

IMPS : Negotiating the GLP/GMP/GCP Interface

How the different GLP/GMP/GCP guidelines interact

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Genocentre, Evry , 6 Oct. 2008

THE SCOPE OF REGULATIONS

NON-CLINICAL SAFETY
STUDIES

Good
Laboratory Practice

CLINICAL STUDIES
PHASE I, PHASE II, PHASE III, PHASE IV

Good Clinical Practice

Good Manufacturing Practice

Good Distribution Practice

THE REGULATIONS

The Good Laboratory Practice

REFERENCE REGULATION :
THE OECD PRINCIPLES OF GOOD LABORATORY PRACTICE (GLP)

SCOPE:

These principles of good laboratory practice should be applied to the non-clinical safety testing of test items contained in **pharmaceutical products, pesticide products, cosmetic products, veterinary drugs as well as food additives, feed additives, and industrial chemicals**. These test items are frequently synthetic chemicals, but may be of natural or biological origin and, in some circumstances, may be living organisms. The purpose of testing these test items is to obtain data on their properties and/or their safety with respect to human health and/or the environment.

Non-clinical health and environmental safety studies covered by the principles of good laboratory practice include work conducted **in the laboratory, in greenhouses, and in the field**.

THE REGULATIONS

The Good Manufacturing Practice

REFERENCE REGULATION :
**EudraLex - The Rules Governing Medicinal Products in the European Union
Volume 4 - EU Guidelines to Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use**

SCOPE

European Directive 2003/94

This Directive lays down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use whose manufacture requires the authorisation referred to in Article 40 of Directive 2001/83/EC and in respect of investigational medicinal products for human use whose manufacture requires the authorisation referred to in Article 13 of Directive 2001/20/EC.

THE REGULATIONS

The Good Clinical Practice

REFERENCE REGULATION :

GUIDELINE FOR GOOD CLINICAL PRACTICE - ICH Harmonised Tripartite Guideline

SCOPE:

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

GXP DEFINITIONS

GLP	GMP	GCP
Good Laboratory Practice (GLP) is a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.	Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation or product specification. Good Manufacturing Practice is concerned with both production and quality control.	Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected

GXP REGULATIONS

What is “Quality Assurance “ ?

GLP	GMP	GCP
<p>General</p> <p>1. - (1) The test facility should have a documented quality assurance programme to assure that regulatory studies performed are in compliance with the principles of good laboratory practice.</p>	<p>Quality Assurance</p> <p>1.2 Quality Assurance is a wide ranging concept which covers all matters which individually or collectively influence the quality of a product. It is the total sum of the organised arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide.</p>	<p>5.1 Quality Assurance and Quality Control</p> <p>5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).</p>

GXP REGULATIONS

What is “Quality Assurance “ ?

GLP	GMP	GCP
<p>General</p> <p>(2) The quality assurance programme should be carried out by an individual or by individuals designated by and directly responsible to management and who are familiar with the test procedures.</p> <p>(3) This individual or these individuals should not be involved in the conduct of the regulatory study being assured.</p>	<p>Quality Assurance</p> <p>The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that:</p> <p>(i) medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice and Good Laboratory Practice;</p> <p>(ii) production and control operations are clearly specified and Good Manufacturing Practice adopted;</p> <p>(iii) managerial responsibilities are clearly specified;</p> <p>(iv) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;</p> <p>(v) all necessary controls on intermediate products, and any other in-process controls and validations are carried out;</p> <p>(vi) the finished product is correctly processed and checked, according to the defined procedures;</p> <p>(vii) medicinal products are not sold or supplied before a Qualified Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products;</p> <p>(viii) satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;</p> <p>(ix) there is a procedure for Self-Inspection and/or quality audit which regularly appraises the effectiveness and applicability of the Quality Assurance system.</p>	<p>5.1 Quality Assurance and Quality Control</p> <p>5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.2.1) to all trial related sites, source data/documents , and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities. 5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.</p> <p>5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.</p>

QUALITY SYSTEM IN THE THREE DISCIPLINES

ITEMS

Main Important Responsibilities
Quality Unit And The Organization
Quality System Management In The Three Disciplines

THE MAIN RESPONSIBILITIES

Function	GLP	GMP	GCP
Ownership	Facility Management	Manufacturer/Holder of the Authorization	Sponsor
Main responsibility for the activity	Study Director	Qualified Person	Principal Investigator
Responsibility for "Production"	Principal Investigator	Head of Production	Pharmacist
Quality	Quality Assurance	Head of Quality Control	Monitor Quality assurance
Archive	Archivist		Archivist

THE QUALITY UNIT AND THE ORGANIZATION

GLP	GMP	GCP
The Quality Assurance Unit is fully independent from the activities being assured. There is no definition of Quality Control	Quality assurance, as organization, is not described in the regulations. Most of the duties are located under Quality Control aspects.	Quality Assurance Unit

THE QUALITY UNIT AND THE ORGANIZATION

GLP	GMP	GCP
<p>Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations (2006)</p> <p>Current industry practice generally divides the responsibilities of the quality control unit (QCU), as defined in the CGMP regulations, between quality control (QC) and quality assurance (QA) functions.</p> <ul style="list-style-type: none">• QC usually involves (1) assessing the suitability of incoming components, containers, closures, labeling, in-process materials, and the finished products; (2) evaluating the performance of the manufacturing process to ensure adherence to proper specifications and limits; and (3) determining the acceptability of each batch for release.• QA primarily involves (1) review and approval of all procedures related to production and maintenance, (2) review of associated records, and (3) auditing and performing/evaluating trend analyses.		

