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Guidance Document for Receiving Authorities on the Review of the GLP Status of Non-Clinical Safety Studies

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GUIDANCE FOR RECEIVING AUTHORITIES ON THE REVIEW OF THE GLP STATUS OF NONCLINICAL SAFETY DATA

FOREWORD

At the 31st meeting of the OECD Working Group on Good Laboratory Practice (GLP) in March 2017, members agreed to establish a drafting group to investigate and, if necessary, develop a guidance document for Receiving Authorities on the verification of the GLP status of nonclinical safety test data submitted for regulatory purposes. ("Receiving Authorities" are the official government bodies who receive test studies and are responsible for the assessment and management of chemicals.) The drafting group under the leadership of The Netherlands (Dr Rob Jaspers) included representatives of Belgium, EU, Germany, India, Japan (Medical Products), Malaysia (Pesticides and Industrial Chemicals), Poland, Switzerland, United Kingdom and United States (Pesticides and Industrial Chemicals). Initially, members of the drafting group discussed an early proposal with their national Receiving Authorities and the European Medicines Agency (EMA), European Chemicals Agency (ECHA) and European Food Safety Agency (EFSA). The draft went through a few iterations, and it was agreed at the 33rd meeting of the Working Group in March 2019 – pending a few additional changes - and that it be distributed to the Joint Meeting for declassification under written procedure.

1. INTRODUCTION

National and European Union Regulatory Authorities (Receiving Authorities) evaluate nonclinical safety studies[1] submitted for the registration of industrial chemicals, human pharmaceuticals, veterinary medicines, pesticides, biocides, food and feed additives and other products. Nonclinical safety data serve as a basis for risk assessment to protect human and animal health and environment. In addition, nonclinical data are pivotal in the context of authorization of first-in-human as well as other clinical trials (i.e., phase III). To ensure the reliability, reproducibility and quality of data, many countries require that nonclinical safety studies should be conducted according to the OECD Principles of Good Laboratory Practice[2].

Thus, to ensure that nonclinical safety data submitted to a Receiving Authority are reliable, reproducible and of high quality, there should be a mechanism to verify their GLP status. Receiving Authorities play a crucial role in the verification of the GLP status of the submitted nonclinical safety data as part of their scientific review. Therefore, it is of paramount importance that assessors are aware of all requirements related to GLP compliance that can be evaluated during the review process of these data.

Receiving Authorities and GLP Monitoring Authorities (GLPMAs)[3] are separate organizational entities in many countries. For efficiency reasons, Receiving Authorities may address relevant aspects of GLP during their routine evaluation of submitted safety data without consulting the GLPMA. The current document aims to assist Receiving Authorities in this task.

2. SCOPE

The purpose of this document is to give guidance to Receiving Authorities on the evaluation of the GLP compliance status of nonclinical safety studies submitted for regulatory purposes. This guidance does not address the scientific evaluation and interpretation of the submitted data or the risk assessment based on these data.

This guidance for assessors in a Receiving Authority promotes an adequate and time-efficient evaluation of the GLP status of nonclinical safety data. If there is doubt on the GLP status of the data, the assessor should consult the relevant national GLPMA to discuss the impact and potential consequences of any GLP-related issues identified during the

[1] Nonclinical safety study: 'An experiment or set of experiments in which a test item is examined under laboratory conditions or in the environment to obtain data on its properties and/or its safety, intended for submission to appropriate regulatory authorities' (OECD Principles on Good Laboratory Practice, as revised in 1997 [ENV/MC/CHEM(98)17]).

[2] Principles of GLP as defined in national legislation/regulation of any OECD member or non-member that is a full adherent to OECD's Mutual Acceptance of Data (MAD) Council Acts, are considered as being equivalent to the OECD Principles of GLP. (For more information on MAD, see Section 3.1 below.)

[3] A GLP Monitoring Authority is a body established within an OECD Member or full MAD adherent country with responsibility for monitoring the good laboratory practice compliance of test facilities within its territories and for discharging other such functions related to good laboratory practice as may be nationally determined.

evaluation process before accepting GLP claims on the submitted data or requesting a GLP inspection and/or study audit.

