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Conducting GLP Inspections in Germany

Manual

National and Länder Working Party
Chemicals Safety Committee "GLP and other quality assurance systems" BLAC-AS GLP

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Preamble

Good Laboratory Practice was converted into German law with the revision of the Chemicals Law in 1990. The first manual appeared in 1997 and was intended as an instruction manual for the conducting of GLP inspections. To this end, various GLP documents were gathered together which had been prepared for the clarification of open questions, thus constituting an overview of legal sets of rules combined with a wealth of practical experience made by inspectors on-site. Since this time, all changes and new regulations have been in the legal area. A number of suggestions and tips were given by the inspectors at the same time, with the result that after 20 years, it was time for a comprehensive revision. This consist essentially of an update of the legal foundations, the revision of the annexes and restructuring. The purpose of the manual is still to help inspectors in the preparation and conducting of GLP inspections.

Note

This manual including all annexes does not claim to be complete and has no legally binding character. Only the wording of each respective legal regulation is legally binding.

BLAC-AS GLP, AG “GLP Manual”

The working party would like to extend its sincere thanks to all colleagues who laid the foundations for this manual and to all those who made valuable contributions to the revision.

List of Contents

Note on numbering:
The chapters are numbered to facilitate the quoting of individual passages from the manual. The text is also subdivided into numbered sections.
The first three numbering levels are reserved for the headings, the fourth for the text. This has been applied consistently, even if this has meant that not all numbering levels are used in some chapters.

Abbreviations

FR	final report
AM	Archives Manager
DP	data processing
GLP	Good Laboratory Practice
IC	in compliance (with GLP Principles)
TFM	Test Facility Management
TSM	Test Site Management
MS	Master Schedule
NIC	not in compliance (with GLP Principles)
TF	test facility
SP	study plan
TS	test site
SD	Study Director
PI	Principal Investigator
TRI	test and reference items
QA	Quality Assurance
SOP	Standard Operating Procedure

I. GLP RULES (NATIONAL AND INTERNATIONAL)

The international set of rules for Good Laboratory Practice (GLP) is based on the OECD Council Decisions of 1981 and 1989 which, together with its annexes (Principles of good laboratory practice, Guides for Compliance Monitoring Procedures for Good Laboratory Practice, Guidance for the Conduct of Laboratory Inspections and Study Audits) was converted into European law with Directives 2004/10/EC (87/18/EEC) and 2004/9/EC (88/320/EEC). It was converted into German law by Chemicals Law 2013 (1990) and the General Administrative Provision Relating to the Procedure for Official Monitoring of Compliance with the Principles of Good Laboratory Practice 2011 (1990).

Detailed, internationally coordinated explanations and interpretations of GLP are summarised in the OECD Series on GLP, which is published on the OECD website and elsewhere. In addition to the OECD Council Decisions, which are legally binding for OECD Member countries under international law (OECD GLP Documents 1, 2, 3), these include a number of other documents which, even though they are not legally binding per se, are of great significance through the divergent inclusion of various addressees and unanimous adoption on OECD level.

OECD Series on GLP

GLP Principles (1)

- OECD Council Decision

Compliance Monitoring (2,3)

- OECD Council Decision
  and document (9) declassified through OECD Joint Meeting

Consensus Documents (4, 5, 6, 7, 8, 10, 13)

- Prepared in a one-week workshop with consensus found between GLP-monitoring authorities, regulatory authorities and industry.
  Declassified through OECD Joint Meeting

Advisory Documents (11, 12, 14, 15, 16, 17)

- Prepared in the OECD GLP Working Group with the involvement of interest associations from industry as well as public commentary option via the OECD website since Document 17. Responsibility for the final version lies with the OECD GLP Working Group.
  Declassified through OECD Joint Meeting

Position Papers (18, as well as accreditation (1994) and outsourcing inspection functions (2006))

- Position Papers are not detailed technical interpretations, but rather statements, positions or decisions of the OECD GLP Working Group on the facts of a matter. No inclusion of other addressees (e.g. industry).
  Declassified through OECD Joint Meeting

Frequently Asked Questions (FAQs) (supplemented continuously since 2014)

- Technical statements of the OECD GLP Working Group on individual technical interpretation issues of industry which do not justify a comprehensive Advisory Document. Industry is not involved in the reply.
  Declassified through OECD Joint Meeting

II. CONDUCTING GLP INSPECTIONS

According to the administrative regulation, a GLP inspection is an on-site inspection conducted during a tour of a test facility (TF). The questioning of employees and perusal of documentation are the most important activities. The following information is intended to support the execution of the procedure and explain individual points in more detail.

1. Preparation of an Inspection

1.1. Questions to put to the Test Facility/Test Site before an inspection

1.1.1.1. Type, size of TF (e.g. number of personnel, scope of testing, any sponsors)

1.1.1.2. Nature of studies/test categories (any specification/limitation of test categories), see also explanatory notes in Annex 7 (test categories)

1.1.1.3. Statement as to whether inspections are made in accordance with Art. 19a or Art. 19b of the Chemicals Act (GLP as an obligation or justified interest)

1.1.1.4. Organisational structure (changes since the last inspection):

- Clarification of responsibilities within the TF, e.g. Test Facility Management (TFM), Study Director (SD), Quality Assurance (QA), Archives Manager (AM)
- Responsible person for data processing (DP), responsible persons for the granting of user rights in the DP system
- Establish responsibilities, contractual relations or procedures between the TF and dependent and independent TSs (see explanations in Annex 4)
- Make the following inquiries for each test site (TS): exact description, address (perhaps a different federal state, country) with or without its own GLP certification. Compare the information with the records kept by the GLP Federal Bureau on officially inspected TF or TS

1.2. Formation of the inspection team

1.2.1.1. At least two inspectors (appoint lead); as a rule with a specialist knowledge of the TF's area of expertise

1.2.1.2. In animal experiments: as a rule with the participation of a veterinarian or an inspector with a veterinary background; prior check by the responsible authority that animal protection regulations are complied with

1.2.1.3. If necessary, participation of experts (confidentiality must be assured and guaranteed in writing)

1.2.1.4. If necessary seek administrative assistance if dependent TSs, independent TSs or TFs in other federal states (*Länder*) are participating. If TFs or TSs abroad are to be involved, contact the GLP Federal Bureau.

1.3. Request for documents and organisational agreements

The dispatch of documents electronically or by post must be in compliance with measures to guarantee confidentiality.

The following in particular should be requested to prepare the inspection:

1.3.1.1. Master Schedule (MS): Complete list of all on-going, completed and terminated studies with details of study code, test item, test system, type of test, SD, study initiation/completion date or status of test, sponsor, requirements regarding multi-site studies (see Annex 4) since the last inspection at least (if necessary: GLP/Non-GLP studies)

1.3.1.2. Organigrams (company/GLP structure; IT organisation structure showing the connection and inclusion of IT management in the GLP structure), consider dependent / independent TSs if necessary, list of GLP personnel

1.3.1.3. Standard Operating Procedures (SOP) from the QA area

1.3.1.4. List of all SOPs, if necessary copies of the most important SOPs (see Annex 1)

1.3.1.5. List of important apparatus (equipment, including validated computerised systems used for the acquisition, recording and reproduction of data and for the control of the environmental conditions of significance for the study) - see also 1.3.1.7

1.3.1.6. Building/site plans (marking of GLP areas); if necessary also for dependent TSs

1.3.1.7. List of all computerised systems and software used in connection with GLP studies (see Annex 3)

1.3.1.8. Overview of IT structure

The documents are examined together with information already on hand, such as previous inspection reports, documentation on the rectification of deficiencies , modification notifications etc. in order to become acquainted with the TF.

The information required in 1.3.1.7 and 1.3.1.8 does not necessarily have to be requested in advance, but it should be on hand for the pre-inspection so that the effort required for the inspection of IT systems within the scope of the main inspection can be better estimated.

1.4. Pre-inspection

A pre-inspection in the TF is required as technical-organisational preparation prior to the first inspections. It can also be helpful after essential changes in the TF. If not all of the documents listed under 1.3 are available in advance, they can be examined during pre-inspection at the TF. This can e.g. apply, for specifications concerning 1.3.1.7 and 1.3.1.8 to enable a more precise estimation of the expense and effort required for the inspection of IT systems during the main inspection.

1.4.1. Introductory discussion

1.4.1.1. Participants: inspection team, TFM, SD, QA management, possibly AM, PI/TSM if applicable

1.4.1.2. Discussion of documents requested, responsibilities, representation rules, range of duties

1.4.1.3. Confirmation of exact name of TF/TS

1.4.1.4. Participation of external personnel in the conducting of studies

1.4.1.5. Determination of the areas of the TF to be inspected

1.4.2. Tour of the premises for orientation purposes

1.4.3. Final discussion

The following must be clarified once the prerequisites for a main inspection are given:

1.4.3.1. Time and scope of the inspection (coordination of on-going studies during the inspection, decision on inspections of dependent or independent TSs when indicated)

1.4.3.2. Test categories (type of study) for GLP certification

1.4.3.3. appropriate personnel available during inspection

1.4.3.4. Provision of a separate work room and technical facilities for the preparation and duplication of documents (PC, copier, printer) for the inspection team during the inspection

Deficiencies determined during the pre-inspection should be reported to the TF.

1.4.4. Request of documentation prior to the main inspection

1.4.4.1. MS (updated as necessary, see 1.3.1.1)

1.4.4.2. Sample of a study plan (SP), or SP and final report (FR) of one or more studies already conducted (see 2.8.2)

1.4.4.3. Selected SOPs (see Annex 1)

2. Inspection of a Test Facility or Test Site

The relevant items must be inspected accordingly when inspecting test sites.

The sequence of the inspection depends greatly on the conditions in the TF and can vary if certain points of main focus have been set for the inspection. Before the inspection date is agreed, it must be clarified with the TF that

- the persons who carry out or have carried out GLP tasks are present/contactable during the inspection if possible (TFM, SD, QA, if necessary PI and TSM, AM or deputy where applicable.
- the inspection team is accompanied during inspection in the TF by:
  - QA during the entire inspection
  - TFM, if necessary TSM at least during the starting and closing conference
  - SD, if necessary PI and AM within each area of responsibility
  - personnel in each area
- if possible, on-going studies from the applied test categories take place.

The following general inspection sequence is usually followed in standard practice.

- starting conference
  If no pre-inspection was conducted on-site, the items listed in item 1.4 must be dealt with during the inspection.
  - Fixing of the time schedule for the inspection (pay consideration to on-going studies)
  - Provision of a work room for the inspection team
  - If necessary, make selection from on-going studies, related sections of which are inspected during inspection
  - Selection of completed studies for study audits if not already determined during pre-inspection (see 2.8.3)
- Discussion of TF documentation
- Tour of the facilities and questioning of personnel
  The inspection team usually conducts the tour together (groups of at least two)
  Questioning of GLP personnel about, for example:
  - Current SOP understanding
  - Availability of SP on-site among personnel engaged in the study

- Conduct of studies in line with SPs
- Collection of raw data:
  - Direct recording of original and derived data with dated signature
  - Regulation with changes, corrections (the original entry must be recognisable and the changes marked with date, reason for change and signature)
  - If raw data collected by DP systems: acceptance criteria, justification for change to raw data, recording of change via Audit Trail
  - Authentication of raw data copies
- Verification of the function of an Audit Trail by changing a piece of raw data, for example, and checking recording and traceability using a sample file, for instance

- Verification of studies (see Chap. 2.8)
- Closing conference (see 2.13)

2.1. Organisation and personnel

2.1.1. Organisation

2.1.1.1. Presentation of the organisational structure from a GLP point of view (especially independence of individual GLP functions, TFM and where necessary TSM with written authorisation), e.g. organigram, process and documentation of deputy rules

2.1.1.2. Number of GLP/non-GLP studies

2.1.1.3. Number of personnel (SD, other academic, technical, other), thereof part time

2.1.1.4. MS for estimating the workload on GLP personnel and the scope of the TF; management and archiving of MS

2.1.2. Personnel

2.1.2.1. Qualifications and areas of activity of personnel:
- Curriculum vitae
- Education and training (specialist, GLP)
- Description of task
- Language skills as applicable

2.1.2.2. Health and safety precautions; exclusion of employees whose state of health might adversely affect the study (e.g. on biological test systems)

2.1.2.3. List of names/signatures/initials

2.2. Quality assurance

As specific questions about QA frequently arise only in the course of the inspection, it generally makes sense to leave inspection by QA until just before the closing conference. QA requirements resulting from the conducting of Multi-Site Studies are listed in Annex 4. The tasks of QA are subdivided into study, facility and process-based activities.

