Good Laboratory Practices (GLP) Guidelines

ORGANISATION OF PHARMACEUTICAL PRODUCERS OF INDIA

ACKNOWLEDGEMENTS

OPPI Technical Committee 2004-05 led by Mr. Ajit Singh, Managing Director, Associated Capsules Pvt. Ltd. contributed towards OPPI Good Laboratory Practices (GLP) Guidelines.

Members of Technical Committee, Mr. G.K. Nair, Technical Advisor, Associated Capsules Pvt. Ltd. and Dr. A.G. Seshadrinathan, Vice President, Technical, Raptakos Brett & Co. spearheaded the preparation of the publication.

OPPI TECHNICAL COMMITTEE

CHAIRMAN

Ajit Singh	Associated Capsules

VICE-CHAIRMAN

R. Raghunandanan	GlaxoSmithKline

MEMBERS:

G.K. Nair	Associated Capsules
Dr. K.R.P. Shenoy	AstraZeneca
Satish L. Rajkondawar	Sanofi Aventis Group
Ram Parthasarathy	Baxter
Dr. U.C. Shetty	Johnson & Johnson
Pramod Pimplikar	Merck
Dr. Bomi M. Gagrat	Pfizer
Ms. Shweta Purandare	Procter & Gamble
Dr. A.G. Seshadrinathan	Raptakos Brett & Co.
V.N. Phatak	Solvay
Dr. Amit Bhadra	Wyeth

CONTENTS

OPPI
GOOD LABORATORY PRACTICES (GLP) GUIDELINES

1. OBJECTIVE

Compliance with GLP is a regulatory / legal requirement for the acceptance of certain 'studies', undertaken by facilities, to be submitted to Regulatory / Health Authorities, for risk assessment in Health & Environmental Safety. For example in UK the Good Laboratory Practice Monitoring Authority (GLPMA) enforces compliance. The GLP Regulations require that any test facility that conducts, intends to conduct a "regulatory study" must be a member, or prospective member, of the UK GLP Compliance programme. However there are test facilities, typically as part of a manufacturing organization, that conduct studies (Tests) which are not "regulatory studies". This document is intended for such facilities. Besides this, in the arena of Life Sciences, whether in Research or Development or Manufacture, a good testing Laboratory is a must for building confidence that the basis of GMP and product assessment is logically and scientifically correct. However the various branches of Life Sciences need such specific testing facilities from recombinant DNA testing to Pharmacovigilence that it will not be possible to cover all such esoteric testing facilities. This document therefore provides the basic requirements in the running of a general testing Laboratory in terms of good practices. The objective is to facilitate the

proper application and interpretation of GLP principles in a generic manner.

2. SCOPE

This document is designed to facilitate the proper application and interpretation of the GLP principles for the Organization and for the Management of a Quality Control Laboratory and to provide guidance for the appropriate application of GLP principles to testing. This guidance document is organized in such a way as to provide easy reference to the GLP principles by following the sequence of the different parts of these GLP principles.

3. PERSONNEL

The Test Facility must have adequate personnel with the required qualification, experience and training (and 'Approval' from regulatory authorities wherever needed) to carry out the assigned functions in a timely manner according to the principles of GLP.

A Job Description of every category / level of personnel in the Test Facility must be maintained. This must cover every individual engaged in testing / analyzing or supervising the analysis. The Job Description must also specify the limits of authority at each level / category.

The training record for every individual cross-referenced with the Job description and Departmental training including Material Safety Data sheet must be available.

The Test Facility Manager must have sufficient educational background, experience, training and authority to ensure that the Principles of GLP are complied with, in the test facility.

The Test Facility Manager will ensure that the personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions. The Indian Drugs & Cosmetics Act and Rules there under requires that each area of operations in the Laboratory has an "approved" person (competent technical staff) to conduct the tests and /or sign off the documentation.

