

GOOD LABORATORY PRACTICE

UK GLPMA POLICY ON THE USE OF NON-GLP FACILITIES FOR THE CONDUCT OF STUDY PHASES.

Introduction

The information provided in this document is designed to supplement the guidance detailed within Section 4, Parts 1-12 of the Guide to UK GLP Regulations 1999.

The GLP regulations require that regulatory studies are conducted in compliance with the principles of GLP. For a study to be fully GLP compliant, all individual parts of that study must themselves be conducted in compliance with GLP.

The GLPMA recognises that, in exceptional circumstances, it may be necessary for part of a regulatory study to be conducted by a non-GLP facility, i.e. a facility that is not a member of a GLP compliance monitoring programme that is recognised by the OECD GLP Working Group (Refer to the OECD web site for more information or contact GLP@mhra.gsi.gov.uk).

This document considers two specific situations:

- Where there is an intention not to claim GLP compliance for part of a regulatory study.
- Where a test facility extends compliance to a non-GLP site that is conducting part of their GLP study.

Excluding work or the extension of GLP compliance for commercial and financial reasons or as a matter of convenience is unlikely to be acceptable.

This guidance in the main document only applies to the use of test facilities that have a permanent physical presence, i.e. organisations with premises, equipment and their own staff. It does not apply to field trial sites. Further guidance on the use of non-GLP facilities and staff to: characterise a test item, conduct formulation analysis, undertake field trials or target animal safety studies is given in the appendix of this document.

Intention to conduct part of a regulatory study in a non-GLP Facility.

The intention to conduct part of a GLP study in a facility that is not a member of its national compliance monitoring programme should not be undertaken lightly regardless of whether there is an intention to make a claim of compliance for that aspect of the study.

There is a clear statutory requirement for regulatory studies to be conducted in compliance with GLP principles. Consequently, any study phase(s) that cannot be conducted by the test facility (i.e. the study director's organisation) should be subcontracted to facilities that are themselves members of their respective national GLP compliance monitoring programmes whenever possible. If it is not possible to identify a GLP compliant facility that can undertake the necessary work, then the use of a non-GLP facility can be considered.

Test facility management, in consultation with the study director and quality assurance personnel, must consider and justify what constitutes a good reason to conduct part of a regulatory study in a non-GLP

facility. These decisions should be made on a case by case basis and the justification fully documented.

If relatively simple non-critical study phases will be conducted by non-GLP facilities, then the most appropriate course of action might be to exclude this work from the study director's claim of GLP compliance. If the work is critical to the study outcome and the interpretation of the results of the study then it may not be appropriate to exclude the work as to do so would compromise the compliance of the study as a whole.

When considering use of a non-GLP facility to perform part of a GLP study, since the study director has overall responsibility for the GLP compliance of the study he/she should ultimately make the decision on what is critical to the study outcome and objectives.

Intention not to claim GLP compliance for part of a regulatory study

If part of a regulatory study cannot be conducted in accordance with the principles of GLP it may be appropriate to exclude the work from the study director's claim of compliance. Test facility management, in consultation with the study director and quality assurance personnel, must consider and justify what constitutes a good reason for this. These decisions should be made on a case by case basis and the justification fully documented. It will always be necessary to consider the impact that the exclusion of the work will have on the overall interpretation of the results of the study.

The intention not to conduct part of a regulatory study in compliance with GLP should be carefully considered because the decision could compromise the GLP status of the whole study (for example where the data is critical to the interpretation of the study) and depending on the nature of the work could constitute an offence under the GLP Regulations.

On completion of a GLP study the study director is required to make a statement in the final report indicating the extent to which the study complies with the principles of GLP. This statement must clearly and unambiguously identify any phases or activities for which no claim of GLP compliance is made. Additionally, the non compliant work must be identified in the study plan and the narrative of the final report.

There is no longer a requirement to inform the GLPMA of a decision not to claim GLP compliance for part of a regulatory study. However, as part of routine monitoring inspections, GLPMA inspectors are likely to request information on the volume and nature of work which has been excluded from claims of GLP compliance. Consequently, it would be appropriate to ensure that records are maintained which identify studies with partial claims of GLP compliance.

Intention to make a full claim of GLP compliance for work undertaken by a facility which is not a member of a national GLP compliance programme

The intention to make a full claim of GLP compliance for work undertaken by a facility which is not a member of a national GLP compliance programme should not be undertaken lightly and should only be embarked upon in exceptional circumstances.

The GLPMA has established a mechanism whereby a non-GLP facility might perform work for which GLP compliance may be claimed by the study director. The "Guide to UK GLP Regulations 1999" gives advice on this situation {section 4.- (9) paragraphs (a) to (f)}. This extension of a test facility's GLP compliance can only be applied to the work from a specific study, and cannot be used to confer GLP

compliance on the non-GLP facility on an ongoing basis. It should be noted that if a request is submitted to the GLPMA to extend compliance to a non-GLP facility located in a country that is a full member of the OECD GLP Working Group, then the Monitoring Authority of the country concerned must also give their consent to the proposal. The GLPMA will contact the Monitoring Authority directly and include any additional comments in their response to the application.