2.2.1. Quality assurance programme

2.2.1.1. Number and qualification of QA personnel, taking into account dependent and independent TSs

2.2.1.2. Independence of QA from conduct of the study

2.2.1.3. Arrangements for representatives

2.2.1.4. Scope of work:

- Share of GLP activities in relation to total activities, additional tasks if applicable
- Evenly balanced distribution of inspection and GLP office activities
- Determination of critical phases
- Frequency of inspections independent of studies (including dependent and independent TSs)
- Interval between delivery of FR to QA and issue of QA statement
- Number of FRs inspected in the past year taking into account the nature of the studies
- Number of FR inspections still outstanding
- Interval between QA inspection and drafting of QA report to TFM

2.2.1.5. Motivation/acceptance of QA (QA support by TFM and SD)

2.2.1.6. Presence of all current SOPs (including list of SOPs with version numbers) at QA

2.2.1.7. Nature of QA participation in drafting, revision and updating of SOPs

2.2.2. Facility based quality assurance activities

2.2.2.1. Audit of organisation and personnel:

- Building plans, layout, construction and suitability of rooms
- Separation of workflows, test systems, clean/unclean areas, GLP/non-GLP areas
- Safety precautions, health protection measures
- Organigrams, job descriptions, list of names and initials, documentation on initial and continuous training
- Human resources capacity

2.2.2.2. Planning and conducting of study-based, process-based and facility-based inspections:

- Documentation of the QA activity, e.g. for critical phases such as receipt and registration of test items, selection of specimens to be retained, storage (for further details see also 2.6)
- Random sampling in the case of short-term studies (see Annex 2)
- Inspections of dependent or independent TSs
- Inspections of suppliers
- QA reports to SD and TFM; consequences of any deficiencies found (under Art. 21 of the Chemicals Act, inspectors have the right to examine QA inspection reports. They should only make use of this right in justified exceptional cases, however – see OECD GLP Consensus Document No. 4, Section "QA Inspection Reports")
- Audit of measures carried out after complaints arising from the last QA inspection

2.2.2.3. Audit of SOPs:

- SOP administration (drafting, indexing, amendment, updating, distribution)
- Form and content of newly drafted SOPs
- Archiving of all SOPs

2.2.2.4. Documentation of every QA activity

2.2.3. General study based QA audit activities

2.2.3.1. Verification of SP:

- Check for the GLP-compliance of the form and content of the SP before coming into effect; documentation
- Existence of approved SP before the beginning of the practical part of the audit
- Timely notification to QA of amendments to study plan and other GLP-relevant changes, documentation of notification

2.2.3.2. Verification of FR:

- Form and content of final reports
- Compliance with raw data
- Completeness of documentation
- Correct and comprehensive reproduction of results (QA statement, see 2.9)

2.2.4. Quality assurance and animal husbandry

2.2.4.1. Check of husbandry conditions (quarantine, acclimatisation and initial veterinary examination), feed storage and compliance with safety and health precautions by QA

2.2.4.2. Contact to animal welfare officer

2.2.4.3. Critical phases include:

- Randomisation / tagging of animals
- Weight measurement
- Feed consumption
- Preparation of forms of application
- Application
- Observation of experimental animals
- Blood sampling
- Preparation of specimens
- Analysis
- Necropsy and removal of organs

2.2.5. Quality assurance and field studies

Due to the multiplicity of test sites/external branch facilities, special problems may arise here and additional QA personnel may be required on site.

2.2.5.1. QA inspections in the field in critical phases such as:

- Storage of test items for the duration of use
- Preparation of application forms
- Application of the test item
- Sampling
- Preparation of specimens
- Storage of specimens
- Transport of specimens

2.2.5.2. Fixing deadlines

2.2.5.3. Defined communication channels between TFM, SD, QA and PI, if applicable; compliance and documentation (see Annex 4)

2.2.6. Quality assurance and data processing

2.2.6.1. Audit of QA's organisation of DP systems:

- Organigram and network topology of the DP system
- Validation concept
- Physical and logical access restrictions to the DP system
- DP system capacity
- DP system changes

2.2.6.2. Direct read-only access by QA to all raw data, traceability of all entries and corrected entries for QA by means of an Audit Trail

2.2.6.3. Control of all processes of manual or non-validated online data input, processing and output from the DP system in sufficient random samples by QA

2.2.6.4. Check of the validation and revalidation of the DP system by QA where necessary

2.2.6.5. Check of the evaluation of old DP equipment for GLP-compliance by QA

2.2.6.6. Sufficient basic DP knowledge on the part of QA for assessing the validation of the DP system, involvement of external experts if necessary

2.2.7. Quality assurance and instrumental analysis / physical-chemical studies

2.2.7.1. With short critical phases, inform QA of the exact time of conduct or any changed deadlines

2.2.7.2. Examples of critical phases:

- Preparation of solutions
- Drawing of samples
- Charging and start-up of apparatus (e.g. vapour pressure)

See Annex 2 for the procedure in the case of short-term studies

2.3. Facilities / Equipment

2.3.1.1. Size, construction, functionality and location commensurate with purpose on the basis of current building/site plans (incl. TSs)

2.3.1.2. Check the function of rooms for compliance with the designations in the building plans

2.3.1.3. Check the suitability of rooms with regard to their size, fittings, functionality, tidiness, cleanliness etc.

2.3.1.4. Separate rooms or room areas for:

- Storage of test and reference items for the period of use
- Preparation of test items before application
- Collection, storage and disposal of waste, test systems
- Cleaning of materials (washing systems)
- Individual application areas (work processes)
- Individual biological test systems
- Clean/unclean areas
- Archive rooms (separate for wet material), contract archive if necessary
- Network servers, mainframes, node computers
- Stores for apparatus and supplies
- Areas for working with radioactive or sterile materials

2.3.1.5. Adequate separation of the GLP/non-GLP studies

If they cannot be put in separate rooms, suitable organisational separation must be determined

2.3.1.6. Check of room/environmental conditions:

- Temperature

- Lighting conditions
- Airflow
- Relative humidity

and monitoring thereof in line with the SOP, regulations for unforeseeable occurrences, alarm equipment (provisions for public holidays and weekends)

2.3.1.7. What to do in the event of unforeseeable occurrences, e.g. power cuts (is there an emergency power generator, are function tests conducted and documented?)

2.4. Apparatus, reagents and materials

2.4.1.1. Apparatus used for the acquisition, recording and reproduction of data and for the control of the environmental conditions that are of significance for the audit must be stored appropriately and must have a suitable construction and adequate capacity

2.4.1.2. Check of the records on the maintenance, repair and release, calibration and adjustment of equipment (apparatus/logbooks), procedure if tolerance limits are exceeded

2.4.1.3. Check of the proper labelling of the containers of test and reference items (at least with the expiry date, special storage instructions, opening date and shelf life if applicable) and of reagents (origin, identity, concentration, stability data, date of manufacture and expiry, special storage instructions, hazard pictograms where necessary)

2.4.1.4. Disposal of reagents and materials

2.4.1.5. Equipment SOP:

- Responsible person
- Instructions for the operation, maintenance, calibration and verification of the functionality of the equipment (e.g. type and frequency, tolerances and procedure in the event that tolerance limits are exceeded, results to be documented, indication of functional disturbances, information from each responsible SD/supervisor if not clear)
- References to the instructions for use are possible, but must be archived in this case.

2.5. Test systems

2.5.1. Physical and chemical test systems

2.5.1.1. Audit of the following, for example:

- Receipt, labelling and storage of specimens
- Production, labelling and storage of solutions

2.5.1.2. Unambiguous and permanent marking of apparatus and apparatus modules.

2.5.1.3. Unambiguous assignment of:

- Logbooks to apparatus and apparatus modules

- Raw data to apparatus (to the respective parts in modularly constructed systems)
- Printouts (e.g. chromatograms) to the respective specimens or test and reference solutions

2.5.1.4. Gapless documentation of the calculations of raw data up to the results in the FR

2.5.1.5. Raw data that can be assigned to several studies (e.g. one standard for several studies) by means of authenticated copies for each study, for instance

2.5.1.6. Procedure for the organisational and/or spatial separation of GLP and non-GLP studies

2.5.2. Microbial, cellular and sub-cellular test systems

2.5.2.1. The following should be on hand if required:
Official permission to handle pathogenic microorganisms in accordance with infection prevention law
Official permission to handle pathogenic microorganisms in accordance with epizootic pathogens law
Official permission or notification/registration of genetic engineering work in line with GMO law

2.5.2.2. Employees are given sufficient training when necessary on the handling of hazardous biological test systems

2.5.2.3. There are regulations for these test systems regarding:

- Keeping and cultivation (e.g. climatic chambers, production of culture medium, cultivation)
- Hygiene measures, other protective measures, examination of employees' state of health
- Prevention of contamination (sterility)

2.5.2.4. Characterisation of the test system (origin, species, strain)

2.5.2.5. Disposal of biological test systems (collection, storage, decontamination and transport procedures)

2.5.2.6. Documented determination of test item and test system

2.5.3. Studies carried out on animals

2.5.3.1. Animal welfare:

- Animal welfare officers
- Certification from the official veterinarian on compliance with animal welfare provisions
- Obligation to give notice/acquire authorisation is observed

2.5.3.2. Qualification of animal carers

2.5.3.3. Documentation of the origin of animals

2.5.3.4. Quarantine for newly arrived animals; examinations on arrival and continuous documentation of health status (in case of sickness reject if necessary, giving reasons)
2.5.3.5. Randomisation/allocation of animals
2.5.3.6. Dealing with superfluous animals
2.5.3.7. Unambiguous labelling of animals and cages/containers
2.5.3.8. Monitoring of animal health, administration of drugs if necessary
2.5.3.9. Quality and purity of feeds (bill of delivery, certificate on composition and contaminants)
2.5.3.10. Check of feed and water quality, procedure if deficiencies detected
2.5.3.11. Storage condition of feeds (e.g. pest control)
2.5.3.12. Quality and purity of litter, substrate etc.
2.5.3.13. Documentation of all stages of the study for every animal (e.g. application, sampling, necropsy)
2.5.3.14. Pathology has a suitable method for recording data
2.5.3.15. Disposal of animal carcasses
2.5.3.16. General cleanliness
2.5.3.17. Cleaning of cages/containers, feed receptacles and other accessories
2.5.3.18. Separation of clean and unclean areas (cage washing facilities, animal rooms)
2.5.3.19. What to do in case of unforeseeable events
2.5.3.20. Documentation of shipment of materials (sections, blocks etc.) to dependent/independent TSs or other TFs

2.5.4. Studies carried out on plants

Studies in greenhouses and semi-field areas:

2.5.4.1. Test system:
- Species, variety, strain
- Origin
- Quantity
- State of health (quarantine if necessary)
- Type and frequency of health checks

2.5.4.2. Substrate:
- Origin
- Composition
- Nutrient content
- Homogeneity
- No disturbing impurities

2.5.4.3. Care of the test system:
- Cultivation, propagation and husbandry conditions (with plants: sowing, cuttings, grafting, pruning if necessary, singling)
- Nutrition (with plants: water and nutrients supply)

- Measures to protect the test system from infestation with harmful organisms

2.5.4.4. In greenhouses only:
Cleanliness, air conditioning, temperature and humidity recording, lighting (intensity, duration), shading (duration), ventilation (mechanical protection against ingress of foreign and harmful organisms), sufficient size for separate keeping of test systems (in the case of plants: type of standing surface and watering, any measures against hardness of water; in the case of animals: type and size of container/housing)

2.5.4.5. Test item: type and time of application

2.5.4.6. Disposal of test system and substrate

2.5.4.7. Safety measures are in place for personnel, knowledge thereof is guaranteed and compliance is assured (e.g. health protection), monitoring systems where necessary

Field studies:

2.5.4.8. Description of the test system (location, history of plot, plot size, position in relation to wind direction, adjacent areas, labelling, locatability, mapping; in the case of plants: species, variety, origin of seed or plants, state of health, care measures such as pruning, tilling, fertilising, watering, plant protection; in the case of soils: type of soil, organic substances, pH value, tilling)

