Good Laboratory Practice (GLP) Compliance Programme

GLP 01 - Procedures and Conditions for GLP Registration

GLP 01 – 21 November 2019
The GLP compliance Programme is managed by Enterprise Singapore

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1. Introduction

1.1 The Singapore Good Laboratory Practice (GLP) Compliance Programme was launched in November 2006. The Programme aims to support research work in Singapore for generation of high quality and reliable test data related to the safety of chemical substances and preparations.

1.2 The GLP Compliance Programme is available to any facility undertaking non-clinical health and environmental safety studies. The Programme will support studies that are required by local or overseas regulations for the purpose of registering or licensing for use of pharmaceuticals, pesticides, food & feed additives, cosmetics, veterinary drug products, industrial chemicals and similar products. The Programme also covers medical devices.

1.3 Having been peer-evaluated by an evaluation ream from the Organisation for Economic Cooperation and Development (OECD) in 2009 and demonstrated full adherent to the OECD requirements, Singapore became a full member of OECD Mutual Acceptance of Data (MAD) system in January 2010.

SECTION A : REGISTRATION PROCEDURES

2. Organisation Structure

2.1 Enterprise Singapore (then SPRING Singapore) has been appointed by the Ministry of Trade and Industry as the National GLP Monitoring Authority. The role of the GLP Monitoring Authority has been delegated to the Singapore Accreditation Council (SAC).

2.2 As the GLP Monitoring Authority, SAC will administer the GLP Compliance Programme and register test facilities that meet the OECD Principles of Good Laboratory Practice and represent Singapore internationally in OECD committees and working groups.

2.3 SAC has established a Council Committee for Biomedical & Health (CCBH) and a Technical Committee for GLP comprising of various stakeholders such as regulators, industry associations, tertiary and research institutions, and GLP practitioners to provide guidance on the operation of the Programme.

2.4 SAC will maintain a pool of inspectors for inspection of test facilities. They hold appropriate qualifications in various disciplines in science and technology, and are experienced in quality system operation and inspection. Where required, technical expert(s) may be appointed to the team to assist the GLP inspection team for a particular expert area. The expert(s) will provide his/her opinions and recommendations to the team for consideration. Technical experts are chosen for their expert knowledge and experience, and they may

be drawn from the government laboratories, academic and research institutions, and industrial organisations in Singapore and overseas.

2.5 Members of the SAC Council, Council Committee for Biomedical & Health, Technical Committee for GLP, Review Committees and inspectors considered to have commercial, financial or other pressures or conflicts of interest that might cause them to act in other than an impartial or non-discriminatory manner shall not be involved in the inspection and evaluation of a test facility.

3 Operational Standards

3.1 The GLP Compliance Programme is administered in accordance with the relevant requirements of ISO/IEC 17011*: 2017 Conformity assessment – Requirements for accreditation bodies accrediting conformity assessment bodies* and the following OECD Series of documents :

- **Number 2** : Guidance for GLP Monitoring Authorities – Revised Guidelines for Compliance Monitoring Procedures for Good Laboratory Practice (Monograph no. 110)
- **Number 3** : Guidance for GLP Monitoring Authorities – Revised Guidance for the Conduct of Laboratory Inspections and Study Audits (Monographs 111)
- **Number 9** : Guidance for GLP Monitoring Authorities – Guidance for the Preparation of GLP Inspection Reports (Monograph No. 115)
- And any other relevant documents published by OECD from time to time

3.2 Test facilities registered as being GLP compliant are assessed directly against the requirements of the following OECD Environmental Health and Safety Publications from the Series on Principles of Good Laboratory Practice and Compliance Monitoring:

- **Number 1**: The OECD Principles of Good Laboratory Practice (1998)
- **Number 4**: GLP Consensus Document: Quality Assurance and GLP (1999)
- **Number 5:** GLP Consensus Document: Compliance of Laboratory Suppliers with GLP Principles (1999)
- **Number 6**: GLP Consensus Document: The Application of the GLP Principles to Field Studies(1999)
- **Number 7**: GLP Consensus Document: The Application of the GLP Principles to Short-Term Studies (1999)
- **Number 8**: GLP Consensus Document: The Role and Responsibilities of the Study Director in GLP Studies

(1999)

- **Number 13**: GLP Consensus Document: The Application of the OECD Principles to the Organisation and Management of Multi-site Studies (2002)
- **Number 14**: GLP Advisory Document: The Application of the Principles of GLP to In-vitro Studies (2004)
- **Number 15**: GLP Advisory Document: The Establishment and Control of Archives that operate in compliance with the Principles of GLP (2007)
- **Number 16**: GLP Advisory Document: GLP Requirements for Peer Review of Histopathology
- **Number 17**: GLP Advisory Document: Application of GLP Principles to Computerised Systems
- And any other relevant documents published by OECD from time to time.