The GLPMA has legal authority to monitor all facilities that undertake work that constitutes a regulatory study or part thereof. Therefore, if there is an intention to claim GLP compliance for work conducted at a non-GLP facility (located in the UK or overseas) the GLPMA should be notified in advance of the work being conducted, using the form available on the GLP website. Notifications must be made on a study specific basis. Once completed the form should be sent to the GLPMA mailbox at GLP@mhra.gsi.gov.uk

The GLPMA will acknowledge receipt of all such notifications. If the GLPMA is satisfied with the proposed arrangements the submitter will be informed of this decision. Should the GLPMA have any queries or concerns, or require additional information, then the submitter will be contacted directly.

Study Directors should be aware that work must not be conducted at a non-GLP facility before GLPMA approval has been obtained if GLP compliance is to be claimed for that work. Failure to do so could result in the GLP compliance status of the study being compromised, and the commission of a “false instrument” offence at the study reporting phase.

General Guidance

Adequacy of facility

At an early stage and before naming the non-GLP facility in the study plan, the study director should confirm that this facility, and their staff, has the necessary equipment, premises and technical competence to enable them to undertake the work required.

The quality of the work conducted within the non-GLP facility should be determined, For example, does the facility work to another recognised quality standard? To gather this information it might be necessary for the study director to visit the site, ideally accompanied by quality assurance who can assess data quality and GLP compliance aspects.

If it is determined that the facilities and equipment are not adequate and technical competence is lacking then the facility should not be used. If the data quality falls far below GLP standards then the facility should not be used.

If the outcome of this assessment is that the facility in question is able to perform the work, and data quality appears to be of an acceptable standard, then the use of this facility might be considered.

Monitoring of work in progress when conferring compliance

The purpose of this monitoring is to assess whether, or not, conduct of the work does in fact comply with the applicable principles of GLP.

In order for the study director to be assured that the work concerned was in fact conducted in compliance with the applicable principles of GLP, it should be monitored by the study director’s organisation whilst it is in progress. As a minimum, performance of the work should be monitored by quality assurance, but, it is strongly recommended that the study director should also be present to monitor critical phases of the work because they will be making the final claim of compliance for that

work. Each piece of work conducted by the non-GLP facility must be monitored in this way. The study director's test facility cannot monitor the non-GLP facility on one occasion and assume that any future work is of the same standard. This applies equally to work from separate studies, or analysis of different samples from the same study if it will be conducted on separate occasions. The extent of monitoring by the study director and quality assurance should be described (in detail) in the notification sent to the GLPMA.

Any relaxation of monitoring requirements, i.e. that applied to multiple samples sent to the same non-GLP facility over a prolonged period as part of the same study, must be agreed in advance by the GLPMA.

Study director statement

It is essential that the study director statement contained within the final report provides a complete and accurate assessment of the GLP compliance of the entire study.

