regulatory Authorities (RA). Further, in the USA, laboratories do not pay a fee to the MA for the performance of a compliance audit.

The original OECD GLP principles were based on the 1979 FDA GLP. The principles were written and approved with the input and approval of the OECD membership. The OECD principles provide a framework for countries to implement their own national programmes. The principles are written to allow for variations among national programmes such as archival storage periods or the approval sequence of the study plan by the TF management (TFM) and sponsor. Additionally, the OECD GLP principles have numerous consensus documents published (fifteen in total) that give additional definition and clarity to areas of the GLP principles such as: *i*) the quality assurance (QA) unit; *ii*) application of the GLP principles to field studies; *iii*) application of the GLP principles to short

term studies; *iv*) role and responsibilities of the Study Director (SD) and sponsor; *v*) application of GLP to computerized systems; *vi*) organization and management of multisite studies; *vii*) application to *in vitro* studies; *viii*) establishment and control of archives.

Many of the consensus documents are used in the USA GLP community as important reference sources. This is especially true of the OECD Consensus Document No. 13 dealing with multisite studies [4].

USA AND OECD SIMILARITIES AND DIFFERENCES

General

There are numerous similarities between the USA (FDA and EPA) and the OECD GLP principles. All require: *i*) a study plan that is approved by the Sponsor and signed by the SD; *ii*) a QA Unit; *iii*) a substance / article / item that is appropriately characterized; *iv*) trained, qualified personnel to conduct the study; *v*) raw data collection and change procedures; *vi*) a final report that reflects the data generated; *vii*) the final report and all associated raw data and records be archived.

Not all aspects of the USA and OECD GLP principles are the same. There exist many terms in the published documents that differ, although the intent is essentially the same, as set forth in *Table 1*.

These differences, at times, can cause confusion because of the common usage of these words and phrases in different countries. For instance, the word “should” in the OECD GLP principles is intended to be interpreted as required, but in the USA GLP principles should imply that it is recommended, but not absolutely required.

The main differences between the USA and OECD GLP programmes can be traced back to the following key aspects: *i*) responsibilities and compliance; *ii*) statement of compliance; *iii*) approvals; *iv*) laboratory certification; *v*) authority inspections; *vi*) archiving requirements. These differences are illustrated in detail hereafter.

Responsibilities and compliance

In the USA the SD is responsible to assure that all applicable GLP regulations are followed. If there are any deviations from the EPA or FDA GLP principles this must be noted in the final report and in the case of the EPA GLP regulations noted in the GLP statement of compliance. In the OECD context, on the other hand, TFM is mainly responsible to ensure GLP compliance. This is not to say

that the SD is not responsible, but only that the emphasis for compliance is weighted to the TFM.

The OECD requires that the TFM issues a declaration, where applicable, that a study was carried out in accordance with the GLP principles. Moreover, under the OECD GLP programme, the final report should be signed and dated by the SD to indicate responsibility for data and should indicate compliance with the GLP principles.

The EPA requires that each study include a true and correct statement, signed by the applicant, the sponsor, and the SD indicating the level of compliance with 40 CFR, part 160 (GLP statement of compliance) and is required to be page three of the final report [5]. It should be noted that the FDA has no similar requirement.

Statement of compliance in the final report

The EPA requires that each study submitted be accompanied by a GLP compliance statement specifying one of the following: *i*) the study was conducted under the EPA GLP regulations; *ii*) the study was not conducted under EPA GLP regulations with description of the ways it differs; *iii*) the submitter is not the study sponsor, did not conduct the study and does not know whether the study was conducted under the EPA GLP regulations.

Again, unlike the EPA, the FDA does not require such a statement to accompany the final report.

Even though it is not a requirement of many countries to supply a GLP compliance statement as such, they do create a statement for USA submissions. They can have different appearance and wording, but convey what is required by the EPA.

An example of an OECD statement in US EPA PR86-5 format is shown in *Figure 1*.

Because many of these studies are intended for global regulatory submissions the GLP compliance statement has been modified to meet multiple regulatory agency acceptability requirements, as shown by the two examples of *Figures 2* and *3*.

Some TF generate a compliance statement that claims compliance with several GLP programmes including programmes that are outside the scope of their countries' MAs. One question that might be asked is whether it is helpful to claim compliance with GLP regulations other than those of the national programme. Is there value in making these claims given that the additional claims are not monitored by any MA?

Protocol approval

The USA GLP regulations require sponsor approval prior to SD signature on protocol / study plan.

On the other hand, the OECD allows the individual countries to determine when sponsor and TFM need to sign the study plan.

Assignment of study director

In the USA GLP programme there is a single SD for a given study.

With the OECD it is allowed by some RA that the TFM assigns deputy SD for defined durations during a study (only one SD at any given time).

Table 1 | Comparison of terms used in the USA and OECD GLP principles with the same meaning

USA GLP principles	OECD GLP principles
Shall	Should
Assure	Ensure
Substance / article	Item
Equipment	Apparatus
QA unit	QA programme
Experimental termination	Experimental completion

Good laboratory practice
Statement of compliance

This study was conducted in compliance with good laboratory practice regulations, Appendix 1 to § 19a, Section 1, Chemikaliengesetz of 25 July 1994 (Official Bulletin/Federal Republic of Germany, I 1994, p. 1703).

Study director

Date
(Study completion date)

Signature

Fig. 1 | Example of an OECD statement in US EPA PR86-5 format.

Laboratory certification

Laboratory certificates, e.g., official certification documents from country MA are not a specific requirement of the OECD GLP programme.