The guidance aims to offer a step-wise approach of the GLP verification process. The implementation of this guidance is the responsibility of the Receiving Authority and may depend on, for example, requirements regarding the reporting format of the submitted data.

The verification of the GLP status is applicable to nonclinical safety data that, according to national legislation, must be generated in accordance with Principles of GLP and originate in a test facility that is subjected to compliance monitoring of its national GLPMA.

3. KEY CONCEPTS TO UNDERSTAND THE GUIDANCE

3.1 Mutual Acceptance of Data (MAD)

The OECD Council Decisions[4] on Mutual Acceptance of Data (MAD) define the conditions under which nonclinical studies, generated in an OECD member or full MAD adherent[5] country, must be accepted for regulatory purposes by Receiving Authorities in other countries:

a) The study must have been conducted according to OECD Test Guidelines and OECD Principles of GLP;

b) The study must have been conducted in a test facility which has been inspected by a national GLP compliance monitoring program, and

c) The national GLP compliance monitoring program must have undergone a successful evaluation by OECD[6].

OECD member and MAD adherent countries accept nonclinical safety data provided that the test facility is (1) located in an OECD member or full MAD adherent country, (2) inspected by a GLPMA that has undergone a successful OECD evaluation and (3) has been found to operate in compliance with GLP by the national GLPMA. In case of multisite

4 *Decision of the Council concerning the Mutual Acceptance of Data in the Assessment of Chemicals* C(81)30(Final) (with Annex I OECD Test Guidelines and Annex II The OECD Principles of GLP; the Principles of GLP are published as Number 1 of the OECD series on Principles of GLP and Compliance Monitoring); *Decision-Recommendation of the Council on Compliance with Principles of Good Laboratory Practice* C(89)87(Final) (with guidance for GLP monitoring authorities in Annex I and II, which are published as Number 2 and 3, respectively, of the OECD series on Principles of GLP and Compliance Monitoring); *Decision concerning the Adherence of Non-Member Countries to the Council Acts Related to Mutual Acceptance of Data in the Assessment of Chemicals* C(97)114(Final) concerning adherence of non-member countries to the Council Acts related to MAD.

5 Full MAD adherent countries are not members of OECD but are parties to the MAD system with the same rights and obligations as OECD members.

6 The status of countries National GLP Compliance Monitoring Programs which participate in MAD can be found here: http://www.oecd.org/chemicalsafety/testing/contact-points-working-group-on-good-laboratory-practice.htm

studies[7], this requirement applies to any test site[8] used in the study. Further details will be given below.

OECD member and MAD adherent countries are obliged to accept data from another country if a formal determination has been made that the country's GLP monitoring programme is implementing the 1989 Council Act on Compliance with the Principles of Good Laboratory Practice (C(89)87). (Please refer to the OECD public website to see which OECD members (and non-members) have undergone a successful evaluation.) The following scheme is suggested as a guide for countries (OECD, provisional and full MAD adherents) when data must be accepted from another OECD member or full MAD adherent country.

	When was the study completed?	Accept data from OECD member country that was evaluated?	Accept data from Non-member country/full adherent that was evaluated?
1	Before a successful OECD on-site evaluation was conducted	Voluntary[9]	Voluntary[9]
2	After a successful OECD on-site evaluation visit	Voluntary[9]	Voluntary[9]
3	On or after the date the Working Group on GLP concludes the country complies with the relevant Acts	Mandatory	Voluntary[9]
4	On or after the date the country signs a letter to the OECD Secretary General affirming it will adhere to MAD.	N/A	Mandatory

Claims of GLP compliance on nonclinical safety data need not to be accepted if the conditions (a), (b) and/or (c) listed above are not met, or acceptance of data is not mandatory. For example, if the study was conducted in a GLP compliant test facility but GLP compliance is not claimed by the study director for (part of) the study; or the study was carried out in an OECD member or full MAD adherent country but the GLP status of the test facility and/or test site(s) was never verified by the national GLPMA. Another example that may prevent acceptance of data would be if the study, or part of the study in case of a multisite study, were conducted in a non-OECD or non-full MAD adherent country or in an economy that is a provisional MAD adherent.

[7] A multi-site study means any study that has phases conducted at more than one site.