4. FACILITIES

The test facility should ideally be situated with direct access to personnel working in them, without the need to enter through the manufacturing area, and should be separated from manufacturing areas. This is particularly important for laboratories involved in the control of biologicals, microbiologicals and radioisotopes, which should also be separated from each other. Steps should be taken in order to prevent the entry of unauthorized personnel. The area must not be used as a right of way by personnel who do not work in them. Laboratory personnel, however, must

have access to production areas for sampling and investigation as appropriate.

Facilities should be designed to suit the operations to be carried out in them. Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect the products being tested or the accurate functioning of equipment. If sterility testing is conducted then the area should mimic the aseptic production conditions and gowning and entry procedures, with the final stage of the changing room being, in the at-rest state, of the same air quality / air classification as that into which it finally opens, viz. the aseptic testing area. Sterility test must be conducted under Grade A conditions, typically in a Laminar Flow Module, placed in class 100 conditions. Sufficient space should be available to avoid mix-ups and cross-contamination. There should be adequate storage space for samples and records.

All laboratory instruments and equipment should be qualified and calibrated in accordance with the manufacturer's recommendations and pharmacopoeial requirements. All the test instruments and equipment must have unique identification numbers,(for their use, cleaning, calibration, service & maintenance) that can be linked to analytical raw data, calibration reports and logbooks.

Separate rooms which are climate controlled, may be necessary to protect sensitive instruments from electrical interference, humidity, vibrations etc.

Control samples or reference samples also will need a separate room which is equipped with temperature and humidity control capable of achieving the same storage conditions as stated on the labels of the materials being tested. Proper consideration should be given to ventilation requirements of the areas depending on the activities carried out therein e.g. extraction, handling of fuming chemicals, organic solvents, distillation involving heating etc.

Personal protective equipment should be worn by personnel in the laboratory (see chapter on Safety). Ideally a distinctive overall or Lab-coat is advisable for laboratory personnel.

If part or all of the testing is contracted out and a contract testing laboratory is used, this should be audited and approved based on compliance with GLP. A technical agreement must be in place between the contract giver and the contract acceptor with a system in place to provide updated authorized analytical methods and specifications for the analysis involved. A change control system must also be in place with the contract testing laboratory.

5. DOCUMENTATION

The availability of a complete set of SOPs necessary to govern all the pertinent activities and procedures in the test facility is an absolute prerequisite. They define how to carry out protocol specific activities. They

should be written in a chronological order listing different steps in the accomplishment of an activity. There must be a clear mention of responsibilities. SOPs must be subjected to periodic reviews for updating, if required, while it must remain user friendly. Major consideration should be given to the degree of details incorporated in them. Some of the key SOPs which need to be addressed include:

a. Samples handling and accountability.

b. Receipt, identification, storage, method of sampling of test and control articles.

c. Record keeping, reporting, storage and retrieval of data.

d. Operating of technical audit personnel in conducting and reporting audits, inspections, reports, reviews.

e. Routine inspection of cleaning, maintenance, testing, calibration of equipment.

f. Handling of Out Of Specification (OOS) results.

g. Calibration management.

h. Validation of analytical methods.

i. Change control procedure.

j. Health and safety protection.

k. Animal room preparation and animal care.

l. Storage, maintenance and traceability of microbial cultures.

m. Storage, use of reference standards and Reagents.

n. Laboratory waste handling.

There must be a SOP in place in the laboratory for glassware cleaning & it should be based on glassware washing efficiency both related to chemical labs & micro labs. Sensitive items like cells for photometry readings must have cleaning procedures that demonstrate adequate cleaning.

All documents used should be reviewed, approved, authorized prior to use. In case of exclusive use of the electronic media, the software and processes used should be validated and suitable measures put in place to ensure password controls.

Documents should be periodically reviewed and where necessary, revised to ensure continuing suitability. Invalid or superseded documents must be promptly removed or otherwise assured against unintended use. Changes to documents should be reviewed and approved by the same function that performed the original review.

Procedures should be established to describe how changes in documents in computerized systems can be made and controlled. Additionally, clear-cut procedures must be evolved for storage, distribution, retrieval and

destruction of documents.

