Recommendation paper on principles of Good Laboratory Practices (GLP) for clinical trial applications under the EU Clinical Trials Regulation (Regulation (EU) No 536/2014)

Version 01

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1. Introduction and scope

With the Clinical Trials Regulation (CTR) (EU) No 536/2014 in force, a harmonized European Union (EU) approach on acceptability of the Good Laboratory Practice (GLP) status of non-clinical studies submitted to support clinical trials is needed. Through the principles of Mutual Acceptance of Data (MAD), non-clinical safety data are accepted when a particular study has been conducted in a test facility that is part of the national GLP monitoring programme of an EU member state (MS), Organisation for Economic Co-operation and Development (OECD) member country or MAD full adherent country[1], and found to be in compliance with the OECD principles of GLP. However, regulatory harmonization is needed for non-clinical data generated in a country which has not joined the OECD MAD system. Guidance published by relevant organizations (EC, OECD, CTCG) is available, but has shown in practice to be open for different interpretations.

The scope of this recommendation paper is to:
- share the common approach agreed, on the requirements regarding OECD GLP compliance of pivotal non-clinical data submitted to support a clinical trial application (CTA);
- provide transparency on regulatory acceptability for sponsors and test facilities, and other interested parties.

This document is fully compliant with Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and provides more in-depth clarification and guidance.

2. Clarification on EU requirements for acceptability of non-clinical data in support of CTAs

In accordance with article 25 (3) of the CTR, non-clinical information submitted in a CTA dossier shall be based on data derived from studies complying with Union law on the principles of GLP as laid out in Directive 2004/10/EC, as applicable at the time of performance of those studies.

Hence, all pivotal non-clinical safety studies submitted to support the CTA (i.e., studies identified in the relevant ICH guidelines, that support the non-clinical safety conclusions) need to be conducted in accordance with GLP. Those studies are accepted when conducted in test facilities that are part of the national GLP monitoring programme of an EU or MAD adherent country, and found to be in compliance with the OECD principles of GLP.

Generally, in a GLP monitoring programme, test facilities are periodically inspected for OECD GLP compliance. Ideally the test facility is part of a routine inspection programme prior to the study conducted to support the CTA. However, GLP compliance assessment is per definition a

[1] MAD adherents: OECD Members and non-Members who are full (and not provisional) adherents to the MAD act. In the context of this recommendation paper, this implies that pharmaceuticals must be within the scope of the GLP compliance monitoring programme. Country status can be verified with the following link: https://www.oecd.org/chemicalsafety/testing/contact-points-working-group-on-good-laboratory-practice.htm. Special note on EU MS: even if the EU MS is not an OECD member, studies conducted in all EU MS countries should be considered on the same basis as they have to implement a GLP compliance monitoring program according to EU regulation (Directive 2004/9/EC).

post-hoc assessment. A full inspection by a GLP compliance monitoring authority (CMA) within a period of 3 years after completion of the study(ies) is therefore considered appropriate, even in absence of prior inspections (ENV/JM/MONO(2019)25).

If the above principles are strictly applied (i.e., requesting an inspection following non-clinical study conduct and prior to the CTA), clinical development might be delayed. In addition, no clock-stops are foreseen during the procedure for assessment of a CTA, unlike a marketing authorization application procedure. Consequently, time-wise it is not feasible for the national receiving authority of a CTA to request and receive a study audit in order to assess OECD GLP compliance. Therefore, recent GLP studies completed up to 3 years after a successful full inspection can be considered acceptable to support a CTA.

Special attention should be paid to the following situations:

(1) A facility inspection, as opposed to a full inspection, does not include study audits. GLP claims on studies should therefore not be accepted when solely based on a facility inspection (ENV/JM/MONO(2019)25);

(2) OECD GLP compliance of a study can be claimed when the area of expertise[2] covered by a full inspection is relevant for the type of study under review. The fact that an area of expertise is declared as GLP compliant after a full inspection implies that one or more studies in this area of expertise have been audited by the GLP CMA during this inspection.

(3) If a test facility has been removed from the inspection programme, e.g. when it goes out of business, the GLP status of the studies completed by the test facility after the last successful inspection, is not confirmed.

To summarize, pivotal non-clinical safety studies submitted to support a clinical trial may be accepted when conducted in a test facility in an EU or MAD adherent country, that went through a full inspection by the relevant GLP CMA within 3 years before or after study completion.

Studies conducted at a test facility located in a non-MAD adherent country may be accepted if the test facility has been subject to a full inspection by an EU GLP CMA and found to be compliant at the time the data was generated[3]. The EU Working Group on GLP[4] (E01322) recognizes that inspections by EU GLP CMAs in these facilities are conducted with the same standard as inspections of a test facility in the EU and may therefore be considered valid, provided that the test facility has been acknowledged as being OECD GLP compliant during a full inspection 3 years before or after study completion (i.e. same criteria as described above for MAD adherent countries apply).