Document Number 1 is the primary criteria document against which all GLP compliant test facilities are inspected. These publications are available at no charge at the OECD's website at: https://www.oecd.org/env/ehs/testing/

4 Registration Process

4.1 Scope

4.1.1 Participation in the Singapore GLP Compliance Programme is voluntary. Any test facility that wishes to conduct studies, for submission on behalf of their sponsors, on environmental safety studies that are in compliant with the requirements of OECD Principles of Good Laboratory Practice may apply. A facility may also apply on the request by a Receiving Authority either from Singapore or overseas.

4.1.2 All applications must comply with the requirements, procedures and conditions as set out in this document (GLP 01). These requirements, procedures and conditions should be read in conjunction with all other compliance criteria documents as set out above. SAC reserves the right to vary, revise and/or amend these requirements, procedures and conditions from time to time as may be specified and deemed necessary by SAC.

4.1.3 Any test facility interested to obtain registration as a GLP compliant facility is encouraged to study in detail the documents specified in Section 3.2. The facility is encouraged to have an ISO/IEC 17025 accreditation for the testing component associated with the GLP activities. This is, however, not mandatory.

4.1.4 The scope of application for the OECD Principles is restricted to non-clinical safety testing of test items contained in products mentioned in Section 1.2. The testing of these items is for the purpose of obtaining data on their properties and/or safety with respect to human health and/or the environment. These non-clinical health and environment safety studies are intended to be submitted to regulatory or receiving authorities for the purpose of registering or licensing the pharmaceutical, pesticide, food or feed additive, cosmetic or veterinary drug product or for regulating the industrial chemical. Other types of trials on test items (such as clinical trials) related to non-safety testing (eg efficacy) are outside the scope of the Programme.

4.1.5 Once a test facility is satisfied that the OECD Principles of GLP are applicable to the scope of studies it conducts, and has documented its technical and quality systems to comply with the OECD Principles of Good Laboratory Practice and associated consensus documents, an application for registration can be made to SAC.

4.2 **Application**

4.2.1 All applications shall be made through the online platform, SACiNet, in the manner as may be prescribed by SAC from time to time.

4.2.2 All applications are to be supported with documents or other information necessary or requested by SAC for the assessment of the facility. Some of the important information required include :

a. The type of non-clinical safety studies conducted at the facility for which GLP registration is sought. In accordance with OECD recommendations, these can be detailed under the following groupings :

   i. Physical- Chemical Testing
   ii. Toxicity Studies
   iii. Mutagenicity Studies
   iv. Environmental Toxicity Studies on Aquatic and Terrestrial Organisms
   v. Studies on Behaviour in Water, Soil and Air, Bioaccumulation
   vi. Residue Studies
   vii. Studies on the Effects of Mesocosms and Natural Ecosystems
   viii. Analytical and Clinical Chemistry Testing
   ix. Other Studies

   In addition, further detail on the scope of capability within these groupings for which the facility is seeking GLP compliance should be submitted to the Secretariat.

b. Organisation chart(s), Curriculum vitae and job descriptions of key facility staff such as CEO, Test Facility Management, Quality Assurance Personnel, Study Directors/ Principal Investigators, Pathologist, Veterinarian, Section Managers, etc.

c. Quality manual and/ or key standard operating procedures (SOPs) providing the framework for the GLP quality system.

d. Information on the physical facilities for which GLP compliance is sought, including any remote test sites.

e. A copy of the master schedule of studies.

4.2.3 Once an application is received, Deputy Director (GLP) will review the application and a staff officer will be assigned to manage the inspection planning. The staff officer will compose an inspection team and make arrangements with the test facility.