Provision must be made to retain raw data, SOPs, documents, final reports for a predetermined period. There should be archives for orderly storage and expeditious retrieval. Conditions of storage should minimize deterioration. Persons responsible for archiving must be identified and only authorized persons must enter the archives.

Raw data should be recorded on duly controlled raw data sheets or pre-paginated authorized logbooks. It should be verified independently by another competent person. The raw data including the automated instrument printouts should be immediately signed and dated by the analyst performing the test. The data stored on temporary storage media (e.g. thermal paper) should be transferred to a robust storage media (e.g. photocopy or scan of the print out) and duly authorized establishing traceability to the original raw data. Data should be recorded, wherever possible, so as to facilitate trending.

Tests performed must be recorded and the records should include at least the following data:

i. Name of the material and where applicable dosage form.

ii. Batch no. and where appropriate the manufacturer and/or the supplier.

iii. Reference to the relevant specifications and test procedures.

iv. Test results, including observations and calculations, and reference to any Certificates of Analysis.

v. Date of testing.

vi. Initials of the person/s that performed the test.

vii. Initials of the person /s who verified the testing and the calculations where appropriate.

viii. A clear statement of the status decision (release or reject etc.) and the dated signature of the designated Facility Manager or Responsible Person.

6. CALIBRATION

All test and measuring equipment are likely to influence the test results directly or indirectly and must be subject to calibration.

The frequency of calibration depends on the instrument, the recommendation from manufacturers, laboratory experience and extent of use. Procedures employed for calibration must be clearly written down and test report must conclude with a statement of 'status'. In case of non-conformity, the report must indicate corrective and preventive action.

All the test instruments and equipment must have a unique identification number that should be linked to analytical raw data, calibration reports and

logbooks for their use.

Calibration certificate / calibration record / calibration report should carry a unique identification number, the name and address of the agency, if outside expert is involved, in addition to the identification and description of test procedure including traceability to primary standards if used. The certificate should also indicate the calibration results and the due date for next calibration. The equipment should have a tag displaying the status of calibration.

When an instrument for calibration has been adjusted or replaced, the calibration results before and after repair, if available, should be reported. Reference materials used must be characterized, certified, purchased from reputable sources and traceable to national and international measures. When an instrument is found "Out of Calibration" it should be conspicuously labeled as such so that its use for testing is prevented. The test results between non-compliant calibration results and last successful calibration should be reviewed to confirm the correctness of the test results reported and appropriate action should be taken based on the outcome of the investigation. In case of frequent failures, the frequency of calibration and preventive maintenance should be reviewed and revised if necessary.

7. OUT OF SPECIFICATION (OO S)

Out Of Specification (OOS) results are those results, generated during

testing, that do not comply with the relevant specifications or standards or with the defined acceptance criteria. If at any time during the process of study or testing, a result is obtained that is out of specification or is considered "atypical" (for example during stability testing), a defined procedure must be followed to investigate the result and determine the course of action.

The objective of the procedure is to ascertain if the OOS or atypical result is valid (i.e. that the result is an accurate representation of the measured attribute of the sample taking into consideration the precision of the analytical method) and, if the result is valid, to determine its probable cause and impact. OOS or atypical results can arise from causes that can be divided into 3 main categories:

- Laboratory Error
- Operator error – Non-Process Related
- Process related – Manufacturing Process Error

The first stage of the procedure is a laboratory investigation to determine if the OOS is clearly assignable to laboratory error. If so then the result may be discarded and the test repeated. If the OOS is not clearly due to laboratory error then the investigation is expanded outside the laboratory testing and can include re-sampling. The aims of the expanded investigation are to identify the probable cause of the OOS or atypical result and to determine

the significance of the result when making decisions about the material or product under test.

