Part I
The OECD Principles of Good Laboratory Practice

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TÁMOP-4.2.2/B-10/1-2010-0012 projekt

MAGYARORSZÁG MEGÚJUL

A projekt az Európai Unió támogatásával, az Európai Szociális Alap társfinanszírozásával valósul meg.

Overview

Background information
Implementation of the GLP
Principles
Final remarks

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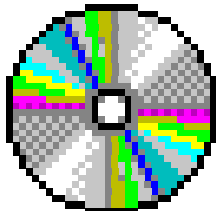
Overview

- **Background information**
- Implementation of the GLP Principles
- Final remarks



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Background information (1/14)

Important decisions are often taken on the basis of experimental data.

Hence, it is crucial that such data be comparable, reliable and valid.

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Background information (2/14)

In the early 1960's the US Food and Drug Administration (FDA) became aware that some studies on the safety of new chemicals performed by Test Facilities (TFs) for regulatory purposes were basically unreliable.

Evidence was in fact provided of major adverse effects of such substances. Such effects had not been reported at the time when the authorization to production and commerce was granted.

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Background information (3/14)

In the early 1970's the US Congress undertook the re-assessment of studies on new substances submitted by some TFs to Regulatory Authorities (RAs) and suspected to be fraudolent.

In the case of G. D. Searle, Inc., *e.g.*, strong evidence was found that many studies were completely unreliable in terms of quality and integrity.

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Background information (4/14)

Another striking, even worse, case was that of the Industrial Bio-Test Laboratories. FDA Inspectors found the animal house flooded by 10 cm of water with dead rats and mice everywhere.

Under such conditions thousands and thousands of safety studies on new industrial chemicals, pesticides, herbicides, drugs, cosmetics and food and feed additives were conducted for years (about 35 – 40 % of all toxicological studies authorised in the USA in that period).

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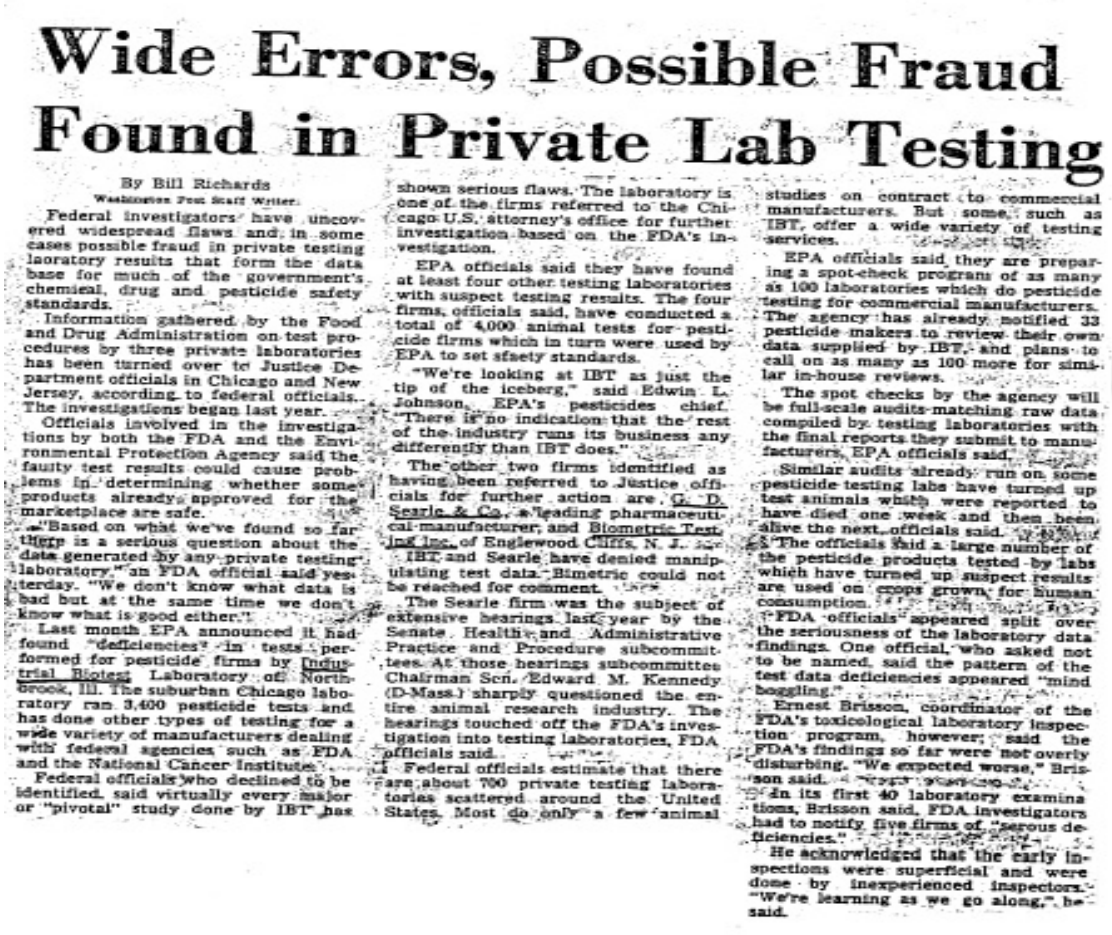
Background information (5/14)