4.3 Management Representative

4.3.1 Each applicant and registered facility is required to nominate a senior staff member to represent it in all dealings with SAC. This person will be the point of contact between SAC and the facility, and is known as the Management Representative. All correspondences and invoices will be addressed to the Management Representative.

4.3.2 The Management Representative may be a senior technical or managerial staff who holds an appropriate position in the organisation with the authority to ensure their facility complies with the criteria for registration at all times. The facility is obliged to inform SAC immediately whenever there is a change of responsibilities or resignation of the Management Representative. The Management Representative is expected to be present at opening and closing meetings for the GLP inspection.

4.4 Preliminary Inspection

4.4.1 The facility may request for a preliminary inspection (prior to a formal initial inspection) to review the existing systems and procedures. The objective of the visit is to evaluate on the readiness for the initial inspection and also on any aspects of the GLP quality system that need further development. A man-day charge is levied for such visit. Information on the various inspection fees can be found in the GLP Fee Schedule.

4.5 Documentation Review

4.5.1 Before initial inspection and subsequent surveillance inspection(s) of the facility, the facility's SOPs and supporting documents making up the framework of the GLP system will be reviewed to ensure compliance with the OECD Principles of Good Laboratory Practice and applicable consensus and advisory documents.

4.6 Initial Inspection

4.6.1 The initial inspection involves a full facility inspection and study audits conducted by SAC inspection team, and where necessary, may be supported by technical expert(s).

4.6.2 The objective of inspection is to confirm that the test facility is implementing what it has documented in its SOPs and that its system is in accordance with the OECD Principles of Good Laboratory Practice. For an inspection to take place, the prospective facility shall have completed at least one study that has been conducted in compliance with the Principles. During the on-site visit, the inspector(s) will focus on the operation of the GLP system. Information gathered will include, but is not limited to, review of records, discussions with management and key GLP personnel, and observation of relevant activities. A significant element of the inspection will involve study audits - of studies in progress and/or completed studies from the archive.

4.6.3 The time to conduct an on-site inspection will depend on the size of the test facility, the number of test sites and the scope of registration.

4.6.4 The on-site inspection starts with an opening meeting between the SAC inspector(s) and senior / key staff of the facility. The entry meeting provides an opportunity for:

- introductions between the key GLP personnel and the inspection team;
- confirmation of the scope of inspection (considering both studies conducted and test sites) and the timetable for inspection; and
- clarification of any queries that the inspector(s) or staff may have.

4.6.5 The facility will be asked to provide appropriate guide(s)/ escort(s) for each phase of the inspection. These escorts should be senior staff of the organisation who have sufficient authority to ensure the inspector(s) have access to all documents, personnel and activities they may wish to see.

4.7 Classification of Deficiencies

4.7.1 Observations made during the inspection will be recorded on a checklist. These will include observations of compliance as well as any deficiencies.

4.7.2 Following the information gathering, the inspector(s) will meet in private to review their notes and summarise their findings.

4.7.3 The on-site inspection will end with a closing meeting where the facility representatives are given a summary report including any deficiencies that have been found. All findings will be fully discussed with the facility representatives before the departure of the team.

4.7.4 The findings will be placed into four categories:-

a. **Critical deficiency** - A *critical* deficiency is one which seriously threatens the credibility of the Singapore GLP Compliance Programme. It includes gross lack of technical competence, persistent violation of Procedures and Conditions, regulations, gross lack of commitment of the organisation to quality or compliance with OECD GLP Principles and existence of serious doubt on the integrity and impartiality of the organisation. A management system breakdown, as indicated by a series of *significant deficiences,* which seriously threaten the quality of all activities under the system, warrants a *critical* deficiency.

Note:

Gross lack of competence may arise from lack of competent staff for critical activities, inappropriate environment for critical activities, lack of critical equipment, lack of critical traceability, totally invalid raw data test, calibration or inspection method, total breakdown of the record or documentation system, lack of or totally ineffective quality assurance procedures or other causes.

b. **Significant deficiency** - A *significant* deficiency has serious adverse effect on the validity of an activity, its results or the competence of the organisation or a violation of SAC Procedures & Conditions for registration.