[8] Test site: A location, identified by name and address, at which a phase of a study is conducted; test site management is responsible for GLP compliance of that location.

[9] Consult with GLPMA in the country if necessary.

3.2 Monitoring GLP Compliance

OECD member and MAD adherent countries recognise the results of GLP compliance monitoring inspections of other members and full adherents. To inform each other of the results of their inspections, GLPMAs of OECD members and full MAD adherents issue an annual overview of inspected test facilities and their compliance status. The annual overviews of monitoring programmes that have undergone a successful evaluation are published on a *password protected* website of OECD and are also available for Receiving Authorities (please contact the national GLPMA to gain access to this website). Consultation of the annual overviews allows a Receiving Authority to verify the GLP status of a test facility without the need to contact the GLPMA. In case of multisite studies, this would also apply to any test site used in the study.

3.3 Claiming GLP Compliance

The study director should indicate in the final study report the extent of compliance of the reported data with the OECD Principles of GLP in the study director's statement. A claim to GLP constitutes any claim of having conducted the study in accordance or compliance with the OECD Principles of GLP (or using any other expression with the same meaning). Less stringent claims (for example 'study conducted in the spirit of GLP', or 'study conducted in a GLP environment') may raise doubt as to the GLP status of the study. A claim of GLP compliance should also extend to phases of a study conducted at other (remote) test sites. The Receiving Authority may assess relevant aspects of the GLP compliance of the submitted data by, for example, checking the study director's claim of GLP compliance in the study report as part of their routine data evaluation process. Further details will be given below.

4. VERIFICATION OF THE GLP STATUS OF SUBMITTED DATA

This guidance is based on the assumption that the Receiving Authority has direct access to (1) the OECD password-protected website of annual overviews of GLPMAs (or access to this information via the national GLPMA) and (2) the complete final study reports of the relevant nonclinical safety studies. If study reports are not available for review, the Receiving Authority may have to explore alternatives such as verification of summarized information submitted by the applicant, to verify the GLP compliance status of the submitted data[10]. Some Receiving Authorities require the verification of the GLP status of all submitted studies claimed to be GLP compliant whereas others have adopted a risk-based approach to conduct the verification. If in doubt, the national GLPMA should be consulted.

It is recommended to first verify the compliance status of the test facility and, if applicable, any test site used in the study (see Section 4.1). Once this has been confirmed the compliance status of the submitted data should be verified (see Section 4.2).

[10] For example, in the framework of clinical trial applications in Europe; see Q&A on GLP, 2017 (EU CTFG): http://www.hma.eu/ctfg.html

4.1 Verification of GLP compliance status of a test facility or test site

Annual overviews of inspections conducted by GLPMAs that are recognized by all OECD member and full MAD adherent countries are available on the password-protected website of the OECD. Annual overviews of GLP monitoring programs of non-OECD members or provisional adherent countries that have not (yet) been evaluated are not included on this website.

Only the results of inspections conducted by a GLPMA in an OECD or full MAD adherent country that are conducted within that GLPMA country are binding for all members and MAD adherents. GLPMAs of some OECD member or full MAD adherent countries also conduct inspections of facilities in non-member/non full adherent countries. However, such inspections are not covered by the MAD system and therefore other OECD members and MAD adherent countries are not obligated to accept the studies. This also holds true for test sites located in non-member countries and used in multisite studies. Finally, results of inspections conducted by a GLPMA of a non-OECD member or provisional MAD adherent country are not binding and acceptance of GLP claims on data is not mandatory.

Most GLPMAs operate a program of routine full inspections (test facility inspections including study audits) conducted every two to three years. However some GLPMAs may not routinely inspect all test facilities in their country on a two to three year cycle (for example, GLP inspections may be triggered by data submitted to a national Receiving Authority). For that reason, information on the GLP status of a specific test facility or test site in some countries may not always be available (see section 4.3 for next steps that should be taken).

GLPMAs may issue a declaration confirming the test facility's adherence to the Principles of GLP following a full inspection. Although such declarations may be used by Receiving Authorities to verify the GLP compliance status of a test facility, it is recommended to consult the annual overviews on the OECD protected website as a final proof to confirm the status. Please note that some GLPMAs do not issue such declarations.