2.5.4.9. Application of test item (calculation of dose, information on stability and behaviour for specific pH values of the water; type of application, e.g. pouring, spraying, scattering, dusting; type of apparatus, nozzle type, linkage; testing of application; frequency and times; if necessary fixing of dates on the basis of phenomenological information; recording of temperature and wind speed during application; removal of liquid residues; measures to prevent contamination, e.g. through drift)

2.5.4.10. Labelling, maintenance and cleaning of apparatus (e.g. scales, pipettes, application equipment including nozzles, cooling equipment, meteorological data recording instruments)

2.5.4.11. Samples for residue analyses (type and date of sampling, labelling and storage of specimens, check of storage conditions, suitable transport to analytical laboratory, maintenance of cold chain)

2.5.4.12. Prevention of contamination (test item kept sufficiently separate from specimens during storage and handling; measures in the case of apparatus, work tables, containers, rooms)

2.5.4.13. Availability of SOP, SP and blank forms in the branch facility, recordings of communications (telephone calls, faxes), interim storage of raw data at the branch facility

2.5.4.14. Cleanliness (equipment, containers, rooms)

2.5.4.15. Disposal of residues of the test item and the test system, documentation

2.5.4.16. Communication between TFM, SD, PI, TS if necessary, and QA; procedure for informing QA about critical phases such as application of test item and the drawing, preparation, storage and transport of specimens (dates to be specified in SP, see Annex 4)

2.6. Test and reference items

2.6.1.1. Procedure for the receipt of the test item from the sponsor to the TF (e.g. safe handling, environmental conditions such as temperature and relative humidity, storage conditions)

2.6.1.2. Authenticity of the test item upon receipt at the TF:
Procedure for verification of identity (OECD Principles of Good Laboratory Practice, Chap. 6.2, Nos. 2 and 3: the identity, including batch number, purity, composition, concentration or other properties for characterizing each batch of the test or reference item must be known for each test. If the test item is delivered by a sponsor, a procedure must be established in cooperation between the sponsor and the TF as to how the identity of the test item used in the study is to be confirmed unambiguously). In exceptional cases, return of a specimen to the manufacturer for confirmation or other traceable method for establishing identity; otherwise a clear indication must be given in the SP and FR

2.6.1.3. Microbiological tests: determination of TI/test system

2.6.1.4. Labelling as test or reference item, unambiguous coding

2.6.1.5. Distribution of the test item in the TF; documentation

2.6.1.6. Accounting of quantity received; use and disposal of the test item (possibly return to manufacturer)

2.6.1.7. Archiving of samples of test and reference items (TRI)

2.6.1.8. Preparation of the application form of the TRI:

- Cleanliness of apparatus
- Avoidance of contamination

2.6.1.9. Labelling, homogeneity, stability and storage of the application form

2.7. Standard operating procedures

2.7.1.1. Covering of the test areas by means of an SOP in the test categories to be certified

2.7.1.2. SOP on the structure, generating, modifying, revision, indexing, authorisation, distribution and archiving of SOPs

2.7.1.3. SOP on the QA programme

2.7.1.4. All study based SOPs (e.g. receipt of test item, coding of studies, archiving etc.), see Annex 1

2.7.1.5. Verification of SOPs on site:

- Availability
- Last version
- Legibility
- Authorisation
- Completeness
- Clarification of responsibilities for the distribution and exchange of invalid for valid SOPs
- No unauthorised short versions
- No unauthorised changes

(see Annex 1)

2.8. Performance of the study

Compare Annex 4 here too - Requirements for Multi-Site Studies

2.8.1. Study plan

The study plan (SP) must (if applicable due to the type of study) contain the below-listed information. The requirements for standardised SPs with short-term studies are outlined in Annex 2.

- Identification of the study, study code
- Descriptive title
- Explanation of type and purpose
- Identification of the test item by means of
  - Trade name
  - Code
  - Name (IUPAC, CAS No. etc.)
  - Chemical formula
  - Structural formula
  - Batch
- Reference item (chemical name) name and address of the sponsor
- Name(s) and address(es) of the TF(s), and dependent or independent TSs
- Name and address of the SD, deputy where applicable
- Dated signatures for SP
  - SD

- TFM (only required with standardised SP for short-term studies)
- QA (documented verification)

- Deadlines (scheduled experimental starting and completion date)
- Study methods
  - Individual description
  - OECD test guidelines or similar
  - Special SOPs
  - General SOPs
- Individual details (if applicable)
  - Justification for selection of test system
  - Characterisation of the test system
  - Application method (justification)
  - Dosages
  - Detailed information on study sequence
  - Field studies: acquisition of climatic data
  - Statement where applicable on the inclusion of DP-prepared documents in the SP (e.g. reference to the corresponding annex to the SP)
- Complete list of records to be kept
- Amendments, deviations and corrections
  - Justification and dated signature of SD
  - Timely documented acknowledgement by QA
  - Notification of TFM and/or sponsor if necessary
  - Retention of amendments with the SP
  - Retention of deviations with the raw data

<u>Stipulations for field test systems:</u>

- Test area
  - Location
  - Soil type, pH-value, org. substances
  - Arrangement, size and number of repetitions of test and comparison plots
  - Size and properties of separation strips/ areas

- Marking and mapping to ensure traceability
- History (e.g. preceding crop, fertilisation measures, plant protection) of at least the two previous vegetation periods
- Recording of environmental conditions such as temperature, precipitation, duration of sunshine, special occurrences; with greenhouses: bright/dark periods etc.

- Test system
  - Plant species, variety, age, spacing
  - Soil parameters
  - Permitted care measures (avoidance of interference with the test item)
  - With seeds: clone, origin, pre-treatment
- Test method
  - Description of the type of application and equipment (indoor or outdoor treatment, size of boom, type of nozzle, pressure, propulsion, tolerances, removal of spray liquid residues)
  - Application and sampling deadlines
  - Sampling method and equipment if necessary, for soil and plant specimens
  - Labelling, preparation, transport and storage of specimens
  - Method of shipment to sponsor, analysis lab or processing business
  - Archiving of specimens when necessary

2.8.2. Review of on-going studies (study audit)

An important part of the on-site tour is the inspection of an on-going study where it can be observed how familiar the personnel is with the conducting of the study, whether written SPs are on hand and whether the conducting of the study is in compliance with GLP Principles and/or the specifications in the SOP are implemented.

2.8.2.1. The inspection team should ensure that:

- the SP has been signed by the SD
- amendments to the SP have been signed by the SD with date
- where applicable, the date is listed on which the sponsor approved the SP
- measurements, observations and examinations comply with the SP and relevant SOPs

- the results of these measurements, observations and examinations are listed directly, immediately, carefully and legibly, before being dated and signed (or initialled)
- any changes to the raw data, including those recorded in computerized-systems, do not obliterate previous entries, the reason for the changes is given and the person responsible for the changes as well as the date on which they were made can be seen

2.8.3. Audit of completed studies (study audit)

2.8.3.1. Selection as shortly as possible before or at beginning of inspection (see 1.4.4.2)

2.8.3.2. Studies should be relevant to test categories applied for and if possible suitable for submission to an regulatory authority

2.8.3.3. Terminated studies should also be audited if possible

2.8.3.4. Studies should be carried out, completed and archived in compliance with GLP and as a rule should not be older than the previous inspection

2.8.4. Preparation for study audits

2.8.4.1. Preparation of copies of SPs and where appropriate FRs for memos, comparisons, etc., also translations if necessary

2.8.4.2. If appropriate, consultation with SD of the study in question and/or QA

2.8.4.3. Audit for completeness of documents (contents list, pagination as necessary), arrangement criteria and consistent coding

2.8.4.4. Audit of dated signatures in original

2.8.4.5. Audit of SP

2.8.4.6. Audit of raw data (random if necessary) for:

- Reproducibility
- Completeness (laboratory journals, delivery bills, air conditioning control data, apparatus logbooks, substance data sheets, etc.)
- Corrections
- Dated initials

2.8.4.7. In case of Completed studies: check of the FR (see 2.9)
If parts of the study were not carried out in compliance with GLP, this must be noted in the SD's statement of compliance

2.8.4.8. Check congruence of SP, raw data and FR (systematic approach from SP via raw data to the FR or vice versa), e.g.:

- Comparison of experimental starting and completion date and other relevant data between SP, raw data and FR if applicable
- Comparison of study data with the MS

- Completed studies: check whether all requirements of study plan including those of the SOPs mentioned (disclosure) have been fulfilled in the FR (observe any changes including date). Check time of notification of QA
- In the case of animal experiments, random checking or examination of individual animals on the basis of the reproducibility of the raw data throughout the entire study (possibly with the inclusion of an animal which died during the study)
- Check of the function and appropriateness of physical and chemical test systems at the time the study was conducted (e.g. validation, maintenance, calibration, area of application)
- Completed studies: random check of individual raw data against the FR, also with regard to the correct presentation of the results

2.8.4.9. If appropriate, supplementary audit of:

- Personnel documents
- QA documentation (matching of QA inspections with the QA statement (dates, study phases and reports to TFM))
- Rooms, archives
- Animal husbandry
- Samples of TRI, specimens
- SOPs valid at the time of study conduct
- Raw data covering more than one study
- Interfaces between TF and dependent or independent TSs and procedure in the event of terminated studies

2.8.4.10. If the study audit is not carried out in the framework of an routine or inspection in accordance with General Administrative Provision GLP (ChemVwV-GLP) but in response to enquiries from regulatory authorities, the following points are to be observed:

- Clarification of the points inquired about by the regulatory authority on the basis of the documented sequences of events
- Determination of human resources requirement for the study selected and inspection of personal documents
- Inspection of selected equipment
- Inspection of records on the test item (possibly physical inspection of archive, comparison of quantities), systematic checking of raw data in light of enquiry
- Possibly take a brief look around the laboratory and question relevant personnel

2.8.4.11. Possibly take a look at particular procedures in a comparable on-going study

2.8.5. Discussion of results of study audits

2.8.5.1. Consultation within inspection team

2.8.5.2. Discussion with SD, QA, TFM and other persons if required, e.g. PI
2.8.5.3. Request for a supplement to the FR if there are relevant deficiencies
2.8.5.4. In the event of serious deficiencies, classification of study as not GLP-compliant and immediate notification of GLP Federal Bureau (see 2.14)

2.9. Reporting of study results

The report on the study results (final report, FR) must contain certain information. Some simplifications are possible for short-term studies (standard final report, see Annex 2).

- Identification of the study, code
- Descriptive title
- Identification of the test item through
  - Trade name
  - Code
  - Name (IUPAC, CAS No., etc.)
  - Chemical formula
  - Structural formula
  - Characterisation
  - Batch
  - Purity
  - Stability
  - Homogeneity
  - Indication as to whether and if not why any authentication was done
- Reference item (chemical name)
- Name(s) and address(es) of the TF(s), dependent or independent TSs
- Name of SD and deputy where applicable
- Names and where applicable PI or executive scientists from cooperating specialised areas. Dated GLP declaration of the SD (listing of phases not conducted in line with GLP where applicable). Dated signatures of SD and PI or executive scientists where applicable
- Dated and signed QA Statement
  - Dates of inspections
  - Type of inspections
  - Inspected phases of studies
  - Dates of reports to SD and TFM

- Deadlines (experimental starting and completion date)
- Description of materials used
- Test methods
  - Individual description
  - OECD test guidelines or similar
  - Special SOP
- Presentation of results
  - Summary
  - All of the information and data requested in SP
  - Calculations and statistical methods
  - Evaluation and discussion
  - Conclusions
- Details of the storage location of all
  - Samples of test and reference items
  - Specimens
  - Raw data (in which form?)
  - SPs, including amendments/supplements
  - FR
- Documentation
  - Arrangement criteria
  - Uniform coding
  - Completeness of raw data (list of contents)
  - Error-free collection of raw data (dating, initialling, justified, dated and initialled corrections)
  - Error-free presentation of results (avoidance of errors due to the use of word processing or text modules, and of transfer and calculation errors)
  - Pagination or comparable control options
- Subsequent entry of corrections and supplements
  - Justification and dated signature of SD and where applicable the executive employees involved
  - Dated signature of QA

2.10. Archiving of records and materials

See also the consensus document of the Bund/Länder Working Group Good laboratory practice for archiving and storing records and materials.