The existence of a serious doubt on the technical validity of an activity or its raw data, reported studies, as indicated by a series of related *minor* deficiencies is a *significant* deficiency. Furthermore, persistence of a *minor* deficiency for an extended period of time and without any plausible explanation may be a violation of SAC Procedures & Conditions for registration, and warrants a *significant* deficiency.

c. **Minor deficiency** - A *minor* deficiency has no serious adverse effect on the validity of the activity, its results or the competence of the organisation.

Note:

Minor deficiencies have a tendency to grow into significant deficiencies if not addressed appropriately at the time.

d. **Observation** - An inspection finding that does not warrant non-conformity but is identified by the inspection team as an opportunity for improvement.

4.7.5 The test facility will be informed at the closing meeting of the possible outcomes. These outcomes may be :

a. **In Compliance with GLP** - No critical deficiency was identified and registration will be granted/continued following satisfactory provision of documented objective evidence for other significant/ minor deficiencies (if any).

b. **Pending** – Compliance with GLP with some significant deficiencies noted. These deficiencies do not affect the validity of the studies, however clearance of these deficiencies is required. An on-site re-inspection may be conducted to verify for effective implementation. The charges for such follow-up visit are based on the rate in the GLP Fee Schedule. During the pending period, the status of the studies are deemed to be in compliance.

c. **Not in Compliance with GLP** - The test facility is unable to meet the Principles of Good Laboratory Practice and critical deficiencies have been reported. The registration status of the facility will be withdrawn. SAC will inform the OECD secretariat of the non-compliance status of the facility and associated studies. It is required that a full inspection be conducted after the test facility has addressed all the deficiencies for it to be considered for registration again.

4.7.6 The lead inspector will monitor the progress of the test facility in carrying out the required corrective actions, with objective evidences provided. The final report, incorporating the test facility's responses to the findings and with recommendation for granting or non-granting of registration, will be sent to SAC Review Committee for approval.,

4.8 Scope of Registration

4.8.1 A Certificate of Registration will be issued to the applicant facility who has demonstrated compliance with GLP. In addition to the Certificate of Registration, a Schedule will be issued, which detailed the scope or types of non-clinical safety studies for which GLP compliance can be claimed under the Programme.

4.8.2 The name of the registered test facility together with details of its scope of GLP compliance will be posted in the SAC website for the Programme.

4.9 Surveillance Inspection

4.9.1 Once the test facility is registered, a surveillance inspection is carried out on a yearly basis.

4.9.2 Surveillance inspection involves study audits and targeted inspection of elements of the facility's GLP quality system. The surveillance programme is designed to ensure that the GLP systems continue to meet the criteria for registration and continue to work effectively. SAC reserves the right, however, to undertake additional inspection at any time.

4.9.3 Once the test facility is registered, there is a limit on the time required to carry out any corrective actions. Once compliance has been demonstrated within the agreed time of 1 month (or otherwise specified by SAC), SAC will continue registration of the test facility.

4.9.4 A registered test facility can submit a written request for a change in the scope of registration to the SAC at any time. If the request to extend the range or types of studies that the facility can undertake does not coincide with the scheduled inspection visit, SAC will have to carry out a special inspection to confirm compliance with the OECD Principles for these types of studies. Such an inspection will be chargeable.

4.9.5 If the study audits, surveillance inspections or any special inspections conducted reveal that the test facility's systems no longer meet SAC's criteria for registration or the GLP Principles, or if the test facility refuses to carry out requested corrective actions either at all, or in the specified time, then registration will be withdrawn. SAC will inform the OECD Secretariat of the non-compliance status of the facility and associated studies.

4.10 **Special Inspection Activities**

4.10.1 In addition to the circumstance indicated in clause 4.9.4 where the test facility can request a special inspection at any time to consider an extension to its scope of registration, the following are other circumstances that may require additional special inspections :

a. The facility has had a physical change in accommodation that necessitates an on-site inspection to verify registration criteria are being maintained.

b. Feedback received by SAC that the registered facility is no longer operating in compliance with the GLP Principles.

c. Following a formal request from a regulatory or receiving authority either in Singapore or from another OECD country. Such requests to SAC would normally arise from a particular study conducted or to be

conducted at the facility, and which are intended to or have been submitted to the requesting authority. The scope of such inspection would likely be restricted to an audit of the particular study in question.

d. SAC has been requested to conduct an inspection of a particular test facility or test site by another GLP compliance monitoring authority. This would normally apply to multi-site studies where the main test facility is overseas, with a particular test site in Singapore.