Annual overviews are presented on the protected website in several tables each containing overviews over a 5 to 6 year period. Receiving authorities should select the annual overview of the country in which the test facility or test site is located. In case there is more than one monitoring program in a country, the overview relevant for the test item under review should be selected (e.g., the overviews of the GLPMA covering pharmaceuticals, industrial chemicals, pesticides, etc.). Usually the most recent annual overview will include information on recent as well as historic inspections. If annual overviews from before 2005 are required these can be requested from the relevant GLPMA (please first consult your national GLPMA, if applicable).

When consulting the annual overviews the following information concerning the test facility and, in case of multisite studies, additional test site(s), should be checked in relation to the study report under review.

a. Test facility:
   - Verify the name and address of the test facility and, in case of multisite studies, test site(s) as mentioned in the study report.
   - If the test facility (or, if applicable, test site) is not mentioned, or the address is not similar to the one mentioned in the study report, the GLP status cannot be confirmed.

b. Date of inspection:

- Verify that an inspection (full or re-inspection, see below) relevant for the study under review was carried out. Inspections may have been concluded successfully before and/or after the study under review was carried out.
- Most GLPMAs would consider an inspection conducted up to three years after completion of the study as relevant for the study under review.
- Some Receiving Authorities may require the test facility and, if applicable, additional test sites, to have been inspected and found to operate in compliance with GLP prior to the performance of the study.
- If no relevant inspection is mentioned, the GLP status cannot be confirmed.
- If a test facility has been removed from the inspection program the GLP status of the test facility after the last successful inspection is not confirmed.

c. Status:

- Verify the GLP compliance status of the test facility or test site.
- IC - 'In Compliance'. GLPMA confirms that the test facility/test site operates in compliance with GLP. Studies may be accepted.
- PEN - 'Pending'. 'Pending' is explained as a 'Remark' in each annual overview. Please note that some GLPMAs recommend not accepting GLP claims on studies conducted in a test facility with a pending status (see annual overviews). For further information, the GLPMA should be consulted.
- NIC - 'Not in Compliance'. The GLPMA considers the test facility/test site not to operate in accordance with GLP. Studies conducted at the test facility/test site cannot be regarded as GLP compliant. Study reports may not be used for regulatory purposes. In case a test facility has passed an inspection at an earlier stage, GLP claims on studies completed since the last 'successful' inspection should not be accepted.
- RFP – 'Removed from program'. The test facility has been removed from the inspection programme. The date and reason for removal may be explained as a remark. GLP claims on studies conducted after the last successful inspection should not be accepted.

d. Nature of inspection:

- Verify the relevance of the reported inspection for the study under review.
- Full inspection; this inspection also includes study audits.
- Re-inspection; this inspection may also include study audits.
- Study audit; may only be relevant to the study under review in case that particular study was audited by the GLPMA.

- Facility inspection; this inspection does not include study audits and, therefore, the compliance status of studies is not confirmed. GLP claims on studies should not be accepted.

e. Area(s) of expertise:

- Verify that the area(s) of expertise[11] covered by the inspection is/are relevant for the type of study under review.

1) Physical-chemical testing: physical or chemical properties; e.g., see OECD Test Guidelines[12] (TG) series 100.

2) and 3) Toxicity and mutagenicity studies, respectively: toxicological properties; e.g., see TG series 400.

4) Environmental toxicity studies on aquatic and terrestrial organisms: environmental properties; e.g., see TG series 200.

5) and 7) Studies on behaviour in water, soil and air; bioaccumulation and studies on effects on mesocosms and natural ecosystems; e.g., see TG series 300.

6) Residue studies: residues and metabolism in life stocks, crops, field studies; e.g., see TG series 500.

8) Analytical and clinical chemistry testing (used in a number of TG and in various types of studies).

9) Other studies (specified);

- In case the relevant area of expertise for the study under review is not mentioned in the annual overview, the GLP status of the test facility or test site may not be confirmed for that particular expertise. Some Receiving Authorities may not accept studies if the relevant area of expertise is not covered by the GLPMA.

f. Remarks:

- Information on changes in name and/or address, information on non-GLP compliant studies, pending status, etc.