2.10.1. General aspects of archiving

2.10.1.1. Structural conditions, e.g. protection against fire (fire-retardant design), water, theft and other negative influences
2.10.1.2. Control of access, archive responsibility, representative of AM
2.10.1.3. Inventory list and organisation and indexing system for archived documents and materials (including terminated studies), fast retrievability
2.10.1.4. QA inspection of the data and materials archive
2.10.1.5. Procedure in the event of preparation of several originals of FR

2.10.2. Data archive

2.10.2.1. Audit of documents for completeness, e.g. SP, raw data, FR, miscellaneous documents; source references for data covering more than one study, e.g. on scales, air conditioning control, instrument calibration, any authorised copies
2.10.2.2. Pagination or adequate method for fast retrievability and for protection against loss and mix-up of the raw data belonging to a study, possibly also using SP, FR and miscellaneous data
2.10.2.3. List of contents of archived documents for each study
2.10.2.4. Rules for borrowing and returning archived documents (as a rule, copies should be made)
2.10.2.5. Ensuring legibility when data saved on magnetic media
2.10.2.6. Method for microfilming data, audit
2.10.2.7. Secure intermediate storage of data in dependent or independent TSs and communication to SD or archive (including contract archive)
2.10.2.8. Archiving of QA documentation
2.10.2.9. Chronological collection of all SOPs
2.10.2.10. Archiving of data covering more than one study (logbooks, records of air conditioning checks, etc.)
2.10.2.11. Archiving of building and floor plans
2.10.2.12. Archiving of organisation charts, personal files, MS

2.10.3. Materials archive

2.10.3.1. Archive for samples of TRI, labelling, duration of storage
2.10.3.2. Archive for specimens, temperature control in the case of refrigerated storage
2.10.3.3. Archive for wet specimens, special requirements e.g. for formaldehyde preparations
2.10.3.4. Archive for paraffin wax blocks, sections, smears

2.10.3.5. Intermediate storage of specimens in dependent or independent TSs; refrigeration, maintenance of cold chain during transport

2.10.3.6. Notification of QA before removal from archive at end of storage period

2.11. Electronic data processing systems

See Annex 3 – Inspection of data processing (DV) systems

2.12. Multi-site studies

See Annex 4 – Multi-site studies

2.13. Closing conference

2.13.1.1. Participants: inspection team, TFM, SD, QA management, possibly AM, PI and TSM

2.13.1.2. Summary of inspection results incl. notification of deficiencies found, usually in writing (short report)

2.13.1.3. Setting of a deadline for rectifying deficiencies

2.13.1.4. Announcement of a re-inspection date if deficiencies are serious

2.13.1.5. Binding designation of TF

2.13.1.6. Determination and specific arrangement of test categories (see also 1.1.1.2, Annex 5 and Annex 6)

2.13.1.7. Preliminary vote by inspection team if necessary

A written summary of the inspection results and detected findings is made either in the course of the final discussion or as soon as possible after the inspection. It may prove practicable to have acknowledgement confirmed by the countersignature of the TFM, for example.

2.14. Reporting obligations from the inspection

If it is determined during the inspection that individual studies were not performed in compliance with the GLP Principles (NIC), the integrity of the established data cannot be guaranteed. Similarly, if the TF / TS does not work overall in compliance with the rules of GLP, this must be reported to the GLP Federal Bureau as soon as possible after the inspection has ended. The Excel form "OECD template for non_compliance.xls" should be used for this report.

3. Inspection Report

The minimum requirements for the preparation of inspection reports are listed below. The basis is formed by the requirements of Annex 1 ChemG (Principles of Good Laboratory Practice) in combination with the provisions of OECD Advisory Document No. 9 (Guidance for the Preparation of GLP Inspection Reports).

A work group from several federal states prepared and presented a sample draft of a GLP inspection report on this basis. This harmonised inspection report was accepted at the 38th BLAC meeting. BLAC recommended that the federal states use the GLP inspection report as a template. The draft report is designed as a form that can be adapted to federal state-specific peculiarities. The sample is accessible on the BLAC website at:

BLAC/BLAC-Intern/Ausschuss GLP/Vollzugshilfen GLP

Content of the inspection report:

1. Summary
2. Introduction
    - 2.1. Identification of the test facility (TF)
    - 2.2. Type of GLP monitoring measure
    - 2.3. Characterisation of the test facility
    - 2.4. Inspection team and inspection date
3. Inspection and findings
    - 3.1. TF organisation and personnel
    - 3.2. Quality assurance programme
    - 3.3. Facilities and Equipment
    - 3.4. Apparatus, reagents and materials
    - 3.5. Test systems
        - 3.5.1. Physical and chemical test systems
        - 3.5.2. Microbial, cellular and sub-cellular test systems
        - 3.5.3. Tests on animals
        - 3.5.4. Tests on plants
    - 3.6. Test and reference items (TRI)

4. Publications and Basic Documents on GLP

4.1. OECD

The OECD documents can be accessed at the OECD-GLP website and GLP Federal Bureau website.

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 1: OECD Principles of Good Laboratory Practice
(*as revised in 1997*)

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 2 (revised): Guidance for GLP-Monitoring Authorities, Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice. (1995)
(German translation as Annex 1 of EU Directive 2004/9 / EC section A)

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 3 (revised): Guidance for GLP-Monitoring Authorities, Revised Guidance for the Conduct of Laboratory Inspections and Study Audits. (1995)
(German translation as Annex 1 of EU Directive 2004/9 / EC section A)

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 4: Consensus Document, Quality Assurance and GLP.
(*1999 revised*)

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 5: Consensus Document, Compliance of Laboratory Suppliers with GLP Principles.
(*1999 revised*)

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 6: Consensus Document, The Application of the GLP Principles to Field Studies.
(*1999 revised*)

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 7: Consensus Document, The Application of the GLP Principles to Short Term Studies.
(*1999 revised*)

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 8: Consensus Document, The Role and Responsibilities of the Study Director in GLP Studies.
(*1999 revised*)

OECD series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 9: Guidance for GLP-Monitoring Authorities, Guidance for the Preparation of GLP Inspection Reports.
(no German translation provided)

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 10: Consensus Document, The Application of the Principles of GLP to Computerised Systems.
(Replaced by number 17 in 2016)

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 11: Advisory Document of the Panel on GLP, The Roles and Responsibilities of the Sponsor in the Application of the Principles of GLP. (1998)
(no German translation provided)

OECD series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 12: Advisory Document of the Working Group on Good Laboratory Practice, Requesting and Carrying Out Inspections and Study Audits in Another Country. (2000)
(no German translation provided)

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 13: Consensus Document of the Working Group on Good Laboratory Practice, The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies (2002)

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 14: Advisory Document of the Working Group on Good Laboratory Practice, The Application of the Principles of GLP to in vitro Studies (2004)

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 15: Advisory Document of the Working Group on Good Laboratory Practice, Establishment and Control of Archives that Operate in Compliance with the Principles of GLP. (2007)

OECD series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 16: Advisory Document of the Working Group on Good Laboratory Practice, Guidance on the GLP - Requirements for Peer Review of Histopathology. (2014)

OECD series on Principles of Good Laboratory Practice and Compliance Monitoring,
Number 17: Advisory Document of the Working Group on Good Laboratory Practice, Application of GLP Principles to Computerised Systems. (2016)
(replaces Consensus Document No. 10)

Position Papers:

Number 18: OECD Position Paper Regarding the Relationship between the OECD Principles of GLP and ISO/IEC 17025 (2016)

The Use of Laboratory Accreditation with reference to GLP Compliance Monitoring (1994)

'Outsourcing' of Inspection Functions by GLP Compliance Monitoring Authorities (2006)

Frequently Asked Questions on Technical issues (FAQs):
OECD GLP Website (continuous since 2014)

4.2. European Union

The documents are available on the EU GLP website and the GLP Federal Office website.

Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (codified version)

Directive 2004/9 / EC of the European Parliament and of the Council of 11 February 2004 on the inspection and verification of good laboratory practice (GLP) (codified version).

Good Laboratory Practices – EU Product-specific legal acts (EU-GLP-website, continuous)

Guidance on cross-contamination of control samples with test item in animal studies (EU-GLP- website, 2004)
http://ec.europa.eu/DocsRoom/documents/13222

Guidance for GLP facilities on the implementation and maintenance of a risk-based quality assurance programme (EU-GLP- website, 2017)
http://ec.europa.eu/DocsRoom/documents/22262

Guidance on GLP compliance monitoring of international multi-site studies (EU-GLP-website, 2017)

http://ec.europa.eu/DocsRoom/documents/20821

Questions & Answers (EU-GLP- website, 2017)
http://ec.europa.eu/DocsRoom/documents/22261

4.3. Federal Republic of Germany

Revised version of the Chemicals Act (ChemG) of 28. August 2013; Bundesgesetzblatt Teil I, S. 3498 – 3991, in the currently valid version

GLP Consensus Document: The application of GLP principles to computerized systems; Bundesanzeiger Nr. 231, Jahrgang 1996, S. 12749-12753

Revised version General Administrative Provision Relating to the Procedure for Official Monitoring of Compliance with the Principles of Good Laboratory Practice (ChemVwV-GLP) in the version of 15. Mai 1997; Gemeinsames Ministerialblatt vom 09. Juni 1997, 48. Jahrgang, Nr. 17, S. 257-264

General administrative regulation amending the General Administrative Provision Relating to the Procedure for Official Monitoring of Compliance with the Principles of Good Laboratory Practice of 02. September 2011, Gemeinsames Ministerialblatt vom 14. Dezember 2011, 62. Jahrgang, Nr. 48, S. 967 - 968

Announcement of a consensus document of the Bund-Länder Working Group Good laboratory practice for archiving and storing records and materials of 05.05.1998; Bundesanzeiger Nr. 98, S. 7439-7440

Guideline for the harmonization of GLP monitoring procedures in Germany of the BLAC-AK "GLP und andere Qualitätssicherungssysteme", UMK-Umlaufbeschlüsse 4/2007 u. 5/2007

4.4. Other documents

Schlottmann/Kayser (Hrsg.), GLP Gute Laborpraxis, Textsammlung und Einführung, Behr's Verlag Hamburg, 3. Auflage 1997

G.A. Christ, S.J. Harston, H.W. Hembeck, K.A. Opfer, GLP - Handbuch für Praktiker, 2. Auflage 1998, GIT-Verlag Darmstadt

PIC/S, Draft PIC/S Guidance, Good practices for computerised systems in regulated “GXP” Environments, PI 011-, 20. August 2003

FDA, Guidance for Industry, Part 11, Electronic Records; Electronic Signatures – Scope and Application, August 2003

5. Terminology

Sources:

[1] *OECD No. 1 - Principles,* 1998.

[2] *OECD No. 6 - Field Studies,* 1999.

[3] *OECD No. 14 - In Vitro Studies,* 2004.

[4] *OECD No. 13 - Multi-Site Studies,* 2002.

[5] *Consensus document on archiving,* 1998.

[6] *OECD No. 4 - Quality Assurance and QA,* 1999.

[7] *OECD No. 15 - Archive,* 2007.

[8] *OECD No. 17 - Computerised Systems,* 2016.