In the USA authorities do not certify TF. They perform what is commonly referred to as neutral scheme compliance inspections on a 2-4 year cycle. They can perform audits more frequently if there is evidence to indicate it is warranted. At the completion of the audit neither the EPA nor FDA issue a certificate of compliance.

The majority authorities following the OECD GLP principles certify TF for 2-4 year intervals. At the completion of the TF inspection a GLP certificate is issued. In lieu of certification in some countries RA have requested documentation from the USA GLP authorities, or have requested a more specific document from the EPA Laboratory Data Integrity Branch.

Authority inspections

Within the OECD, authority inspections are normally requested by the TF. If the facility is new they must request an inspection and obtain a GLP certificate prior to claiming GLP compliance for the studies that are conducted. Certificates generally are valid for 2-4 years. Recertification is requested by the TF. There is generally a fairly long lead time between the

notice of inspection and the actual inspection event.

In the USA selection of the TF to be inspected is by the RA. New laboratories are not required to apply for certification from the monitoring authority prior to conducting or claiming GLP compliance. In the case of EPA there is a 10-day notice (every 2-4 years), whereas the TF receives no advance notice of the GLP inspection by the FDA.

Archiving requirements

The length of time that the original raw data and final reports is required to be maintained differs between regulations and MA. The OECD allows the individual RA to determine the appropriate storage interval. In the USA, on the other hand, there are different rules between the FDA and EPA.

Some examples of the OECD approach are, for instance, Germany which requires archival for 15 years and Switzerland which requires 10 years. The FDA has defined an interval of 5 years after results are submitted for research or marketing permit and 2 years after termination if not submitted to the agency. The EPA indirectly defers to the FIFRA books and records requirements (i.e., retained as long as the registration is valid and the producer is in business) or 2 years after study termination if not submitted to the agency [6]. The EPA and FDA require government

GLP Compliance statement

This study was conducted in accordance with the OECD principles of good laboratory practice and the GLP principles of the German "Chemikaliengesetz" (chemicals act), which meets the United States Environmental protection agency good laboratory practice standards [40 CFR Part 160 (FIFRA) and part 792 (TSCA)], with the exception that recognized differences exist between the GLP principles/standards of OECD and the principles/standards of FIFRA and TSCA.

Study Director Signature Date

To be filled for USAEPA submission only:

Sponsor Signature Date

Submitter Signature Date

Fig. 2 | Modified GLP compliance statement. Example 1.

Statement of GLP compliance

This study was conducted according to published good laboratory practice (GLP) for tests of substances regulated under the Federal Insecticide, Fungicide, and Rodenticide Act (40 CFR, Part 160), the OECD Principles of GLP, Paris, France, and the Japanese MAFF (59 NohSan No. 3850) guidelines. The test article / carrier mixture was not assayed to determine concentration. Homogeneity or stability in conjunction with this study.

Submitter:

Sponsor:

Company agent:

.....

Date

Study Director:

.....

Date

Senior Scientific Associate

Fig. 3 | Modified GLP compliance statement. Example 2.

notification if materials are transferred to sponsor archives when a contract facility goes out of business. Notification is not a specific OECD requirement.

CONCLUSIONS

More and more companies are performing or contracting work across the globe. Studies conducted are not used only in the country of origin, but are also submitted to RA in many countries. Global efforts at harmonization within technical arenas of the OECD are currently being developed. One area is the development of endocrine disruptor endpoints. In addition, there is currently an OECD group working to harmonize GLP field residue studies. This will allow for the acceptance of up to 50% field studies from one country to be accepted by other national authorities. When the residue harmonization effort is realized one question that must be asked is whether RA that have a certification programme accept data from field facilities in the USA that have not yet been inspected by the USA GLP authorities even if they are claiming compliance.

FDA and EPA have both begun evaluations of their GLP programmes. Among other things, both of these

programmes are looking at opportunities for greater global harmonization.

As regards the OECD mutual acceptance of data (MAD) programme, it should be noted that all of the new applicants programmes are based on the OECD GLP principles, although they have their own unique requirements as allowed by the OECD GLP principles. Moreover, all current and applying members are or have been audited by other member countries to assure the appropriate level of data quality.

Upon careful analysis one can see that no country can simply apply the OECD GLP principles as written, but must make individual decisions on such aspects as length of archival storage or the timing of sponsor approval.

For any MA GLP regulations that have gone through the MAD evaluation and approval process has demonstrated itself to be at a sufficient level as to assure the quality and integrity of the data regardless the differences that might exist between it and other MAD countries. These differences should not become obstacles to global acceptance of any GLP studies by any country that is a MAD member.

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References

- Code of Federal Regulation. Federal insecticide, fungicide, and rodenticide Act, 40 CFR, Part 160 – good laboratory practice standards.
- Code of Federal Regulation. Toxic substances control Act, 40 CFR, Part 792 – good laboratory practice standards.
- Code of Federal Regulation. Food drug and cosmetic Act, 21 CFR, Part 58 – good laboratory practice for nonclinical laboratory studies.
- Organisation for Economic Co-operation and Development. *Principles on good laboratory practice (as revised in 1997)*. Paris: OECD; 1998. (Series on principles of GLP and compliance monitoring No.1, ENV/MC/CHEM(98)17).
- 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; 2002. (Series on principles of GLP and compliance monitoring, No.13, ENV/JM/MONO(2002)9).
- Code of Federal Regulation. Federal insecticide, fungicide, and rodenticide Act, 40 CFR, Part 169 – books and records of pesticide production and distribution.