In most cases, the information on the test facility or test site in the annual overview will confirm the GLP status in relation to the data submitted to the Receiving Authority. In other cases, the review of the annual overview may raise questions regarding the compliance status of the test facility or test site. For example, a different address, 'pending' status, missing area of expertise, or incongruent date of inspection vs. period in which the study under review was carried out. Finally, the compliance status might not be known because the test facility or test site was never inspected, for example in case there is no GLP monitoring program of periodic inspections.

[11] Areas of expertise as defined in the Appendix to Annex III of C(89)87(Final).

[12] http://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm

Where the GLP status of the test facility or test site cannot be confirmed, GLP claims on the submitted data should not be accepted. The Receiving Authority is recommended to consult the relevant national GLPMA to discuss the next steps. Where necessary the GLPMA will contact its counterpart in the country where the study was carried out to confirm or update the information in the annual report. Based on the collected information the GLPMA will advise the Receiving Authority.

4.2 Verification of GLP-related aspects of a study report

A final study report should be prepared for each individual study following the requirements as defined in the Principles of GLP in order to ensure that all relevant information is included and presented in a harmonized way for an adequate review by the Receiving Authority. Interim study reports may not include all relevant information and may change during finalization. They may not, therefore, be suitable for regulatory purposes. However, some Receiving Authorities require interim reports to be submitted as part of a chemical review process. Where this is required, the interim reports should also comply with GLP.

A final study report is unique for each study and should include (at a minimum):

a. Name and full address of test facility, test site(s), sponsor, study director and, if applicable, principal investigator(s) and contributing scientists.
   - This allows for verification of the compliance status of the test facility. The compliance status of any test site used in a multisite study should also be verified (see Section 4.1).

b. Full identification and characterization of the test item and reference item including expiry date and information on the purity, composition, homogeneity and concentration, as well as data on the stability, concentration and homogeneity when applied in a vehicle to the test system.
   - The origin of this information (e.g. based on in-house analyses, derived from sponsor or supplier, etc.) should be indicated.
   - The validity of the reported data may be jeopardized if the nature of the test and reference items cannot be verified from the available information on the identification and characterization. In that case, the GLP compliance claim on the study should not be accepted and the Receiving Authority may consider rejecting the data for regulatory purposes.

c. Experimental starting and completion dates, and study completion date[13].
   - This information should be used to verify the compliance status of the test facility and, if applicable, test site(s) at the time the study was carried out.

[13] Study completion date: Date on which the final study report is signed by the study director.

d. The final study report should be signed and dated by the study director and should include a GLP compliance statement from the study director indicating the extent of GLP compliance including compliance of any study phase conducted at a test site, if applicable. The claim of compliance does not equate to any guarantee of verification by a GLPMA. For that reason the GLP status of the test facility and, if applicable, test site(s) should be checked (see Section 4.1).

   - Any portion of the study not conducted in compliance with GLP should be identified in the GLP compliance statement of the study director.
   - The impact of any non-compliant phase of the study should be indicated.
   - In case a non-compliant phase of a study jeopardizes the GLP status of the whole study, the Receiving Authority may consider rejecting the data for regulatory purposes.

e. A signed statement of quality assurance listing the types and dates of inspections and dates of reporting to test facility management, study director and, if applicable, test site management and principal investigator.

   - The quality assurance statement should reflect that the conduct of the study was adequately covered by quality assurance inspections of study conduct and should confirm that the report reflects the raw data.
   - In case the information in the quality assurance statement is incomplete, the GLP compliance status of the study is jeopardized and the Receiving Authority may consider rejecting the data for regulatory purposes.

f. A description, in sufficient detail, of the methods and materials including references to test guidelines, if applicable.

   - The description should provide sufficient information to verify the adequacy and correctness of the methods and materials used for the study.
   - Incomplete description of the methods and materials jeopardizes the GLP compliance status of the study and the Receiving Authority may consider rejecting the data for regulatory purposes.

g. Summary as well as full description of all results including calculations and statistical evaluation, if applicable.

   - Incomplete description of the results jeopardises the GLP status of the study and the Receiving Authority may consider rejecting the data for regulatory purposes.
   - Inconsistent results, unexpected variability or data that do not seem to be in line with other scientific sources may also raise concern about the GLP compliance status of the study.

h. Presentation of deviations from the study plan, if applicable.