Basic Terminology – Organisation

Sponsor means an entity which commissions, supports and/or submits a non-clinical health and environmental safety study. (OECD Nr. 1 - Grundsätze, 1998)

Good Laboratory Practice is a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. (OECD Nr. 1 - Grundsätze, 1998)

Test facility management means the person(s) who has the authority and formal responsibility for the organisation and functioning of the test facility according to these Principles of Good Laboratory Practice. (OECD Nr. 1 - Grundsätze, 1998)

Test site management - if appointed- means the person(s) responsible for ensuring that the phase(s) of the study, for which he is responsible, are conducted according to these Principles of Good Laboratory Practice. (OECD Nr. 1 - Grundsätze, 1998)

Master schedule means a compilation of information to assist in the assessment of workload and for the tracking of studies at a test facility. (OECD Nr. 1 - Grundsätze, 1998)

Principal Investigator means an individual who, for a multi-site study, acts on behalf of the Study Director and has defined responsibility for delegated phases of the study. The Study Director's responsibility for the overall conduct of the study cannot be delegated to the Principal Investigator(s); this includes approval of the study plan and its amendments, approval of the final report, and ensuring that all applicable Principles. (OECD Nr. 1 - Grundsätze, 1998)

Test facility means the persons, premises and operational unit(s) that are necessary for conducting the non-clinical health and environmental safety study. For multi-site studies, those which are conducted at more than one site, the test facility comprises the site at which the Study Director is located and all individual test sites, which individually or collectively can be considered to be test facilities. (OECD Nr. 1 - Grundsätze, 1998)

Study Director means the individual responsible for the overall conduct of the nonclinical health

and environmental safety study. (OECD Nr. 1 - Grundsätze, 1998)

Test site means the location(s) at which a phase(s) of a study is conducted. (OECD Nr. 1 - Grundsätze, 1998)

Standard Operating Procedures means documented procedures which describe how to perform tests or activities normally not specified in detail in study plans or test guidelines. (OECD Nr. 1 - Grundsätze, 1998)

Basic Terms – Study

Study completion date means the date the Study Director signs the final report. (OECD Nr. 1 - Grundsätze, 1998)

Experimental starting date means the date on which the first study specific data are collected. (OECD Nr. 1 - Grundsätze, 1998)

Study initiation date means the date the Study Director signs the study plan**.** (OECD Nr. 1 - Grundsätze, 1998)

Experimental completion date means the last date on which data are collected from the study. (OECD Nr. 1 - Grundsätze, 1998)

Field study is a study which includes experimental activities carried out outside the usual laboratory situation, such as on land plots, in outdoor ponds or in greenhouses, often in combination or in sequence with activities carried out in a laboratory. (OECD Nr. 6 - Freilandprüfungen, 1999)

***In vitro* studies** are studies which do not use multicellular whole organisms, but rather microorganisms or material isolated from whole organisms, or simulations thereof as test systems. Many in vitro studies will qualify as short-term studies. (OECD Nr. 14 - In-Vitro-Prüfungen, 2004)

Critical phases: Individual, defined procedures or activities within a study, on the correct execution of which the study quality, validity and reliability is critically dependent. (OECD Nr. 14 - In-Vitro-Prüfungen, 2004)

Short-term study means a study of short duration with widely used, routine techniques. (OECD Nr. 1 - Grundsätze, 1998)

Multi-site-study means any study that has phases conducted at more than one site. Multi-site studies become necessary if there is a need to use sites that are geographically remote, organizationally distinct or otherwise separated. This could include a department of an organisation acting as a test site when another department of the same organisation acts as the test facility. (OECD Nr. 13 - Multi-Site-Prüfungen, 2002)

Non-clinical health and environmental safety study, henceforth referred to simply as "study", means an experiment or set of experiments in which a test item is examined under laboratory conditions or in the environment to obtain data on its properties and/or its safety, intended for submission to appropriate regulatory authorities. (OECD Nr. 1 - Grundsätze, 1998)

Phase is a defined activity or set of activities in the conduct of a study. (OECD Nr. 13 - Multi-Site-Prüfungen, 2002)

Specimen means any material derived from a test system for examination, analysis, or retention. (OECD Nr. 1 - Grundsätze, 1998)

Study plan means a document which defines the objectives and experimental design for the conduct of the study, and includes any amendments. (OECD Nr. 1 - Grundsätze, 1998)

Study plan deviation means an unintended departure from the study plan after the study. (OECD Nr. 1 - Grundsätze, 1998)

Study plan amendment means an intended change to the study plan after the study initiation date. (OECD Nr. 1 - Grundsätze, 1998)

Test system means any biological, chemical or physical system or a combination thereof used in a study. (OECD Nr. 1 - Grundsätze, 1998) In context of field studies it could also include complex ecological systems. (OECD Nr. 6 - Freilandprüfungen, 1999)

Raw data means all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study. Raw data also may include, for example, photographs, microfilm or microfiche copies, computer readable media, dictated observations, recorded data from automated instruments, or any other data storage medium that has been recognised as capable of providing secure storage of information for a time period as stated in section 10, below. (OECD Nr. 1 - Grundsätze, 1998)

Basic Terms – Test item

Batch means a specific quantity or lot of a test item or reference item produced during a defined cycle of manufacture in such a way that it could be expected to be of a uniform character and should be designated as such. (OECD Nr. 1 - Grundsätze, 1998)

Test item means an article that is the subject of a study. (OECD Nr. 1 - Grundsätze, 1998)

Reference item ("control item") means any article used to provide a basis for comparison with the test item. (OECD Nr. 1 - Grundsätze, 1998) In the context of field studies, "reference items" are also understood to include analytical standards. (OECD Nr. 6 - Freilandprüfungen, 1999) Analogous to the purpose of a reference item, the definition of the latter may be regarded as covering the terms "positive, negative, and/or vehicle control items" as well. (OECD Nr. 14 - In-Vitro-Prüfungen, 2004)

Sample (reference sample) is used to subsequently check the identity of a test item.
The quantity of samples and storage conditions is to be determined in accordance with this purpose. (Konsensdokument zur Archivierung, 1998)

Vehicle means any agent which serves as a carrier used to mix, disperse, or solubilize the test item or reference item to facilitate the administration/application to the test system. (OECD Nr. 1 - Grundsätze, 1998)

Basic Terms – quality assurance

Facility-based inspections are not based upon specific studies, but cover the general facilities and activities within a laboratory (installations, support services, computer system, training, environmental monitoring, maintenance, calibration, etc.). (OECD Nr. 4 - Qualitätssicherung und QS, 1999)

Study-based inspections are scheduled according to the chronology of a given study, usually by first identifying the critical phases of the study. (OECD Nr. 4 - Qualitätssicherung und QS, 1999)

Quality Assurance Programme means a defined system, including personnel, which is independent of study conduct and is designed to assure test facility management of compliance

with these Principles of Good Laboratory Practice. (OECD Nr. 1 - Grundsätze, 1998)

Process-based inspections are performed independently of specific studies. They are conducted to monitor procedures or processes of a repetitive nature and are generally performed on a random basis. (OECD Nr. 4 - Qualitätssicherung und QS, 1999)

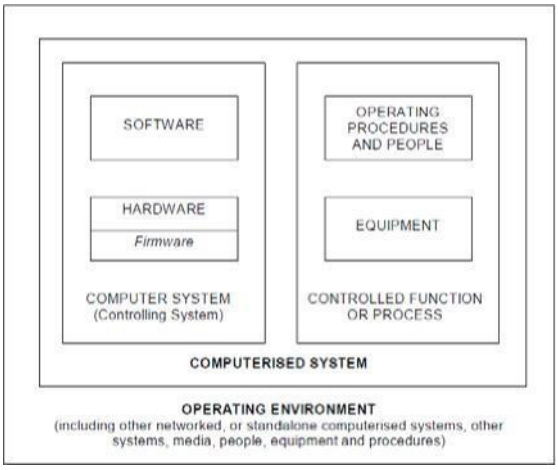
Basic Terms – Archive and computerized systems

Archive is a designated area or facility (e.g. cabinet, room, building or computerised system) for the secure storage and retention of records and materials. (OECD Nr. 15 - Archive, 2007)

Archive Staff are Individuals who work under the supervision of the archivist and who are responsible for the routine archive operations. (OECD Nr. 15 - Archive, 2007)

Archivist is an individual designated by test facility or test site management to be responsible for the management of the archive, i.e. for the operations and procedures for archiving. (OECD Nr. 15 - Archive, 2007)

Computerized System is a function (process or operation) integrated with a computer system and performed by trained personnel. The function is controlled by the computer system. The controlling computer system is comprised of hardware and software. The controlled function is comprised of equipment to be controlled and operating procedures performed by personnel." *PIC/S PI 11-3 "Good Practices for Computerised Systems in Regulated GxP Environments"* (OECD Nr. 17 - Computerised Systems, 2016)



Electronic archives are **f**acilities and systems provided to maintain electronic records as required by the Principles of GLP. (OECD Nr. 15 - Archive, 2007)

Electronic records are all original laboratory records and documentation, including data directly entered into a computer through an instrument interface, which are the results of original observations and activities in a study and which are necessary for the reconstruction and evaluation of the report of that study. (OECD Nr. 15 - Archive, 2007)

Life cycle is an approach to computerised system development that begins with identification of the user's requirements, continues through design, integration, qualification, user validation, control and maintenance, and ends when use of the system is retired. (OECD Nr. 17 - Computerised Systems, 2016)

Metadata are Data that describe the attributes of other data. Most commonly these are data that describe the structure, data elements, inter-relationships and other characteristics of electronic records. (OECD Nr. 15 - Archive, 2007)

Migration: is the transfer of electronic records from one format, media or computerized system to another. (OECD Nr. 15 - Archive, 2007)

Qualification is the action of proving that any equipment including software operates correctly and is fit for its purpose. (OECD Nr. 17 - Computerised Systems, 2016)

System owner is the manager, or designee, of the department that is most impacted by, or is the primary user of, the system. (OECD Nr. 15 - Archive, 2007)

Validation is the action of proving that a process leads to the expected results. Validation of a computerised system requires ensuring and demonstrating the fitness for its purpose. (OECD Nr. 17 - Computerised Systems, 2016)

III. Annexes

The annexes are listed in separate documents:

Annex 1 Standard operating procedures

Annex 2 Short-term studies

Annex 3 Inspection of data processing (DP) systems

Annex 4 Multi-site studies

Annex 5 Areas of application of GLP

Annex 6 Test Categories

Annex 7 Test Methods

Conducting GLP Inspections in Germany

Manual
Annex 1: Standard Operating Procedures

National and Länder Working Party
Chemicals Safety Committee "GLP and other quality assurance systems" BLAC-AS GLP

As of: January 2018

Annex 1: Standard Operating Procedures (SOP)

1. Requirements

The Test Facility must have at its disposal written SOPs in the German language, approved by the Test Facility management. Foreign language SOPs can be accepted in exceptional circumstances if the TF can prove that all employees who have to work with the SOP have a sufficient grasp of the language. In accordance with Art. 23 of the Administrative Procedures Act, the monitoring authority and inspection team have the right to demand at any time that the documents required for the monitoring procedure be presented to them in German.

SOPs must be available on site. It must be ensured that **only** the latest version is kept. Superseded versions must be either removed (collected in) or marked as invalid.

Technical manuals, operating instructions, etc. can be used as an additional help. If they are a part of the SOP, they must be archived along with it. This is not necessary if they are only referred to in the SOP and the main information in the technical manual/operating instructions is already contained in it.

1.1. Formal requirements

- Labelling with descriptive title and name
- Name of TF
- Code and version number on each page
- Total number of pages including annexes
- Area of validity
- Distribution list
- Author and date of drafting
- Approval and date of entry into force (signature of TFM)
- Documented acknowledgement by QA

1.2. Additional requirements

Source references or apparatus manufacturers' operating instructions.

Amendments and changes must be approved and dated (amendments guaranteed on all authorised copies)

Review and updating procedures must be available. There must be historical filing of all SOPs. A list of all GLP-relevant SOPs is helpful.

Standard operating procedures for check of apparatus, equipment, etc., must contain instructions for cases where the prescribed tolerances or conditions are not complied with.