Under certain circumstances there may be justification for not following the above procedure when OOS or atypical result is obtained. Examples of such situations include, but are not limited to:

- Pharmacopoeial specifications which give specific guidance in tests like Content Uniformity, Dissolution, Sterility Testing etc.
- Stability Testing, where prediction from trend analysis indicate that the result is valid
- OOS supported by results for other tests like low assay with high result for impurity content.
- Investigation of OOS for a starting material, raw material or intermediate may, where justified, be restricted to a consideration of the suitability of the material for onward processing.

In circumstances where the procedure is not followed, the justification for this approach must be documented and approved by the Facility Manager.

8. VALIDATION OF ANALYTICAL METHODS

All analytical methods, particularly non-standard and in-house test

methods must be validated by a laid down procedure. All analytical equipment must be appropriately qualified before method validation. The degree of validation should reflect the purpose of analysis and the type of product being tested. For example there should be an increasing degree between tests for packaging materials, raw materials, intermediates and finished products or clinical trial materials. The validation methodology must be clearly documented and should include:

- Selectivity and specificity
- Range
- Linearity and range
- Robustness
- Bias
- Precision
- Limit of detection
- Limit of quantification

A record must be maintained of any modification of the validated method and should include reason for modification and appropriate data to verify that results are as accurate and reliable as the established method. Suitability of all methods should be verified under actual conditions of use and documented. In addition, it would also be useful to perform inter-

laboratory comparison of results periodically.

9. CHANGE CONTROL

All changes in equipment, test environment, test method, services, systems or location that may affect reproducibility, accuracy or standards must be formally requested, documented and accepted. The likely impact of the change should be evaluated and the change control procedure should ensure that sufficient supporting data are generated to demonstrate that change does not affect the end result or the in-house or registered specifications.

10. LABORATORY REAGENTS & REFERENCE STANDARDS

There must be written procedures in place for the handling of reagents and preparation of standard solutions.

A primary standard is one that has been shown by an extensive set of analytical tests to be authentic material of established quality. This standard may be obtained from a recognized source (like USP, BP etc) or may be prepared by independent synthesis or by further purification of existing production material. An “in-house primary standard” is an appropriately characterized material prepared by the manufacturer from a representative lot for the purposes of physicochemical testing of subsequent lots and against which in-house reference material is calibrated. A “secondary

standard" is a substance of established quality, as shown by comparison to a primary reference standard, used as reference standard for routine laboratory analysis.

Reagents should be dated as soon as received and a "use by" date assigned based on experience or alternatively a short date (1 year) first assigned which can then be extended based on retesting. Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardization and the last current factor should be indicated.

Reagents and chemicals should be stored by their hazard class and not by alphabetical order. For example storage should be by segregating into groups of 'oxidizers', 'reactives', corrosives etc. Within the particular group alphabetical storage may then be done.

11. SAFETY

People who work in scientific laboratories are exposed to many kinds of hazards. This can be said of most workplaces; in some, the hazards are well recognized (those of ordinary fire, for example) and the precautions to be taken are obvious. Laboratories, however, involve a greater variety of possible hazards than do most workplaces, and some of those hazards call

for precautions not ordinarily encountered elsewhere. It is however not possible to enumerate each and every safety precaution that should be followed; this chapter consequently sets forth some of the major rules for safety and recommends the reader to the Bibliography at the end for wider reading and understanding of specific hazards and safety practices to deal with these.

The design and construction is the first instance of building safety features in the laboratory. Laboratory must be equipped with adequate fire extinguishers, personal protective equipment (PPE), safety showers, eye wash fountains and first aid kits. The design should facilitate the change of street clothes and footwear to specific PPE needed by the laboratory personnel.

No employee should work alone in a laboratory or chemical storage area when performing a task that is considered usually hazardous by the laboratory supervisor or safety officer. Clothing worn in the laboratory should offer protection from splashes and spills, should be easily removable in case of accident, and ideally should be fire resistant. No food, beverage or cosmetic products should be allowed in the laboratory or chemical storage area at any time.