QUALITY SYSTEM MANAGEMENT IN THE THREE DISCIPLINES

DOCUMENTATION: Management of the SOPs system

GLP	GMP	GCP
<p>QUA does not approve the SOPs QAU only for GLP compliance verification</p> <p>The SOP management is not under the umbrella of the QAU but under the responsibility of the Site management</p>	<p>QA approves each SOP</p> <p>The historical file and the original copies are filed by QA</p> <p>The whole system is generally under QA group.</p> <p>Generally QA helps department in drafting the SOPs</p>	<p>The Sponsor has the responsibility for the SOP system</p>

QUALITY SYSTEM MANAGEMENT IN THE THREE DISCIPLINES

DOCUMENTATION: Approval

GLP	GMP	GCP
<p>The Study Director is responsible for the scientific contents of any final study report.</p> <p>QAU is responsible to: 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;</p>	<p>QP issues the Certificate for authorization for use of the batch manufactured and QAU has the duty to review all the documentation</p>	<p>Not applicable</p>

QUALITY SYSTEM MANAGEMENT IN THE THREE DISCIPLINES

Activities: material management

GLP	GMP	GCP
Records including test item and reference item characterisation, date of receipt, expiry date, quantities received and used in studies should be maintained.	Very strictly controls on the materials (from arrival to the GMP warehouse through the shipping of the final product)	Traceability, Accountability and Reconciliation of the material is mandatory

QUALITY SYSTEM MANAGEMENT IN THE THREE DISCIPLINES

Facilities and equipment: lay out

GLP	GMP	GCP
Criteria to design the lay out are: prevention of cross contamination and mix-ups; separation of the different activities to assure the proper conduct of the study	<p>Principle</p> <p>Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products.</p>	Not applicable

QUALITY SYSTEM MANAGEMENT IN THE THREE DISCIPLINES

Facilities and equipment: qualification

GLP	GMP	GCP
No need for qualification Only maintenance	Facilities, equipment and utilities should be qualified to assure the adequate performance	Not applicable

QUALITY SYSTEM MANAGEMENT IN THE THREE DISCIPLINES

Facilities, equipment and laboratory instrumentation : calibration

GLP	GMP	GCP
Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to standard operating procedures. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement.	Calibration for critical instrumentation should be described in appropriate SOPs and a master calibration plan available	Not applicable

QUALITY SYSTEM MANAGEMENT IN THE THREE DISCIPLINES

Computer systems : validation

GLP	GMP	GCP
<p>Requested</p> <p>The OECD guideline is not so precise about the validation steps</p>	<p>Requested</p> <p>There is a need for a full life cycle validation (URS, validation plan, IQ,OQ, PQ, validation report and associated SOPs)</p>	<p>Requested</p> <p>There is a need for a full life cycle validation (URS, validation plan, IQ,OQ, PQ, validation report and associated SOPs)</p>

QUALITY SYSTEM MANAGEMENT IN THE THREE DISCIPLINES

Laboratory controls: analytical method validation

GLP	GMP	GCP
<p>There is no indication about the needs to validate the analytical methods</p>	<p>Validation of the method is essential for the GMP and scientific values of data generated during the analytical work</p>	<p>Not applicable</p>

QUALITY SYSTEM MANAGEMENT IN THE THREE DISCIPLINES

Laboratory controls: reserve samples

GLP	GMP	GCP
<p>A sample for analytical purposes from each batch of test item should be retained for all studies except short-term studies.</p>	<p>It is mandatory to keep appropriate amount of reference samples of starting materials, packaging materials or finished products and retention samples of finished products.</p>	<p>Not applicable</p>

QUALITY SYSTEM MANAGEMENT IN THE THREE DISCIPLINES

Quality management: audits

GLP	GMP	GCP
<p>Three types of inspections: - study-based inspections, - facility-based inspections, -process-based inspections.</p> <p>A requirement of GLP is to audit a "live" analysis or "live" sample preparation in addition to the historical type</p>	<p>Personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a pre-arranged programme in order to verify their conformity with the principles of Quality Assurance.</p>	<p>The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.</p>

QUALITY SYSTEM MANAGEMENT IN THE THREE DISCIPLINES

Quality management: outsourcing control

GLP	GMP	GCP
Audit at the site	Audit at the site, Quality Agreement to define the responsibilities	Audit before starting the clinical activities

QUALITY SYSTEM MANAGEMENT IN THE THREE DISCIPLINES

Quality management: deviation, oos, change control

GLP	GMP	GCP
Deviations from standard operating procedures related to the study should be documented and should be acknowledged by the study director and the principal investigator(s), as applicable. There is no requirements for starting with investigations	Need formal investigation Specific SOPs should address the way to perform the investigation	Not applicable

QUALITY SYSTEM MANAGEMENT IN THE THREE DISCIPLINES

Quality management: complaints

GLP	GMP	GCP
Not addressed	Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control should normally be involved in the study of such problems.	Not applicable

APPROACHING A MODERN QUALITY SYSTEM

Basic elements for a modern quality system:

- Quality manual
- Continual improvement
- capa system
- Quality planning,
- Management review

As describe in ICH Q10 Pharmaceutical Quality system

WHO WILL THE RUN
AMONG GLP GMP AND GCP?

CONCLUSIONS

For the time being, the approach is different but the principles are much the same: a complete and operative Quality System demonstrating that there is overall control.