In the "Organisation and Personnel" sector the points listed below require adequate written rules, but not necessarily in the form of standard operating procedures:

- Organigram
- Descriptions of tasks
- CVs
- Basic and advanced training
- List of names, initials
- Distribution list for standard operating procedures

2. Areas to be covered

At least the following areas must be covered by standard operating procedures, while several of these points may be combined in a single SOP:

a) Test and reference items (TRI)

- Receipt
- Identification/authentication
- Purity (composition, level of active ingredient)
- Labelling
- Handling
- Removal
- Preparation
- Use
- Stability
- Homogeneity and stability of mixtures (carrier substances)
- Reference samples
- Storage
- Disposal

b) Apparatus, materials and reagents

- Labelling of reagents
- Labelling of apparatus

- Use
- Maintenance (logbooks)
- Cleaning (logbooks)
- Calibration with details of permissible tolerances where applicable
- Validation, operation, maintenance, safety, controlled system changes (change control) and data back-up of/in computerised systems
- Expiry dates
- Preparation of reagents
- Preparation of application form
- Control of environmental conditions

c) Record-keeping, reporting, storage and retrieval

- Coding of studies
- Data collection
- Drafting of reports
- Indexing systems
- Data handling
- Validation of DP systems
- Storage of records and reports
- Access rules
- Registration of borrowings and returns
- Preparation of standard operating procedures (drafting, amendment, updating, authorisation, distribution, archiving)
- Drafting of study plans
- Historical development of standard operating procedures

d) Test systems

- Preparation of facilities
- Preparation and check of room environment conditions
- Receipt
- Quarantine
- Implementation (forwarding)
- Housing/storage
- Handling

- Characterisation
- Identification
- Permanent and unambiguous labelling
- Feeding, maintenance, medical care
- Storage of feed, litter, etc.
- Checking quality of feed and water, procedure if deficiencies are found
- Cleaning of cages, feed containers and other equipment
- Separation of clean and unclean areas (cage washing facilities, animal rooms)
- Preparation of test systems
- Randomisation
- Application
- Observation of test systems
- Examination of test systems
- Dealing with superfluous animals, plants, etc.
- Dealing with moribund or dead individual test systems
- Disposal of test systems
- Collection/taking of specimens
- Naming/labelling of specimens
- Handling of specimens (necropsy, histopathology)
- Placing and choosing of test systems and test areas

e) QA procedures

- Audits
- Inspections
- Checking of study plans and final reports
- Reporting
- Quality Assurance statement
- Participation in the preparation of standard operating procedures

f) Methods – standard operating procedures (analyses, studies)

g) Computerised systems

- Operation of DP system
- Responsibilities of personnel
- Safety measures
- Definition of raw data
- Procedure for determining specifications of apparatus
- Procedure for changing the programme
- Validation procedure
- Documentation procedure
- Regular check of correct function
- Maintenance procedure
- Software development
- Acceptance tests and documentation
- Back-up procedure
- Archiving of data
- Making legible electronically recorded data

h) Dispatch of materials and documents to associated/independent TSs or other TFs

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Annex 2: Short-term studies

National and Länder Working Party
Chemicals Safety Committee "GLP and other quality assurance systems" BLAC-AS GLP

As of: November 2017

Annex 2: Short-term studies

A simplified procedure is possible for short-term studies carried out in accordance with the OECD GLP Principles. It is described in GLP Consensus Document No 7, Application of the GLP Principles to short-term studies.

1. Definition of short-term study

OECD Principles of Good Laboratory Practice / ChemG Annex I:

A short-term study is a study of short duration with **widely used, routine methods**.

Description in OECD Consensus Document No. 7:

There is neither a precise definition nor a comprehensive list of short-term studies. The term "short" can be interpreted differently for biological studies than for physical-chemical studies. Classification is therefore made above all on the basis of parameters such as the:

- Duration of critical phases
- Frequency with which studies are conducted and therefore routine of personnel involved
- Complexity of the test system

It therefore follows that one and the same study cannot necessarily be regarded as a short-term study in every TF. Decisions must be made in each individual instance which must be **documented by the TF**. A very simple test, such as the determination of melting point, may not necessarily be a short-term study either if it is only conducted rarely in a TF.

2. Requirements

2.1. Quality assurance

QA does not have to conduct an inspection of a critical phase for every short-term study. **Process-based inspections** can be conducted instead.

The process-based inspection programme must cover **every single study type** defined by the TF as a short-term study and not inspected in line with a specific study (OECD 7, II.2.2.1.). The frequency should be specified in an SOP and depends on the number, frequency and complexity of the studies in each study type.

It must be clearly described in the QA statement on every study **which type** of inspection (study or process-based) was performed and **when**.

Every single final report must be audited by QA. This must be clearly indicated in the QA statement.

2.2. Standard study plan and final report

A standard study plan (SP) and final report (FR) can be prepared with each containing the repetitive information.

The essential thing here is that **the standard document together with each study-specific supplement contains all of the requested content** for the SP and FR. If a study type is always conducted for the same sponsor, for example, his or her address could be included in the standard SP.

Signature ruling:

Standard SP: TFM, all applicable SDs, QA

Study-specific supplement to the SP: current SD, acknowledgement QA

Standard FR: TFM, all applicable SDs

Study-specific supplement to the FR: current SD, QA statement

Deviations from the standard SP should be dealt with like study plan amendments. Deviations from the standard FR should be dealt with like corrections to the FR (supplement with clear justification and dated signature of the SD).

2.3. Apparatus, test systems, TRI

Regulations have to be established as to how activities which are not conducted for every single short-term study (calibration, characterisation of TRI and microbiological test systems…) are to be conducted and documented regularly in compliance with GLP.

3. Summary of the most important points

- A case-by-case decision on the definition of “short-term study” may have to be made and documented on the basis of frequency and complexity. The duration should not be overestimated as an indicator.
- QA must inspect every study type either study- or a process-based. This must be regulated in an SOP. QA must audit every FR and give precise details of the inspection in the QA statement.
- The facilitating measures for QA and SP/FR may or may not be used at the same time. The regulations regarding QA inspections and SP/FR must be clearly established for every study type, however.
- Standard SP and/or standard FR and each study-specific supplement must collectively have all of the required contents.
- Study-based activities must be regulated to comply with GLP and documented.

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Annex 3: Inspection of data processing (DV) systems

National and Länder Working Party
Chemicals Safety Committee "GLP and other quality assurance systems" BLAC-AS GLP

As of: November 2017 - Draft

Annex 3: Inspection of data processing (DV) systems

Following the release of the new OECD document No. 17 "Application of GLP Principles to Computerised Systems" a revision of this Annex is required.

Conducting GLP Inspections in Germany

Manual
Annex 4: Multi-Site Studies

National and Länder Working Party
Chemicals Safety Committee "GLP and other quality assurance systems" BLAC-AS GLP

As of: January 2018

Annex 4: Multi-Site Studies

Non-clinical health and environmentally safety studies can be conducted as multi-site studies for a variety of reasons. In a multi-site study, phases of this study are conducted at more than one site due to geographical or organisational conditions or because special methods are being used. In OECD Consensus Document No. 13 on multi-site studies, the phase of a study is defined as "...a defined activity or set of activities in the conduct of a study". The term "activities" is understood to comprise all of the individual phases of a GLP study. These include:

- The field part of a field study
- Histopathological diagnosis
- Analytics within the scope of toxicological and/or ecotoxicological studies
- Archiving

Due to the fact that various study activities are carried out at different test sites, the planning, clear assignment of responsibilities, effective communication and traceable control of the study are of decisive importance.

Even though a multi-site study is made up of a number of examinations and activities conducted at more than one test site, it is still a single study. This means that there is only one study plan (SP), one SD who assumes responsibility for the entire study and that only one final report (FR) is prepared. With the definition of a multi-site study in the consensus document, however, it is not ruled out that complex studies (examinations) can continue to be split into individual, independent GLP studies.

The SD is usually located at the TFM site. If this is not the case, the inspection team should nevertheless insist when auditing a study within the scope of an inspection of the TF that the SD can be questioned. It should be checked whether the SD has the capability of assuming responsibility for the supervision of all phases of a study and whether the prerequisites for doing so exist in the TF.

Every phase of a multi-site study must usually be conducted in compliance with the GLP Principles and be verifiable by an inspection committee. An involved TS therefore has its own GLP certification or works as a dependent TS of the TF. If phases of a study at a TS cannot be conducted in compliance with the GLP Principles, this must be reported in the GLP statement of compliance.

Questions are formulated below which can be of significance in the inspection of multi-site studies:

1. Organisation and Personnel

1.1.1.1. Were written agreements reached between the commissioning TF and the contracted TS during study planning regarding the establishment of responsibilities, the type and extent of required information, the communication channels to be maintained, the assurance of the necessary QA measures, the structure of the final report, archiving modalities and measures to be taken in the event of unforeseen occurrences?

1.1.1.2. When was the SD appointed by the TFM? Where is the SD located?

1.1.1.3. Were the SD and QA involved in the selection of the TS and decisions to conduct study activities at other sites? Does the SD assured oneself that the TS could comply with the GLP Principles?

1.1.1.4. Were suitable communication channels established, set up and tested in advance?

1.1.1.5. Did communication between the participants take place directly and was it documented?

1.1.1.6. Were one or more PIs appointed before the beginning of the study or as necessary prior to a corresponding study phase? How did the SD ensure the supervision of the study phases if no PI was appointed?

1.1.1.7. Was a procedure established for the replacement of a PI?

1.1.1.8. Were all persons involved made aware of the requirements of the study?

1.1.1.9. Is proof of qualification and a job description on hand for all persons (even those with temporary employment if they perform study-relevant tasks)?

1.1.1.10. Does the Master Schedule of the TF contain details of the involved TSs, PIs and study phases, where necessary with the appropriate coding, initiation and completion date of the overall study?

1.1.1.11. Does the Master Schedule of a TS contain details of the TF, SD, PI, study phase, where necessary with the appropriate coding of the study, initiation and completion date of the corresponding study phase?

2. Quality Assurance

2.1.1.1. Has a lead QA been appointed?

2.1.1.2. Where is this lead QA located?

2.1.1.3. Was a joint inspection schedule prepared between the lead QA and the local QA active on-site at the TS before the beginning of the study?

2.1.1.4. Was the involved QA personnel appointed?

2.1.1.5. Were the responsibilities and scope of the monitoring tasks of the participating QAs established?

2.1.1.6. Which SOPs are used for the monitoring programme?

2.1.1.7. Does the QA unit involved at the TSs have copies of the study plan and any study plan amendments?
2.1.1.8. How is reporting handled by the QA unit with responsibility at the TSs?
2.1.1.9. Were the inspection results at the TS reported without delay to the PI, TSM, SD, TFM and lead QA?

3. Study Plan

3.1.1.1. Was acknowledgement of the study plan by the PI documented?
3.1.1.2. Was a documented agreement reached to the effect that the PI is to conduct the assigned study phase in compliance with the study plan and GLP Principles?
3.1.1.3. Does the study plan contain details of all involved TSs, as well as the name, address, telephone numbers etc. of the corresponding PI?
3.1.1.4. Are all involved QA units named?
3.1.1.5. If no PI was appointed at a TS, was the personnel with whom the SD was to have direct contact at the test site listed in the study plan?
3.1.1.6. Are the study phases that are to be carried out at a TS presented in detail in the study plan or study plan amendment?
3.1.1.7. Are the SOPs relevant to the execution of the corresponding study phases and/or the procedures to be applied listed in the study plan?
3.1.1.8. Were amendments to the study plan justified and approved exclusively by the SD?
3.1.1.9. Does the study plan contain details of how the data generated at the TSs is to be conveyed to the SD for inclusion in the final report?
3.1.1.10. Does the study plan contain details of all archiving locations?
3.1.1.11. Has the lead QA audited the study plan?
3.1.1.12. Were the parts of study plan relating to activities at the TSs audited by each responsible QA unit?
3.1.1.13. When TFs/TSs with different languages collaborate, does the original study plan contain details of the required translations? Are the translations enclosed with the study plan?
3.1.1.14. How was the correctness and completeness of a translated study plan ensured?

4. Standard Operating Procedures

4.1.1.1. Does the personnel at the TSs have access to all applicable SOPs?
4.1.1.2. If work is to be done at a TS in line with an SOP of the TF, has the TSM given written consent to the use of the SOP of the TF?
4.1.1.3. Has it been ensured that only the latest versions of the SOP of the TF are on hand at the TSs? Are old versions replaced with new ones?

4.1.1.4. When TFs/TSs with different languages collaborate, how was the correctness and completeness of the necessary translations ensured?

5. Performance of the study

5.1.1.1. Are internal coding's of the study phases at the TSs traceable to the original coding of the study?

5.1.1.2. Do the PIs notify the SD in writing about the progress of the applicable phases of the study?

5.1.1.3. Were documented procedures for the transfer of data and materials established which guarantee their integrity? Are there any gaps in documentation? Have appropriate responsibilities been stipulated?

5.1.1.4. Have regulations been established for the storage, return and disposal of excess test and reference items?

5.1.1.5. Were deviations from the study plan or SOP reported to the SD in a timely manner?

5.1.1.6. Were deviations documented at the TS and confirmed by the PI? Has the SD confirmed acknowledgement and taken the necessary measures?

5.1.1.7. Did the PI forward all raw data, specimens etc to the SD upon conclusion of the study phase or archive them in line with the study plan? Was the SD notified of the archiving?

5.1.1.8. Were specimens disposed of at the TS? Is the written consent of the SD on hand?

5.1.1.9. Does the TS personnel have knowledge of the currently applicable procedures? Were the corresponding training measures carried out? Were they documented?

6. Final Report

6.1.1.1. Does the final report contain details of the involved TSs, PIs and the study phases delegated to them, as well as the results thereof and all tasks undertaken within the scope of the overall study?