Laboratories using compressed gas cylinders should ensure that they are secured at all times either to a wall or placed in a holding cage to prevent tipping. Since the gases are contained in heavy, highly pressurized metal

containers, the large amount of potential energy resulting from compression of the gas makes the cylinder a potential rocket or fragmentation bomb. In summary, careful procedures are necessary for handling the various compressed gases, the cylinders containing the compressed gases, regulators or valves used to control gas glow, and the piping used to confine gases during flow. Ideally the cylinders should be located outside the lab, with clearly labeled piping identifying the gas, piped into instruments or parts of the lab.

Storage of flammable solvents should be minimized as far as possible and cabinets used for storage of flammable liquids must be properly used and maintained and only materials that are compatible must be stored together.(refer to 'OSHA' in Bibliography). Reagents, solutions, glassware or other apparatus should not be stored in fume / extraction hoods as this not only reduces the available space but more importantly may interfere with the proper airflow pattern and reduce the effectiveness of the hood as a safety device.

12. TRAINING

Test Facility management must provide training for all personnel whose duties involve the conducting of tests and analysis. Training should also be provided to other personnel whose activities could affect the quality of testing. Besides the basic training on the theory and practice of GLP, newly

recruited personnel should receive training appropriate to the duties assigned to them. This should provide personnel with good motivation to perform the relevant tasks in a manner aiming towards full compliance of GLP.

Following the identification of training needs, general training sessions or small workshops for personnel should be laid down for successful implementation of GLP. These should be followed by 'hands on' exercises leading to practical application of GLP principles. Training programs must lead to change in "cherished habits" of personnel. The importance of documentation used for legible, indelible recording of all events, data and other occurrences together with their dating and initialing, correctly introducing changes into records must be highlighted. Training program should be designed so as to maintain continuity. A constant coaching may be needed to enable the immediate detection, admonition and correction of slips, errors, omission and neglect.

A formal training program, in the form of an SOP, must be in place which includes a procedure for assessing the competence/skills of the personnel undergoing training. Records must be maintained of persons who are adjudged competent and authorized, including dates of authorization to perform specific tasks such as sampling, testing, calibration, operating typical equipment, issuing of test reports, etc.

In addition, the records of their educational and professional qualification,

training undergone, skills and experience shall also be maintained (See chapter on Personnel).

13. QUALITY AUDIT

The test Facility should have a documented Quality Assurance (QA) Program to assure that tests / studies performed are in compliance with these principles of Good Laboratory Practice. The QA program or Self Audit should be carried out by an individual or by individuals who are designated by and directly responsible to the Facility Manager and who are thoroughly familiar with the test procedures. These individuals must not be involved in the conduct of the study / test being assured.

The responsibilities of these QA / Audit personnel include, but are not limited to, the following functions:

a. Maintain a copy of all approved test methods / study plans and SOPs in use in the test facility.

b. Verify that the test methods / study plans contain the information required for compliance with these principles of Good Laboratory Practice.

c. Conduct audits / inspections to assure that tests are conducted in accordance with these principles of Good Laboratory Practice. Inspections can be of three types as specified by the

QA SOP :

i. Study / Test-based inspection

ii. Facility-based inspection

iii. Process-based inspection

d. Document and retain records of all inspections.

e. Inspect the final reports to confirm that the methods, procedures and observations are accurately and completely described and that the reported results accurately and completely reflect the raw data of the studies / tests.

f. Promptly report inspection results in writing to the Facility Manager and ensure that corrective action is put in place if necessary.

14. MANAGEMENT REVIEW

Management of a test facility has the ultimate responsibility for ensuring that the facility as a whole operates in compliance with the GLP principles. This will involve the implementation of Quality Assurance or Quality Audit program which is independent of the actual conduct of test / study and is designed to assure the test facility management of compliance with these principles of GLP.

The individual or individuals responsible for conducting the program must not be involved in the test or in any study program being assured. The implementation of such an audit program is discussed under the chapter "Quality Audit". Records of these inspections along with corrective actions taken should be archived. Archival facilities should enable secure storage and retrieval of all documents like Test methods, raw data, final reports etc.