Wide Errors, Possible Fraud Found in Private Lab Testing

By Bill Richards
Washington Post Staff Writer

Federal investigators have uncovered widespread flaws and, in some cases possible fraud in private testing laboratory results that form the data base for much of the government's chemical, drug and pesticide safety standards.

Information gathered by the Food and Drug Administration on test procedures by three private laboratories has been turned over to Justice Department officials in Chicago and New Jersey, according to federal officials. The investigations began last year.

Officials involved in the investigations by both the FDA and the Environmental Protection Agency said the faulty test results could cause problems in determining whether some products already approved for the marketplace are safe.

"Based on what we've found so far there is a serious question about the data generated by any private testing laboratory," an FDA official said yesterday. "We don't know what data is bad but at the same time we don't know what is good either."

Last month EPA announced it had found "deficiencies" in tests performed for pesticide firms by Industrial Biotest Laboratory of Northbrook, Ill. The suburban Chicago laboratory ran 3,400 pesticide tests and has done other types of testing for a wide variety of manufacturers dealing with federal agencies such as FDA and the National Cancer Institute.

Federal officials who declined to be identified, said virtually every major or "pivotal" study done by IBT has shown serious flaws. The laboratory is one of the firms referred to the Chicago U.S. attorney's office for further investigation based on the FDA's investigation.

EPA officials said they have found at least four other testing laboratories with suspect testing results. The four firms, officials said, have conducted a total of 4,000 animal tests for pesticide firms which in turn were used by EPA to set sfaety standards.

"We're looking at IBT as just the tip of the iceberg," said Edwin L. Johnson, EPA's pesticides chief. "There is no indication that the rest of the industry runs its business any differently than IBT does."

The other two firms identified as having been referred to Justice officials for further action are G. D. Searle & Co., a leading pharmaceutical manufacturer, and Biometric Testing Inc. of Englewood Cliffs, N. J.

IBT and Searle have denied manipulating test data. Bimetric could not be reached for comment.

The Searle firm was the subject of extensive hearings last year by the Senate Health and Administrative Practice and Procedure subcommittees. At those hearings subcommittee Chairman Sen. Edward M. Kennedy (D-Mass.) sharply questioned the entire animal research industry. The hearings touched off the FDA's investigation into testing laboratories, FDA officials said.

Federal officials estimate that there are about 700 private testing laboratories scattered around the United States. Most do only a few animal studies on contract to commercial manufacturers. But some, such as IBT, offer a wide variety of testing services.

EPA officials said they are preparing a spot-check program of as many as 100 laboratories which do pesticide testing for commercial manufacturers. The agency has already notified 33 pesticide makers to review their own data supplied by IBT, and plans to call on as many as 100 more for similar in-house reviews.

The spot checks by the agency will be full-scale audits matching raw data compiled by testing laboratories with the final reports they submit to manufacturers, EPA officials said.