SECTION B: RIGHTS AND DUTIES OF APPLICANT & REGISTERED FACILITIES

5 Conditions for Registration

5.1 Duties of Applicant and Registered Facilities

5.1.1 The test facility must have a written quality management system that states how the facility meets all of the requirements of the OECD Principles of Good Laboratory Practice, applicable consensus and advisory documents and applicable registration criteria. The quality system of the test facility must operate in the way it is documented.

5.1.2 The test facility must allow inspector(s) and observer(s) reasonable access to the premises, facilities, resources, operations, procedures, records and staff so that the inspector(s) can effectively assess the GLP systems and activities.

5.1.3 The test facility must agree to allow inspector(s) the right to take samples, inspect records and produce copies and photographs on site, as may be necessary for reasons of perpetuation of evidence.

5.1.4 The test facility must promptly pay all fees, charges and expenses relating to the initial inspection, registration of facility and any subsequent activities by SAC regardless of the outcome of these activities. Failure to do so may result in withdrawal of the registration, and a requirement for any future fees to be paid in advance. The prevailing rates are detailed in the GLP Fee Schedule. SAC reserves the right to change the fees as and when necessary.

5.1.5 The test facility must maintain impartiality and integrity in its dealings with clients and all interested parties involved in the registered activity.

5.1.6 The test facility may claim to be a registered GLP compliant facility (or make reference to the registration in any advertising or communication medium) only for work covered by the scope of study types which the facility has been registered by SAC and only if that work has been carried out in accordance with the SAC criteria. The facility must not make any statement about its registration that SAC considers misleading or which is not authorised. The

test facility must not use the registration in such a way as to bring SAC into disrepute.

5.1.7 The test facility must not use the registration to imply approval by SAC of any product or item the facility has tested.

5.1.8 The test facility must ensure that the study reports are issued (or parts of them) are not used in a way that could mislead sponsors or others.

5.1.9 The test facility must notify SAC promptly of changes in the facility's status or operations such as:

- changes in key GLP personnel, particularly the GLP management
- changes in senior personnel duties and responsibilities (including change of Management Representative)
- significant changes in accommodation and/or equipment
- changes in legal, commercial or organisational status
- changes in policies and procedures.

5.1.10 The test facility must not vary the technical operations or facilities covered in the scope of registration during the period between inspections, unless notice has been given in writing and a confirmation in writing have been made that such changes do not invalid a registration.

5.1.11 The test facility must conduct at least one completed study within 4 years. The reference to GLP compliant study in any study final report shall adhere strictly to the terms stated in clause 5.1.1.

5.1.12 The registration may be withdrawn either by the test facility or by SAC. In the event of a withdrawal, the facility must immediately stop making reference to terms "GLP (compliant) facility/laboratory", "Registered facility/laboratory" or the like, and all advertising materials which contains the terms or refers to them. The Certificates of Registration and Schedules must be returned to SAC immediately.

5.1.13 If the test facility is temporarily unable to meet the registration conditions, SAC may request the facility to stop making any reference to SAC registration. The test facility may also be asked not to claim compliance with the criteria for registration until SAC is satisfied that the facility is meeting the conditions, or pending the result of any appeal made by the facility.

5.1.14 If the test facility fails to comply with such a request, SAC may:

- withdraw registration, or

- decline to continue or extend the scope of registration, or
- reduce the scope of registration.

Such decisions and the grounds for them will be communicated to the facility in writing.

5.1.15 The test facility shall liaise with the SAC secretariat on all matters relating to GLP inspection, and shall not communicate directly with any of the committee members and inspectors on such matters.

5.1.16 SAC may withdraw or decline to grant or continue registration if the test facility becomes bankrupt or makes any arrangements with its creditors, or enters into liquidation, whether compulsory or voluntary (but not including liquidation for the purpose of reconstruction), or has a receiver appointed, or is sold or is taken over. Such decisions and the grounds for them will be communicated to the facility in writing. In addition, SAC may require the test facility to stop displaying the registration certificate during this period and to refrain from any reference to itself as registered under the GLP Compliance Programme.