- Deviations from the study plan should be identified as such in the study report.
- The impact of deviations on the validity of the data should be discussed by the study director.
- Whilst deviations are not always indicative of a poorly planned or executed study, they may raise concerns about the GLP compliance status of the study. The impact of any deviation should be assessed.

i. Evaluation and discussion of the results and, where appropriate, conclusions.

- Unrealistic explanations or interpretations of the data may raise concern about the GLP compliance status of the study.

j. Storage location of all study related documentation and materials including study plan, samples of test and reference items, specimen, raw data and study report.

k. Corrections and additions to a study report should be written as report amendments. The reason for corrections and/or additions should be explained and should be signed and dated by the study director. Finally, it is expected that a report amendment also include a quality assurance statement.

Incomplete information on one or more of the above-mentioned items may affect the GLP compliance status of the submitted data. In case of concern, the Receiving Authority should consult its national GLPMA to discuss any issues related to the GLP status of the study data and decide on the next steps.

4.3 Follow-up in case of concern about the GLP compliance status

If there is any concern about GLP-related aspects of the submitted data, the Receiving Authority should contact the national GLPMA of its own country. European Receiving Authorities should contact a relevant European GLPMA.

The Receiving Authority may request:

a. Information on the test facility or test site(s). For example: if the test facility or test site is not listed in the annual overviews; the name and/or address is different from the information mentioned in the study report; no relevant inspection is listed; the compliance status is not given as ‘in compliance’; or the relevant area of expertise is not indicated.

If a test facility or test site is located in another OECD member or full MAD adherent country, the national GLPMA will contact the responsible GLPMA in the country in which the test facility/test site is located to update, if possible, the missing information.

b. A study audit if the GLP status of the test facility and, if applicable, test site(s) could not be confirmed (see Section 4.1). Where a test facility or test site is located in another OECD member or full MAD adherent country, the GLPMA will contact its counterpart in that country to conduct the study audit. To ensure that relevant

data are reviewed, the GLPMA will decide together with the requesting Receiving Authority on the extent and depth of the study audit.

c. A study audit if the test facility is located in a non-OECD member or non-full MAD adherent country. The Receiving Authority should contact its national GLPMA to discuss options of such a study audit taking into consideration information, if available, on inspections of the test facility conducted by a GLPMA of an OECD member or full MAD adherent country. If applicable, the GLPMA will decide together with the requesting Receiving Authority on the extent and depth of the study audit. Some Receiving Authorities may decide to reject the data without any study audit if the test facility is located in a non-OECD member or non-full MAD adherent country.

d. A study audit if there is a need to verify the GLP status of the study data because the information in the report raises concerns (see Section 4.2). This may be requested even if the test facility was inspected and found to be in compliance with GLP. In case of a test facility or test site located in another OECD member or full MAD adherent country, the GLPMA will contact its counterpart in that other country to conduct the study audit. The Receiving Authority should provide any details on the concerns that need to be addressed during the audit.

e. Reports of the inspection of the requested study audits and the conclusions of the GLPMA on the GLP compliance status of the submitted data (please note some GLPMAs may not be able to draw a formal conclusion on the GLP status of the reviewed data due to legal restrictions).

Based on the outcome of the study audit the GLP claim on the submitted data may be accepted or, in case of non-compliances, rejected. Where the GLP claim on the study cannot be accepted, the Receiving Authority may consider rejecting the data for regulatory purposes.

5. CONCLUSION

Compliance with the Principles of GLP for nonclinical safety studies provides assurance of the quality and reliability of the submitted data and the validity of the results. For that reason, national regulations/legislations in many countries mandate GLP compliance for such studies when they are used for regulatory purposes and risk assessment to protect human and animal health and the environment. Communication between Receiving Authorities and GLPMAs is crucial in the evaluation of the GLP status of the submitted data.

The Receiving Authority ultimately remains responsible for the evaluation of the submitted nonclinical safety data and for taking decisions on the acceptance of such data based on the scientific evaluation and taking into account the GLP-related information regarding the submitted study report and the test facility (and, if applicable, test sites) at which the study was carried out.