Similar audits already run on some pesticide testing labs have turned up test animals which were reported to have died one week and then been alive the next, officials said.

The officials said a large number of the pesticide products tested by labs which have turned up suspect results are used on crops grown for human consumption.

FDA officials appeared split over the seriousness of the laboratory data findings. One official, who asked not to be named, said the pattern of the test data deficiencies appeared "mind boggling."

Ernest Brisson, coordinator of the FDA's toxicological laboratory inspection program, however, said the FDA's findings so far were not overly disturbing. "We expected worse," Brisson said.

In its first 40 laboratory examinations, Brisson said, FDA investigators had to notify five firms of "serous deficiencies."

He acknowledged that the early inspections were superficial and were done by inexperienced inspectors. "We're learning as we go along," he said.

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Background information (6/14)

THE WASHINGTON POST Saturday, October 6, 1979 A 3

2 Plead Guilty in Falsification Of Animal Test Data on Drugs

By Bill Richards
Washington Post Staff Writer

Two former executives of a New Jersey research laboratory pleaded guilty in federal court yesterday to a charge that they conspired in the falsification of animal tests on drugs being investigated to see if they caused cancer.

Federal investigators said the guilty pleas were the first of their kind in animal-testing cases. Biometric Testing Inc., the Englewood Cliffs, N.J., firm that employed the two, and three other past and present executives of the company still face similar charges.

Robert J. Del Tufo, U.S. attorney for northern New Jersey, said one of the drugs under investigation by the laboratory, GK 101, which is used to prevent dental disease, has been dropped from the market. The second drug, an anti-inflammatory medicine known as Catrix-S, still is being tested.

The two drugs were undergoing testing by two chemical firms, which had contracted with the laboratory, before they could be cleared by the Food and Drug Administration for marketing.

Dr. Steven Carson, of Brooklyn, N.Y., a former vice president of Biometric Testing, and Samuel Posner, of Pleasantville, N.Y., former executive vice president of the laboratory, entered the guilty pleas in U.S. District Court in Camden, N.J.

The two men are scheduled for sentencing next month. They face a maximum sentence of five years in jail and a $10,000 fine.