6.1.1.2. Were phase-reports prepared by the PI? Were they integrated into the overall report, signed by the responsible PI and was it clarified to what extent the phase of the study was conducted in compliance with GLP Principles? Was the phase-report reviewed by the QA unit responsible at the TS?

6.1.1.3. Were all study phases and all contributions of the PI taken into account in the final report? Do the contributions of the PI contain written assurances that GLP Principles were complied with?

6.1.1.4. Has the SD signed and dated the final report and assumed responsibility for the reliability of all data by declaring the extent to which the overall study complies with GLP Principles?

6.1.1.5. Does the final report contain details of all storage sites of study-related raw data, documentation, samples of test and reference items and specimens?

6.1.1.6. Was the final report audited by the lead QA?

6.1.1.7. Is a signed statement from the lead QA enclosed with the final report?
Does it contain details of the inspections conducted at all TSs or is reference made to a declaration of the QA unit responsible at the TS?

6.1.1.8. Were corrections and supplements to a final report made in the form of addenda by the SD? Did the SD and PI confer if it involved an addendum to a delegated phase of a study?

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Manual
Annex 5: Areas of application of GLP

National and Länder Working Party
Chemicals Safety Committee "GLP and other quality assurance systems" BLAC-AS GLP

As of: January 2018

Annex 5: Areas of application of GLP

1. GLP requirements in EU legislation

This section is based on the document „EU legislation with Good Laboratory Practice (GLP) provisions“ of the European Commission from March 2016 (downloadable on the website of the European Commission).

In italics are supplements and updates that have emerged since the publication of the document until July 2017.

1.1. chemicals

1.1.1. Directive (EC) No 2004/10 (GLP)

Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (codified version)

1.1.2. Regulation (EC) No 1907/2006 (REACH)

Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals ('REACH') establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

- **Ecotoxicological and toxicological tests** and analyses shall be carried out in compliance with the principles of good laboratory practice (Regulation (EC) No 1907/2006 Article 13, paragraph 4)

  Note: In addition to GLP, the REACH Regulation also allows other international standards. These are recognized as equivalent by the Commission or the European Chemicals Agency (ECHA). However, such standards are currently not available (see also Q & A of ECHA, ID number 0117).

1.1.3. Regulation (EC) No 1272/2008 (CLP)

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

- **toxicological and ecotoxicological tests** shall be carried out in accordance with the principles of good laboratory practice by reference to Article 13 (4) of the REACH Regulation (CLP Regulation Article 8 (4))
- according to "ECHA Guidance on the Application of the CLP Criteria (November 2013)" it is possible to apply regulations of EN ISO/IEC 17025 (competence assessment for testing and calibration laboratories) or other internationally recognized standards for testing **physical hazards** (CLP Regulation Article 8 (5)), in addition to GLP

1.2. biocides and pesticides

1.2.1 Regulation (EU) No 528/2012 (biocidal products)

Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products

- **toxicological and ecotoxicological tests** shall be carried out in accordance with the principles of Good Laboratory Practice (Regulation (EU) No 528/2012, Annex II No 6 with reference to Directive 2004/10 / EC.)

  Note: In addition to GLP, the biocides regulation also allows other international standards. These are recognized as equivalent by the Commission or the European Chemicals Agency (ECHA). However, such standards are currently not available (see also Q & A of ECHA, ID number 0989).
- For tests on **physico-chemical** properties, just established international standards are required (Regulation (EU) No 528/2012, Annex II, No 6)

1.2.2 Regulation (EC) No 1107/2009 (pesticides)

Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 is the Regulation on placing plant protection products on the market and repealing Council Directives 79/117 / EEC and 91/414 / EEC in conjunction with Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013

- **Test and study reports** shall be prepared in accordance with GLP Principles.

Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market

- **Tests and analyzes** that serve to obtain data on the properties or safety with respect to human health, animal health or the environment (Regulation (EU) No 283/2013 Appendix Introduction No 3.1) shall be conducted in accordance with the GLP Principles.

Deviating regulations appear in the annex introduction No 3.2 of the regulation for example e.g. for experiments and analyzes to obtain data on small-scale crops.

Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market

- **Tests and analyzes** that serve to obtain data on the properties or safety with respect to human health, animal health or the environment Regulation (EU) No 284/2013 Appendix Introduction no. 3.1) shall be conducted in accordance with the GLP Principles. Deviating regulations appear in the annex introduction No 3.2 to 3.4 of the regulation

1.3 feed/food additives

1.3.1 Regulation (EC) No 429/2008 (feed additives)

Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives

- Implementation and documentation of investigations with appropriate quality standards, e.g. Good Laboratory Practice (Regulation (EC) No 429/2008 Annex II)
- for in vivo or in vitro studies conducted outside the Community: evidence that the facilities comply with the OECD Principles of Good Laboratory Practice or ISO standards (Regulation (EC) No 429/2008 Annex II)

  Further information on GLP requirements can be found in sections 2 and 3 of Annex II to Regulation (EC) No 429/2008, including on toxicological studies

1.3.2 Regulation (EU) No 234/2011 (food additives)

Commission Regulation (EU) No 234/2011 of 10 March 2011 implementing Regulation (EC) No 1331/2008 of the European Parliament and of the Council establishing a common authorisation procedure for food additives, food enzymes and food flavourings

- **toxicological tests** in accordance with GLP Principles (Regulation (EU) No 234/2011 reason to consider No 7)
- **toxicological studies** shall be conducted in facilities which comply with the requirements of Directive 2004/10 / EC (Regulation (EU) No 234/2011, Article 5 (7))

1.3.3 Commission Implementing Regulation (EU) No 503/2013 (genetically modified food and feed)

Commission Implementing Regulation (EU) No 503/2013 of 3 April 2013 on applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No 1829/2003 of the European Parliament and of the Council and amending Commission Regulations (EC) No 641/2004 and (EC) No 1981/2006

- **toxicological studies** shall be conducted in facilities
    - which comply with the requirements of Directive 2004/10 /EC (Commission Implementing Regulation (EU) No. 503/2013 Article 4 (1)(b)

      or
    - in accordance with "OECD Principles of Good Laboratory Practice", if carried out outside the EU (Commission Implementing Regulation (EU) No 503/2013, Article 4 (1) (b)).
- Studies, **other than toxicological studies**, shall:
    - comply with the principles of Good Laboratory Practice (GLP) laid down in Directive 2004/10/EC (Commission Implementing Regulation (EU) No 503/2013 Article 4 (2)(a))

      or
    - conducted by accredited facilities according to the relevant ISO standard (Commission Implementing Regulation (EU) No 503/2013 Article 4 (2)(b))

1.3.4 97/618/EC: Commission Recommendation of 29 July 1997 (novel foods)

97/618/EC: Commission Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council

- Studies to **determine the allergen potential** (Annex Part I No. 3.10 of Recommendation 97/618 / EC)) should comply to the corresponding principles and ethical principles of good clinical practice and good laboratory practice
- **Studies for the determination of nutritional information** on the novel food (Annex Part I, No 5, Section XI of Recommendation 97/618 / EC) should comply to the corresponding principles and ethical principles of good clinical practice and good laboratory practice

1.4 medical products and medical devices

1.4.1 Commission Directive 2003/63/EC (medicinal products for human)

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use and Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC

- **Preclinical (pharmaco-toxicological)** studies shall be conducted in accordance with Good Laboratory Practice (Directive 2003/63 / EC, Annex I "Introduction and General principles", paragraph 9)
- **Toxicological trails** of radiopharmaceuticals precursors for radioactive labeling purposes (Directive 2003/63 / EC Annex I Part III Number 2.2 Module 4)

1.4.2 Regulation (EU) No 536/2014 (clinical trials)

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

- **Non-clinical information** shall be based on data derived from studies complying with the principles of good laboratory practice (Regulation (EU) No 536/2014, Article 25 (3))

1.4.3 Commission Directives 2009/9/EC (medicinal products for veterinary use)

Commission Directives 2009/9/EC of 10 February 2009 amending Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to medicinal products for veterinary use

- **Pharmacological, toxicological, residue and safety tests** shall be carried out in conformity with the provisions related to good laboratory practice (GLP) (Commission Directives 2009/9/EC (Annex I "Introduction and general principles", paragraph 6)

1.4.4 Regulation (EU) 2017/745 (medical devices)

Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

Note: The Regulation entered into force on 25 May 2017. It applies from 26 May 2020 (deviations see Article 123 paragraph 3 of the Regulation)

According to Annex II "Technical Documentation" No. 6.1 (Preclinical and Clinical Data), proof of compliance with the GLP Principles may be required for certain test.

1.5 cosmetic products

1.5.1 Regulation (EC) No 1223/2009

Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products

- **Non-clinical safety studies** (after 30.06.1988) must be carried out in accordance with the principles of good laboratory practice (Regulation (EC) No 1223/2009 Article 10 (3))

  Note: In addition to GLP, the Regulation also allows other international standards. These are recognized as equivalent by the Commission or the European Chemicals Agency (ECHA). However, such standards are currently not available

1.6 detergents

1.6.1 Regulation (EC) No 648/2004

Regulation (EC) No 648/2004 of the European Parliament and of the Council of 31 March 2004 on detergents

- **tests specified for the biodegradability of surfactants** should be carried out in laboratories meeting an internationally recognised standard, namely EN/ISO/IEC/17025 or the principles of good laboratory practice (Regulation (EC) No 648/2004, reason to consider 30, Article 7)

2 GLP obligation in German law

The Chemicals Act requires compliance with the GLP Principles for non-clinical health and environmental safety studies of substances or mixtures. The results should enable authorities to assess possible hazards to humans and the environment

In the General Administrative Provision Relating to the Procedure for Official Monitoring of Compliance with the Principles of Good Laboratory Practice (ChemVwV-GLP)[1], the area of application for biocides (1), chemicals (2), plant protection products (3), pharmaceuticals (4), explosives (5) and food/feed additives (6) is specified in number 2.

In particular, the following non-clinical experimental studies are subject to the scope of § 19a (1) ChemG:

1. Testing of biocidal products requiring authorisation with regard to the testing proofs to be included in the authorisation procedure in line with Article 12d para. 2 sentence 1 of the Chemicals Act;
2. Testing of substances for ecotoxicity and toxicity in line with Article 13 para. 4 of Regulation (EC) No. 1907/2006;
3. Testing of plant protection products requiring authorisation with regard to the trial reports and studies to be submitted in line with Article 8 para. 2 and Article 33 para. 3 of Regulation (EC) No. 1107/2009;
4. Testing of pharmaceuticals requiring authorisation in line with Article 21 of the Medicines Products Act, with regard to the toxicological trials specified in Article 22 para. 2 no. 2;
5. Testing of substances for explosion hazard in line with Article 2 in conjunction with Article 1 para. 1 sentence 2 of the Explosives Act (Sprengstoffgesetz) in conjunction with the test method according to Annex Part A.14 of Regulation (EC) No. 440/2008;
6. Testing of food additives in the event of the implementation of legal regulations based on Article 4 para. 3 no. 2 and Article 7 of the Food and Feed Code (Lebensmittel- und Futtermittelgesetzbuch).

“This Administrative Provision is also applicable to studies which do not come under Art. 19 a para. 1 of the Chemicals Act in cases where, on the basis of legal actions taken by a body of the European Union, the studies have to be conducted according to the Principles of Good Laboratory Practice.”

[1] Recast of the General Administrative Regulation on the Regulatory Compliance of 15 May 1997 and the General Administrative Regulation amending the General Administrative Provisions on the Regulatory Compliance of 16 November 2011 with the Principles of Good Laboratory Practice.