Although study audits cannot be requested during a CTA procedure, as explained above, it is possible that in exceptional cases an OECD GLP study audit is available even though a full inspection of the test facility, according to the conditions stated above, has not or not yet been carried out. Such a study can be accepted in a CTA when OECD GLP compliance is

[2] *Area of expertise according to OECD classification, summarized in Annex 3 of ENVIRONMENT MONOGRAPH NO. 110, Revised guides for compliance monitoring procedures for GLP; https://doi.org/10.1787/9789264078550-en*

[3] *EU MSs support the OECD MAD-adherence system. This possibility to accept non-MAD data should therefore be seen as a transitional measure until a non-MAD adherent country joins OECD MAD.*

[4] *https://ec.europa.eu/transparency/expert-groups-register/screen/expert-groups/consult?lang=en&groupID=1322*

confirmed and when the audit is conducted by a relevant GLP CMA: if the test facility is located in an EU or MAD adherent country, the study audit can be done by its national GLP CMA, while for a study conducted in a non-MAD country, the study audit should be conducted by an EU GLP CMA. Of note, a study audit (as opposed to a full inspection) is only relevant to the study under review in case that particular study was audited by the GLP CMA (ENV/JM/MONO(2019)2).

3. Practical considerations to ensure a harmonized approach among EU member states under CTR

- Information on GLP compliance needs to be provided in the CTA by the sponsor. As the CTA dossiers do not include individual study reports, sponsors should include a statement confirming the OECD GLP status of the studies or equivalent standards (i.e. principles of GLP recognized by other countries) preferably in an annex to the cover letter, as an acceptable alternative to inclusion in the Investigational Medicinal Product Dossier (IMPD) (as requested in Annex I point 44 of the CTR). Hence, a summary table needs to be provided, listing the pivotal non-clinical safety studies and indicating the following information for each study:

  (a) study title and study code (unique identifier assigned to the study by the test facility);

  (b) date of study initiation (signature by the study director of the study plan) and completion of the final report;

  (c) test facility and test sites at which the study was conducted, with complete addresses (including the country);

  (d) Indicate whether a full inspection of the test facility and test sites was carried out and concluded to be in compliance with OECD GLP for the area of expertise[2] relevant for the study type, up to 3 years before or after the final study report (Note that specific requirements apply to acceptable inspecting CMAs for studies conducted in non-MAD countries, as indicated in section 2 and in the template table). If not, deviations should be clarified in an annex to the table;

  (e) In the exceptional situation where OECD GLP compliance is supported only by a study audit as explained in section 2, the sponsor should clearly indicate this in the annex to the table and document the successful audit in the CTA, e.g. by providing a certificate or an audit report.

- Absence of or incomplete information will lead to a Request for Information (RFI) to the sponsor and, if not resolved, to the rejection of the CTA.

- If the investigational medicinal product (IMP) is authorized or has a marketing authorization in an ICH country and is used in the clinical trial within the conditions of the SmPC, the SmPC may serve as a simplified IMPD. In this case the lack of the table as described above is considered acceptable (Regulation (EU) No 536/2014, Annex I point 52).

Study title/ code	Test Facility(es) /test site(s) in which the study was conducted (name and complete address)*	Date of study start	Date of completion of the Final Report	For studies conducted in EU, OECD or fully MAD adherent countries: indicate (Y/N/NA) whether a successful inspection by its national GLP compliance monitoring authority took place within 3 years before or after final study report date*	For studies conducted in non-MAD adherent countries: indicate (Y/N/NA) whether the test facility and all test sites have been inspected and acknowledged as being OECD GLP compliant by an EU GLP compliance monitoring authority within 3 years before or after final study report date*

**Deviations should be clarified in annex to the table; NA not applicable.*

List of abbreviations

CMA: Compliance monitoring authority

CTA: Clinical trial application

CTR: Clinical Trials Regulation

CTCG: Clinical Trial Coordination Group

EC: European Commission

EU: European Union

GLP: Good Laboratory Practice

ICH: International Council for Harmonization

IMP: Investigational Medicinal Product

IMPD: Investigational Medicinal Product Dossier

MAD: Mutual Acceptance of Data

MAD adherents: OECD Members and non-Members who are full (and not provisional) adherents to the MAD act (see note 1)

MS: Member State

MSC: Member State concerned

NA: not applicable

OECD: Organization for Economic Co-operation and Development

RFI: Request for Information

RMS: Reporting Member State

References

- Guidance Document for Receiving Authorities on the Review of the GLP Status of Non-Clinical Safety Studies, OECD series on principles of good laboratory practice and compliance monitoring No 20, ENV/JM/MONO(2019)25
- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use
- Clinical trial regulation (EU) No 536/2014 Questions & Answers (question 1.19)