5.1.17 Unless SAC otherwise allows, the test facility whose registration has been withdrawn may re-apply after one year from the anniversary date as stated on the letter of withdrawal. The registration process follows clause 4.6 of this document.

5.2 Rights of Applicant and Registered Facilities

5.2.1 Application under the GLP Compliance Programme is open to all organisations that come within the scope detailed in clause 4.8 above, regardless of size or professional affiliations.

5.2.2 SAC will confine its requirements, inspections and registration decisions to the scope of registration requested.

5.2.3 Once the application is accepted, an invoice for payment of application fee will be issued. An estimated time required, fees and expenses (where relevant) for inspection activities will be provided.

5.2.4 Upon the granting of registration, SAC will issue test facility with a Certificate of Registration and Schedule. Registration details of the facility will be posted in the SAC website.

5.2.5 SAC will notify the test facility of any changes in the criteria for registration and give the facility reasonable time to adjust its procedures to meet the new requirements.

5.2.6 Registration is continued once a test facility is registered in the Programme. Surveillance inspections will be conducted annually to ensure continued compliance with registration requirements.

5.2.7 A test facility has the right to veto any proposed inspector or technical expert whom the facility considers may have a conflict of interest when conducting the inspection.

5.2.8 Complaints or appeals can be made to SAC.

5.3 **Confidentiality**

5.3.1 All information provided by any applicants in relation to preliminary enquiries or to an application for GLP registration and all information obtained in the course of, or in connection with, an inspection of a test facility shall be completely confidential.

5.3.2 SAC requires its inspectors, staff and technical experts to abide by a code of ethics, professional standards and confidentiality. They agree in writing to keep information about the test facility confidential and to declare any conflicts of interest.

5.3.3 All inspectors, observers (such as members of Mutual Joint Visit teams from OECD), committee members and SAC Staff sign undertakings of confidentiality and independence. For inspectors and technical experts, an additional undertaking has to be signed prior to the appointment as inspectors or experts for a particular test facility's inspection.

5.3.4 From time to time, SAC may be asked to submit reports of inspections or study audits to regulatory authorities. In addition, compliance statements or summaries of inspections or reports of study audits may be made by SAC to the requesting authority. SAC will evaluate such request and if it has been determined that there is a need, the request will be acceded where all commercially sensitive and confidential information has been excised.

6 Appeals and Complaints

6.1 Appeals and complaints fall into two categories:

- appeals on registration decisions
- complaints on registration and inspection activities.

6.2 Any appeals or complaints should be made in writing to the SAC Director and such appeals or complaints should bear the name, designation, company and signature of the sender.

6.3 **Appeals on Registration Decisions**

6.3.1 An appeal may be made about withdrawal of registration or part of the registration scope.

6.3.2 For disagreements related to inspector procedure, decision or activities, the facility should attempt to resolve any technical issues with the Lead Inspector.

6.3.3 For formal appeal on registration decisions, it must be made in writing no later than two weeks from the date of withdrawal. The SAC Director, in consultation with the SAC Chair will appoint an independent appeal committee to look into the appeal. The appeal will consider whether:

- current SAC policies and procedures have been properly followed
- current SAC policies and procedures are adequate and appropriate
- registration decisions have been soundly based on objective evidence.

6.3.4 The Appeal Committee appointed in respect of each appeal shall consist of a Chairman drawn from the SAC Council and at least two members drawn from the relevant Council Committee or Technical Committee, none of which shall have any direct commercial interest in the subject of appeal. The Committee may co-opt technical experts as and when required.

6.3.5 The Appeal Committee investigates the appeal according to defined procedures and terms of reference and reports its decision to the SAC Chairman. Once endorsed by the Chairman, the decision of the Appeal Committee is final. The decision of the Appeal Committee shall not be called into question or subject to review or appeal by any court of law.

6.4 **Complaints on Registration Activities**

6.4.1 Any complaints about the performance of SAC services or staff or inspectors will be investigated by the Deputy Director (GLP) or an appropriate person appointed by the SAC Director in accordance to the SAC complaints procedure. The facility will be advised of the result of the investigation and of corrective action taken.