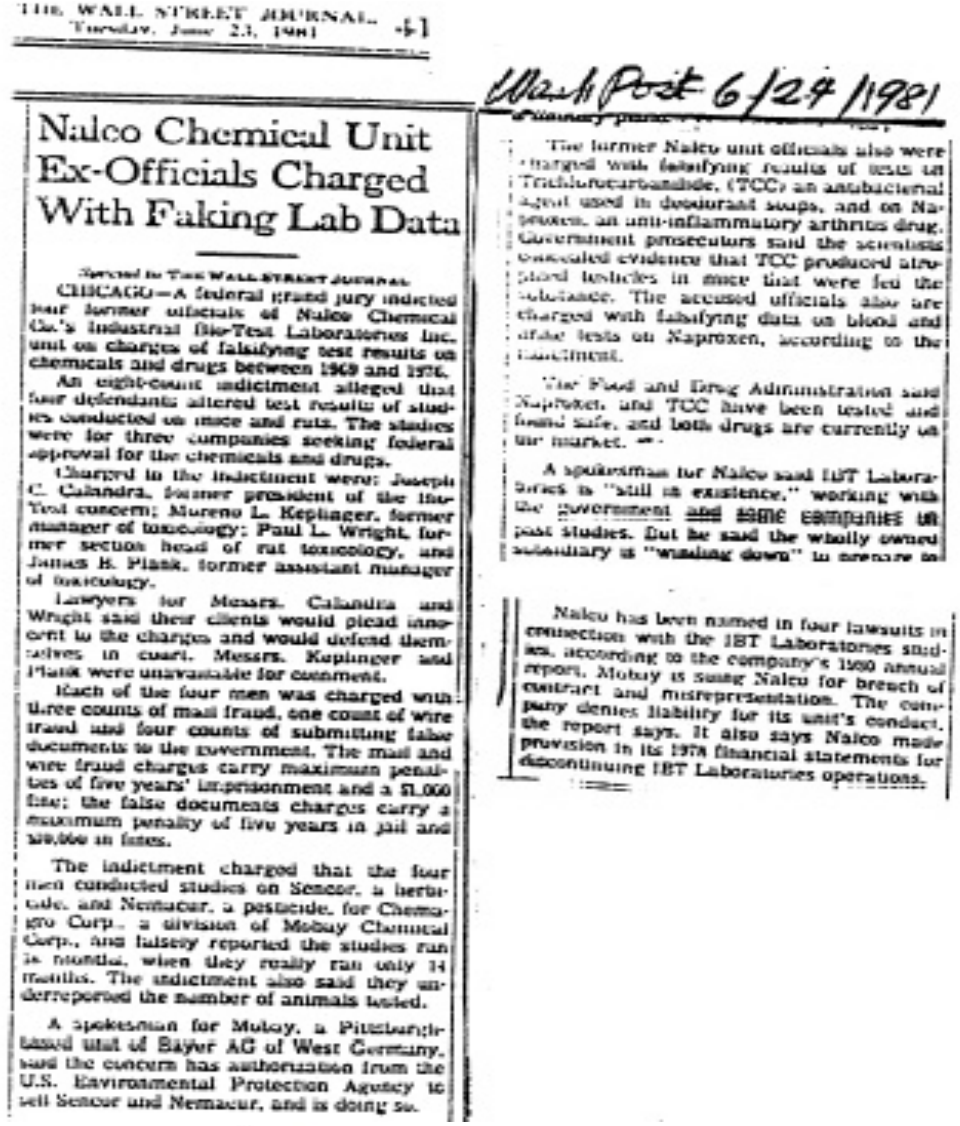
Posner and Carlson were named in an indictment returned this year by a federal grand jury in Newark. The indictment stemmed from irregularities disclosed during hearings in 1976 by Sen. Edward M. Kennedy's health subcommittee on the adequacy and safety of independent laboratories testing drugs and other chemicals for government clearance.

According to the original federal indictment, Biometric Testing Inc. was hired by two manufacturing firms to test their drug products in 1975 and 1976.

The indictment charged that the research laboratory and its indicted officials supplied the manufacturers with fabricated animal test data, including feeding records, blood and urine test results and even tissue samples that supposedly came from test animals. The manufacturers, who were not implicated in the scheme, then passed on the false data to the FDA as proof that their drugs were safe for human use.

In addition to the testing laboratory, the indictment includes Dr. Max A. Tesler, chairman of the laboratory's board of directors, and Dr. Eugene R. Jolly, of Neenah, Wis., and Edward J. Rogers, of North Grosvernorvale, Conn. The case is scheduled to go to trial next week in Camden.

Background information (7/14)



THE WALL STREET JOURNAL
Tuesday, June 23, 1981 -1

Nalco Chemical Unit Ex-Officials Charged With Faking Lab Data

Special to THE WALL STREET JOURNAL

CHICAGO—A federal grand jury indicted four former officials of Nalco Chemical Co.'s Industrial Bio-Test Laboratories Inc. unit on charges of falsifying test results on chemicals and drugs between 1969 and 1976.

An eight-count indictment alleged that four defendants altered test results of studies conducted on mice and rats. The studies were for three companies seeking federal approval for the chemicals and drugs.

Charged in the indictment were: Joseph C. Calandra, former president of the Bio-Test concern; Moreno L. Keplinger, former manager of toxicology; Paul L. Wright, former section head of rat toxicology, and James H. Plank, former assistant manager of toxicology.

Lawyers for Messrs. Calandra and Wright said their clients would plead innocent to the charges and would defend themselves in court. Messrs. Keplinger and Plank were unavailable for comment.

Each of the four men was charged with three counts of mail fraud, one count of wire fraud and four counts of submitting false documents to the government. The mail and wire fraud charges carry maximum penalties of five years' imprisonment and a $1,000 fine; the false documents charges carry a maximum penalty of five years in jail and $10,000 in fines.