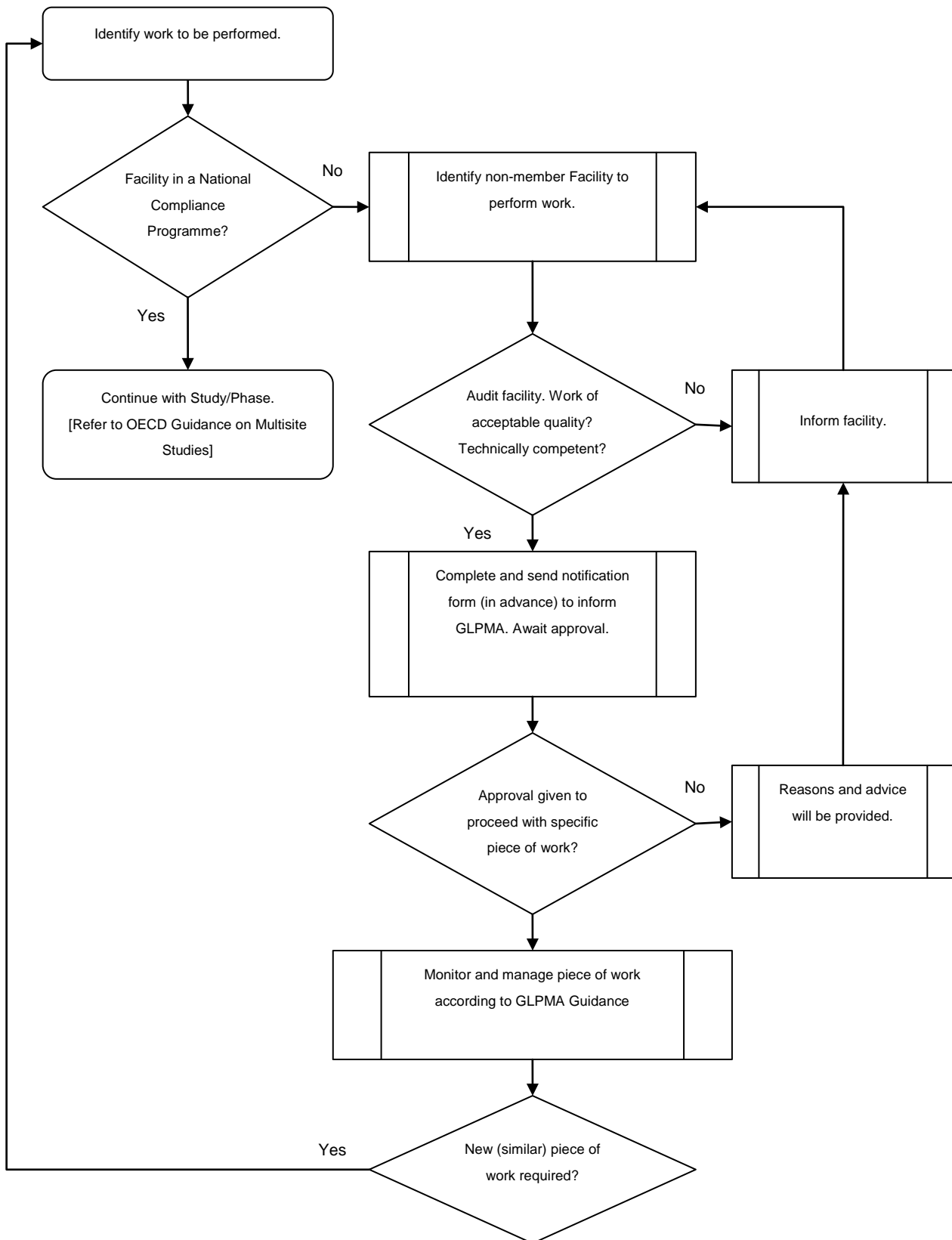
If a non-GLP facility has performed any work on the study then the study director should make this clear in their statement and justify why they consider that the data generated by this non-GLP facility is acceptable.

GLPMA monitoring

The GLPMA may wish to monitor work for which compliance is conferred to a non-GLP facility. In this event, the GLPMA would liaise with the study director's organisation to arrange the inspection. Any such inspection would be conducted in accordance with current GLPMA procedures. Any GLP deficiencies identified by the GLPMA would be reported to the management of the study director's test facility as they, and the study director, have legal responsibility for the work being conducted by the non-GLP facility.

The GLPMA monitors the notifications received and is therefore able to identify those non-GLP facilities that are undertaking significant amounts of work from regulatory studies. Depending on the specific circumstances, these facilities might be required to become members of the UK GLP Compliance Programme.

Appendix 1: Intention to make a full claim of GLP compliance for work undertaken by a facility which is not a member of a national GLP compliance programme.



Appendix 2 Field Trial

When conducting some field trials it will usually be necessary to use agricultural facilities such as field plots, orchards, horticultural facilities such as greenhouses, polytunnels, or farming units such as cattle sheds and fish farms etc. The following examples should assist in determining whether or not the GLPMA should be notified.

Scenario 1: A pesticide residue study using defined plots within a larger field of a commercially grown crop. Key study activities will be performed by (GLP) test facility personnel.

This is the most common type of field trial. The whole field of commercial crop, including the test plots, will be subject to normal pesticide and fertiliser application by the farmer. All applications of test item to the test plots, and subsequent harvesting of the agricultural commodity is performed by personnel from the GLP compliant test facility. In this situation, all key study activities are performed by personnel from the GLP test facility using their own equipment. The GLPMA does not need to be notified of the use of such field sites. The situation is the same when using a number of fruit trees or bushes within a larger commercial stand, or the use of test plots within normal commercial greenhouses or 'polytunnels'.

Scenario 2: A pesticide residue study using defined plots within a larger field of commercially grown crop. Some key study activities (e.g. application or sampling) will be undertaken by persons not working for the test facility.

In contrast to scenario 1 above, the GLP compliant test facility will need to extend its compliance to cover the critical study activities undertaken by these 'non-GLP' persons. This would include e.g. appropriate training and monitoring by the study director and/or quality assurance. In these circumstances the GLPMA should be informed of the work to be performed by such persons.

Scenario 3: A pesticide residue study using defined plots within a larger field of commercially grown crop. Key study activities will be performed by (GLP) test facility personnel, but additional processing of the raw agricultural commodity will be conducted by persons not working for the test facility.