Normally an inspector from a Regulatory Agency will not request to see an actual report of an audit as such requests could inhibit auditors when preparing inspection reports. It is sufficient to show that a program of self audit exists through documented evidence and to show that a procedure for corrective action is also in place.

15. DEFINITIONS

15.1 GLP :

Good Laboratory Practice is concerned with the organizational processes and the conditions under which laboratory tests are planned, performed, monitored, recorded, archived and reported. Adherence by test facilities to the principles of GLP ensures proper planning of tests and the provision of adequate means to carry them out. It facilitates the proper conduct of tests, promotes their full and accurate reporting and provides means whereby the validity and integrity of the tests and analytical data can be verified. It also facilitates an audit trail of the products manufactured.

15.2 Test Facility :

Means the Operational Unit, including the premises, equipment, instruments and persons, which are necessary for conducting the studies.

15.3 Test Facility Manager:

Means the person who has the authority and formal responsibility for the organization and functioning of the Test Facility according to these principles of Good Laboratory Practice.

15.4 Study Plan / Test method

Means a document which defines the objectives and experimental design for the conduct of the test / study including specified instruments to be used

and the acceptance criteria of the data.

15.5 Raw data

Means all original test records and documentation, or verified copies thereof, which are the result of original observations and activities in a study / test. Raw data also could include hand written notes, computer printouts, recorded data from automated instruments, or any other data storage medium that has been validated as capable of providing secure storage of information. These should be linked to final outcome such that traceability is possible.

15.6 Standard Operating Procedures (SOP) :

Means documented procedures which describe how to perform all the pertinent activities and procedures in the test facility. The compilation of topics for SOPs will involve the logical dissection of whole processes, such as conduct of studies / tests, into their single activities, as well as an effort to list equipment, apparatus or instrument which would be used in the GLP relevant areas. The SOP should also include the necessary precautions to be taken while performing a particular test.

15.7 Quality Assurance Program

Means a defined system, including personnel, which is designed to assure test facility management of compliance with these principles of Good Laboratory Practices.

BIBLIOGRAPHY

1. OECD (Organization for Economic Co-operation and Development, Paris 1998) Principles of Good Laboratory Practice
2. OECD QA and GLP, 1999
3. OECD in Vitro GLP, 2004
4. Guide to UK GLP Regulations, Feb 2000 (by GLPMA)
5. ICH Q7A GMP section 11 Laboratory Controls
6. OSHA (Occupational Safety and Health Administration USA; www.osha.gov)
7. ISO / IEC 17025; 1999
8. GLP Why & How by Dr Jurg Seiler. Publ. Springer-Verlag.
9. MCA "Orange Guide" (Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2002)

About OPPI

OPPI is an organisation of pharmaceutical manufacturers established in 1965. Its membership consists of Research based International and large Indian pharmaceutical companies.

OPPI members account for a substantial share of the industry's total investment, export and R&D. The market share of its Member-Firms in total Pharmaceuticals Market in India is over 60%.

OPPI is not only an industry association but also a scientific and professional body. It organises national and international seminars and workshops relating to key issues of the pharmaceutical industry and healthcare. It supports scientific research by professional and academic institutes. It also brings out technical publications, like Quality Assurance Guide and Environment, Health & Safety Guide, Pharmaceutical Compendium, Research report on outsourcing opportunities, Model Guidelines etc.

OPPI members adhere to the Code of Pharmaceutical Marketing Practices of International Federation of Pharmaceutical Manufacturers Associations (IFPMA). OPPI has developed operational guidelines for its members for interpretation and implementation of this Code of Ethical Marketing Practices. OPPI is also a member of the WorldSelf-Medication Industry (WSMI), France and has developed code of ethics for advertisement of drugs.

OPPI identifies itself with the country's national health objectives and encourages its members to make substantial contributions to social concerns. It also co-ordinates its Members' efforts in national calamities like epidemics, floods, earthquakes and cyclone.

OPPI also assists other scientific and educational programmes besides having its own on-going programmes of health education and supports the country's national objectives of health improvement.