Conducting GLP Inspections in Germany

Manual
Annex 6: Test Categories

National and Länder Working Party
Chemicals Safety Committee "GLP and other quality assurance systems" BLAC-AS GLP

As of: November 2017

Annex 6: test categories

Test category	Field of Application	
1	Prüfungen zur Bestimmung der physikalisch-chemischen Eigenschaften und Gehaltsbestimmung	Physical-chemical testing
2	Prüfungen zur Bestimmung der toxikologischen Eigenschaften	Toxicity studies
3	Prüfungen zur Bestimmung erbgutverändernden Eigenschaften (in vitro und in vivo)	Mutagenicity studies
4	Ökotoxikologische Prüfungen zur Bestimmung der Auswirkung auf aquatische und terrestrische Organismen	Environmental toxicity studies on aquatic and terrestrial organisms
5	Prüfungen zum Verhalten im Boden, im Wasser und in der Luft; Prüfungen zur Bioakkumulation und zur Metabolisierung	Studies on behaviour in water, soil and air; bioaccumulation
6	Prüfungen zur Bestimmung von Rückständen	Residue studies
7	Prüfungen zur Bestimmung der Auswirkungen auf Mesokosmen und natürliche Ökosysteme	Studies on effects on mesocosms and natural ecosystems
8	Analytische Prüfungen an biologischen Materialien	Analytical and clinical chemistry testing
9	sonstige Prüfungen (mit Erläuterung)	other studies (specify)

With the entry into force of the new version of the General Administrative Regulation concerning Chemicals - Good Laboratory Practice (ChemVwV-GLP) of May 1997, the subdivision of the GLP studies into nine categories was introduced in Germany.

The definition of the term "study" is left wide open in the GLP Principles so as to give the national authorities and industry plenty of leeway in practical implementation. For example, a field study that takes place at a number of locations can be carried out as an overall study or split up into several self-contained independent studies. Every self-contained study has to have a study plan, a Study Director and a final report.

The regulatory authorities make some suggestions as to what they mean by a study, but it is ultimately the test facility itself which defines what it regards as a study in the sense of the GLP Principles.

The purpose of the test categories is to improve the information exchange between the OECD Member countries and to inform regulatory authorities and potential sponsors about the areas taken into account in the national GLP inspections. Studies which do not obviously fit into any of the given categories are not rejected by the regulatory authorities for formal reasons. If the regulatory authorities have serious reservations as to whether the studies submitted are covered by the test categories in the GLP certificate/list, this can be clarified from case to case on the basis of the inspection reports or an enquiry to the competent monitoring authorities.

All parts of a study, e.g. stock-keeping, breeding, analysis etc. in the case of toxicological studies, are contained in the relevant test category. If, in addition to carrying out complete studies, a test facility also works as contract partner/ test site for studies in the same category, e.g. on behalf of other test facilities, these are also covered, even if in this case the whole study is not carried out. Analysis, for example, is contained in test categories 2-7 and so it is not necessary to additionally assign category 8 as well in cases of this kind.

A special case exists with specialised analytical laboratories, which often carry out parts/phases of GLP studies for different sponsors. If this is done under a subcontract, the analytical laboratories have to be included in any GLP inspection carried out by the sponsor. It may be more practical and make more sense in this case for the analytical laboratories to have their own GLP certificate. That is why the OECD introduced test category 8, although the analysis reflects more often a parts of a GLP study than a self-contained study. The prerequisite for laboratories to be given their own GLP certificate is the full implementation of the GLP Principles.

Even if the full range of a test category is not conducted, the whole category should still be designated as a rule. Particular attention should then be given in the next inspection to the possibility of an intermediate extension of the scope of the study. Only if there are justified reservations, e.g. about certifying a complete test category on the basis of a very small amount of testing done at a particular test facility, can narrowly defined test areas in categories 1 to 7 also be placed into category 9.

A few explanations and examples of the individual OECD test categories are given below:

test category 1:

Studies to determine physical-chemical properties and content

This category contains studies whose results are used exclusively for determining physical, chemical and physical-chemical parameters. These studies are listed in Regulation 440/2008/EC - Section A: Methods for determining physical-chemical properties.

test category 2:

Studies to determine toxicological properties

The prerequisite for a study to be placed in this test category is that a test item is applied to the animal and the results of the study are to be used for evaluating toxic effects on humans. All areas necessary for carrying out the study, such as breeding, husbandry and caring for the experimental animals, and the accompanying analyses, also fall into this category. These studies are listed in Regulation 440/2008/EC - Section B: Methods for determining toxicity and other effects.

Examples are studies on:

acute toxicity (oral, dermal, inhalative); sub-acute toxicity (28 days); sub-chronic toxicity (90 days); chronic toxicity; skin and eye irritation; sensitisation; behaviour-disturbing properties; carcinogenicity; reproductive toxicity, teratogenicity; embryotoxicity; toxicokinetics.

test category 3:

Studies to determine mutagenic properties (in vitro and in vivo)

This test category comprises studies on genotoxicity, in particular in vitro mutagenicity tests. In the case of in vivo studies there are overlaps with test category 2. These studies are also listed in Regulation 440/2008/EC - Section B: Methods for determining toxicity and other effects.

Examples are studies on:

reverse mutation (*E. coli, S. typhimurium*); gene mutation, mitotic recombination (*Saccharomyces cerevisiae*); lethal mutation (*Drosophila melanogaster*); mammalian cells in vitro (DNA damage and repair, sister chromatid exchange, cell transformation); in vivo mammalian (micronucleation test, dominant lethal test, germ-cell cytogenetic test, spot test, translocation test).

test category 4:

Ecotoxicological studies to determine impact on aquatic and terrestrial organisms

This category groups all ecotoxicological tests on individual species which are used for evaluating risks to the environment. The studies focus primarily on the effects of the substance on organisms. A distinction is made between aquatic and terrestrial habitats/ecosystems on account of their sharply contrasting structures. In aquatic habitats it is the medium - water - which determines the biotope. The terrestrial habitat is determined at least by soil and air, which are also understood to be subdivisions of the terrestrial habitat. The term "terrestrial organisms" is therefore more comprehensive than "soil organisms", and category 4 therefore also includes useful animals, bees, insects and birds.

These studies are listed in Regulation 440/2008/EC- Section C: Methods for determining ecotoxicity.

Examples are studies of toxicity/effects on:

fish (acute, prolonged), daphnia (acute, prolonged); birds, bacteria, soil organisms (soil fauna); soil microflora; higher plants; green algae; honey bees; other useful organisms. Feeding studies with investigations of the metabolism and kinetics of residues in the feed in order to assess damage to the health of farm animals or wild animals are also covered by this category.

test category 5:

Studies on behaviour in soil, water and air; studies of bioaccumulation and metabolisation

The studies mainly cover assessment of the behaviour of the substance, such as its volatilisation, conversion, binding and distribution. In this way, the availability of a substance in the environment is examined, which can have an influence on the nature and duration of possible effects and which forms the basis for an exposure analysis. Direct harmful effects on organisms are not covered by studies in this category.

Examples are studies on:

retention in soil, water and air, photolysis, volatility from plants and from the soil, photochemical-oxidative decomposition, adsorption/desorption, bioaccumulation in fish and lysimeter studies.

test category 6:

Studies to determine residues

Test category 6 mainly comprises residue experiments in accordance with the guidelines of the Federal Biological Institute for the Testing of Plant Protection Products in Authorisation Procedures. If studies of residues in water and soil have to be carried out as a fixed part of these experiments, they should also be included here. All subsectors of these studies, e.g. application, sampling, specimen preparation and analysis, are covered.

test category 7:

Studies to determine impact on mesocosms and natural ecosystems

In these studies the entry, retention and ecological effects of test items in artificially created complex ecosystems or directly in the field are examined. These studies can be decisive in the framework of the authorisation procedure for plant protection products if comparisons

of exposure analysis and ecotoxicological results on individual species do not permit any conclusive risk analysis. The design of the study varies according to the specific task. For the aquatic sector, the so-called "pond studies", in which different concentrations of the test substance are applied to several parallel artificial ponds, are the most common type of study on mesocosms. In the USA, GLP studies have been carried out on aquatic and terrestrial ecosystems in accordance with the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) since 1989.

test category 8:

Analytical studies on biological materials

Category 8 concerns those test facilities which exclusively carry out analytical tests in categories 2 to 7.

test category 9:

Other studies (with explanation)

This category covers all studies not included in categories 1 to 8. These can also be studies which are not required to comply with GLP Principles (Art. 19a Chemicals Act) in Germany but which were inspected for compliance with the GLP Principles pursuant to a "justified interest" in accordance with Art. 19b (1) Chemicals Act. Narrowly defined test areas in test categories 1 to 8 may also be placed in this category if subdivision of the corresponding overall test category appears to be too extensive.

An updated overview of GLP test facilities and certified study types in test category 9 is contained in the “List of test facilities/test sites with GLP certification in Germany”. It is published once a year in the Federal Gazette. The latest version can be downloaded from the website of the Federal Institute for Risk Assessment.

Conducting GLP inspections in Germany

Manual
Annex 7: Test Methods

National and Länder Working Party
Chemicals Safety Committee "GLP and other quality assurance systems" BLAC-AS GLP

As of: November 2017

Annex 7: Test Methods

In accordance with Commission Regulation 440/2008 / EC of 30 May 2008 laying down test methods in accordance with Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) - Status February 14, 2017 (EU 2017/735):

Part A: METHODS FOR THE DETERMINATION OF PHYSICO-CHEMICAL PROPERTIES

A.1	MELTING/FREEZING TEMPERATURE
A.2	BOILING TEMPERATURE
A.3	RELATIVE DENSITY
A.4	VAPOUR PRESSURE
A.5	SURFACE TENSION
A.6	WATER SOLUBILITY
A.8	PARTITION COEFFICIENT
A.9	FLASH-POINT
A.10	FLAMMABILITY (SOLIDS)
A.11	FLAMMABILITY (GASES)
A.12	FLAMMABILITY (CONTACT WITH WATER)
A.13	PYROPHORIC PROPERTIES OF SOLIDS AND LIQUIDS
A.14	EXPLOSIVE PROPERTIES
A.15	AUTO-IGNITION TEMPERATURE (LIQUIDS AND GASES)
A.16	RELATIVE SELF-IGNITION TEMPERATURE FOR SOLIDS
A.17	OXIDISING PROPERTIES (SOLIDS)
A.18	NUMBER-AVERAGE MOLECULAR WEIGHT AND MOLECULAR WEIGHT DISTRIBUTION OF POLYMERS
A.19	LOW MOLECULAR WEIGHT CONTENT OF POLYMERS

A.20	SOLUTION/EXTRACTION BEHAVIOUR OF POLYMERS IN WATER
A.21	OXIDISING PROPERTIES (LIQUIDS)
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A.23	PARTITION COEFFICIENT (1-OCTANOL/WATER): SLOW-STIRRING METHOD
A.24	PARTITION COEFFICIENT (N-OCTANOL/WATER), HIGH PERFORMANCELIQUID CHROMATOGRAPHY (HPLC) METHOD
A.25	DISSOCIATION CONSTANTS IN WATER (TITRATION METHOD — SPECTROPHOTOMETRIC METHOD — CONDUCTOMETRIC METHOD)

Part B: METHODS FOR THE DETERMINATION OF TOXICITY AND OTHER HEALTH EFFECTS

B.1 bis	ACUTE ORAL TOXICITY — FIXED DOSE PROCEDURE
B.1 tris	ACUTE ORAL TOXICITY — ACUTE TOXIC CLASS METHOD
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B.3	ACUTE TOXICITY (DERMAL)
B.4	ACUTE TOXICITY: DERMAL IRRITATION/CORROSION
B.5	ACUTE TOXICITY: EYE IRRITATION/CORROSION
B.6	SKIN SENSITISATION
B.7	REPEATED DOSE (28 DAYS) TOXICITY (ORAL)
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B.9	REPEATED DOSE (28 DAYS) TOXICITY (DERMAL)
B.10	MUTAGENICITY — *IN VITRO* MAMMALIAN CHROMOSOME ABERRATION TEST
B.11	MUTAGENICITY — *IN VIVO* MAMMALIAN BONE MARROW CHROMOSOME ABERRATION TEST
B.12	MUTAGENICITY — *IN VIVO* MAMMALIAN ERYTHROCYTE MICRONUCLEUS TEST
B.13/14	MUTAGENICITY: REVERSE MUTATION TEST USING BACTERIA
B.17	MUTAGENICITY — *IN VITRO* MAMMALIAN CELL GENE MUTATION TEST
B.21	*IN VITRO* MAMMALIAN CELL TRANSFORMATION TESTS
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B.23	MAMMALIAN SPERMATOGONIAL CHROMOSOME ABERRATION TEST
B.25	MOUSE HERITABLE TRANSLOCATION
B.26	SUB-CHRONIC ORAL TOXICITY TEST REPEATED DOSE 90 — DAY ORAL TOXICITY STUDY IN RODENTS
B.27	SUB-CHRONIC ORAL TOXICITY TEST REPEATED DOSE 90 — DAY ORAL TOXICITY STUDY IN NON-RODENTS
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