The use of the field plots would not need to be notified to the GLPMA, but the use of processing facilities where harvested commodities are treated to prepare other items such as juice, sauce etc. would normally need to be notified. This is because the premises, equipment (and possibly staff) at a non-GLP facility will be used to conduct important study activities that could affect study outcome.

Scenario 4: Veterinary residue trial in farm animals

Such trials are usually conducted in animal facilities belonging to the GLP compliant test facility. However, there may be studies that require a larger number of animals than can be accommodated in their own animal facilities, and therefore it becomes necessary to utilise the premises of commercial farms. The intended use of these premises should normally be notified to the GLPMA since the design, construction and use of the cowsheds could impact on the conduct of the study. Also, it is likely that in these situations farm staff will be undertaking routine husbandry activities such as feeding and so will be responsible for generating data that will be used in the final study report.

The situation would be the same if using commercial fish farms when it is necessary to house a large number of fish, or to use fish of larger sizes that cannot be handled in a GLP compliant laboratory.

Scenario 5: Trials requiring the use of specialised facilities

Where specialised facilities are necessary to conduct a field study, these will usually need to be notified to the GLPMA since they will consist of premises and equipment belonging to another organisation, and due to the specialised nature of the work, it will often be performed by staff from the non-GLP organisation. Examples of specialised facilities notified to the GLPMA have concerned potato fogging, chestnut fumigation and seed treatment.

Scenario 6: Operator exposure studies

In these studies, operators at commercial farms conduct routine pesticide applications using their own (farm) equipment and following normal (farm) procedures. Indicators, including cloth samples or swabs from the clothing or skin of the operator, are taken by the GLP compliant test facility for subsequent pesticide analysis. Sampling is performed by test facility personnel, and subsequent analyses are conducted within the GLP test facility, and so the GLP compliance status of this work is clear.

The intention of the study is to obtain representative exposure data from 'ordinary' farm hands following standard agricultural practice; making them follow more defined (GLP) procedures would compromise the validity of the results obtained. For this reason the actual pesticide preparation and application procedures must be conducted by farm staff using farm equipment and according to their established practice. This requirement should be clearly stated in the study plan, and should be verified by the study director during their monitoring of the work.

The GLPMA would usually expect to be notified of the use of a non-GLP facility (a commercial farm) to perform critical study activities such as the preparation and application of pesticides. However, given the intended purpose of these studies, the GLPMA has adopted the position that it does not need to be notified of the use of non-GLP facilities when they are engaged solely in the preparation and application of pesticides as part of operator exposure studies. The final report should provide additional information concerning how these activities were conducted (and controlled) and the study director should provide a justification why they consider that the data obtained are valid for the purposes of risk assessment.

Appendix 3 Test item formulation analysis and characterisation

Formulation Analysis

Even when there is no specific requirement for formulation analysis in a test guideline (OECD, ICH etc.), the OECD Principles of GLP require that if a test item is administered or applied in a vehicle the homogeneity, stability and concentration of the test item in the vehicle should be determined. Consequently, this information should be generated as part of a GLP study if the study director intends to make a full claim of GLP compliance, regardless of whether or not it is specifically required by a test guideline.

In some instances, and particularly when testing pharmaceuticals, a study director may receive a formulated test item that has been supplied by a facility that works in compliance with the principles of GMP (Good Manufacturing Practice). In these cases it would be acceptable for the GMP facility's own laboratory or an associated GMP contract laboratory to determine the homogeneity, concentration and stability of the formulation. In such circumstances, the study director has a responsibility to assess the extent of which the laboratory complies with GMP and whether they have been subject to a GMP inspection by an appropriate regulatory body. The study director must also indicate in their statement within the final report that the work was performed in accordance with the principles of GMP, however there is no need to notify the GLPMA.

Test item Characterisation and GLP compliance

Although there is no requirement to characterise the test item in a GLP compliant test facility, it would not be acceptable to conduct a GLP study on a test item where no information has been provided.

The GLP Principles state that information relating to a test item's identity (code, CAS number, name etc) and characteristics (batch, purity, composition etc) should be known and that records relating to expiry date and quantities received and used should be maintained (Schedule 1, Part VI 1.- and 2.-). In addition the GLP Principles stipulate that the study director and their test facility management have a responsibility to establish a mechanism by which the identity of the test item can be verified (Schedule 1, Part VI, 2.-(3)). If the sponsor is determining the test item characteristics, this information should be made available to the study director, but there is no need to notify the GLPMA.

The study director should be satisfied that the information has been generated in a facility where the results obtained are considered to be accurate and reliable. To conduct a GLP study on a test item where the study director and their facility take no responsibility for verifying the identity and nature of the test item is not acceptable. For example, a claim in either the study plan or the report that "The Sponsor is responsible for the characterisation of the test item" is not acceptable.

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REVIEWED JANUARY 2015