The indictment charged that the four men conducted studies on Sencor, a herbicide, and Nemacur, a pesticide, for Chemagro Corp., a division of Mobay Chemical Corp., and falsely reported the studies run 24 months, when they really ran only 14 months. The indictment also said they underreported the number of animals tested.

A spokesman for Mobay, a Pittsburgh-based unit of Bayer AG of West Germany, said the concern has authorization from the U.S. Environmental Protection Agency to sell Sencor and Nemacur, and is doing so.

Wash Post 6/24/1981

The former Nalco unit officials also were charged with falsifying results of tests on Trichlorocarbanilide, (TCC) an antibacterial agent used in deodorant soaps, and on Naproxen, an anti-inflammatory arthritis drug. Government prosecutors said the scientists concealed evidence that TCC produced atrophied testicles in mice that were fed the substance. The accused officials also are charged with falsifying data on blood and urine tests on Naproxen, according to the indictment.

The Food and Drug Administration said Naproxen and TCC have been tested and found safe, and both drugs are currently on the market.

A spokesman for Nalco said IBT Laboratories is "still in existence," working with the government and some companies on past studies. But he said the wholly owned subsidiary is "winding down" to operate as

Nalco has been named in four lawsuits in connection with the IBT Laboratories studies, according to the company's 1980 annual report. Mobay is suing Nalco for breach of contract and misrepresentation. The company denies liability for its unit's conduct, the report says. It also says Nalco made provision in its 1978 financial statements for discontinuing IBT Laboratories operations.

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Background information (8/14)

The Case against Industrial Bio-Test Laboratories (Keith Schneider) (1/2)

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Background information (9/14)

The Case against Industrial Bio-Test Laboratories (Keith Schneider) (2/2)

This paper is from *The Amicus Journal*, 1983 edition, and was published by the Natural Resources Defense Council (NRDC). It is not an easy article to read and may indeed be one of the most disturbing things ever read. It chronicles the scandal that destroyed the credibility of the safety testing laboratory industry in the late 1970's and early 1980's, particularly Industrial Bio-Test (IBT) Labs of Northbrook, Illinois. The article reveals the fraudulent practices of IBT and other laboratories, the horrendous treatment of animals, and the total disregard of human health and integrity of the regulatory process. Many of the products the safety of which was declared falsely are still on the market.

Background information (10/14)

The Principles of Good Laboratory Practice (GLP) were conceived to harmonize the conduct of non-clinical safety studies and to minimize the risk of fraud.

The Principles of GLP are a quality system concerned with the organisational process and the conditions under which safety studies are planned, conducted, controlled, recorded, reported and archived. They form a body of mutually dependent documented items that make the falsification of a study more time-consuming and expensive than its actual performance.

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Background information (12/14)

The three major acts of the OECD in the field of GLP are as follows:

Decision of the Council concerning the Mutual Acceptance of Data (MAD) in the Assessment of Chemicals [C(81)30(Final)]

Council Decision-Recommendation on Compliance with the GLP Principles [C(89)87(Final)]

Council Decision concerning the Adherence of Non-member Countries to the Council Acts related to the MAD in the Assessment of Chemicals [C(97)114(Final)]

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Background information (13/14)

Annexes to the MAD Decision of 1981

OECD Test Guidelines for Chemical Substances

OECD Principles of GLP

Permanent activities in the framework of the *Environment, Health and Safety* Programme

Updating

Activities for the harmonisation of the compliance with the Principles of GLP and their interpretation

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Background information (14/14)

In the European Union all this matter is basically managed through two GLP Directives, *i.e.*:

- Directive 2004/9/EC of 11 February 2004 (on the inspection and verification of the principles of GLP);
- Directive 2004/10/EC of 11 February 2004 (on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of GLP).

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Categories of OECD Documents

- Legal documents: adopted by the Council (*e.g.*, the Principles of GLP);
- Consensus documents: drafted by the OECD GLP Working Group in cooperation with the private sector and approved by the OECD Joint Meeting;
- Guidance documents: legal provisions approved by the Council;
- Advisory documents: agreed upon by the GLP Working Group and the Joint Meeting.

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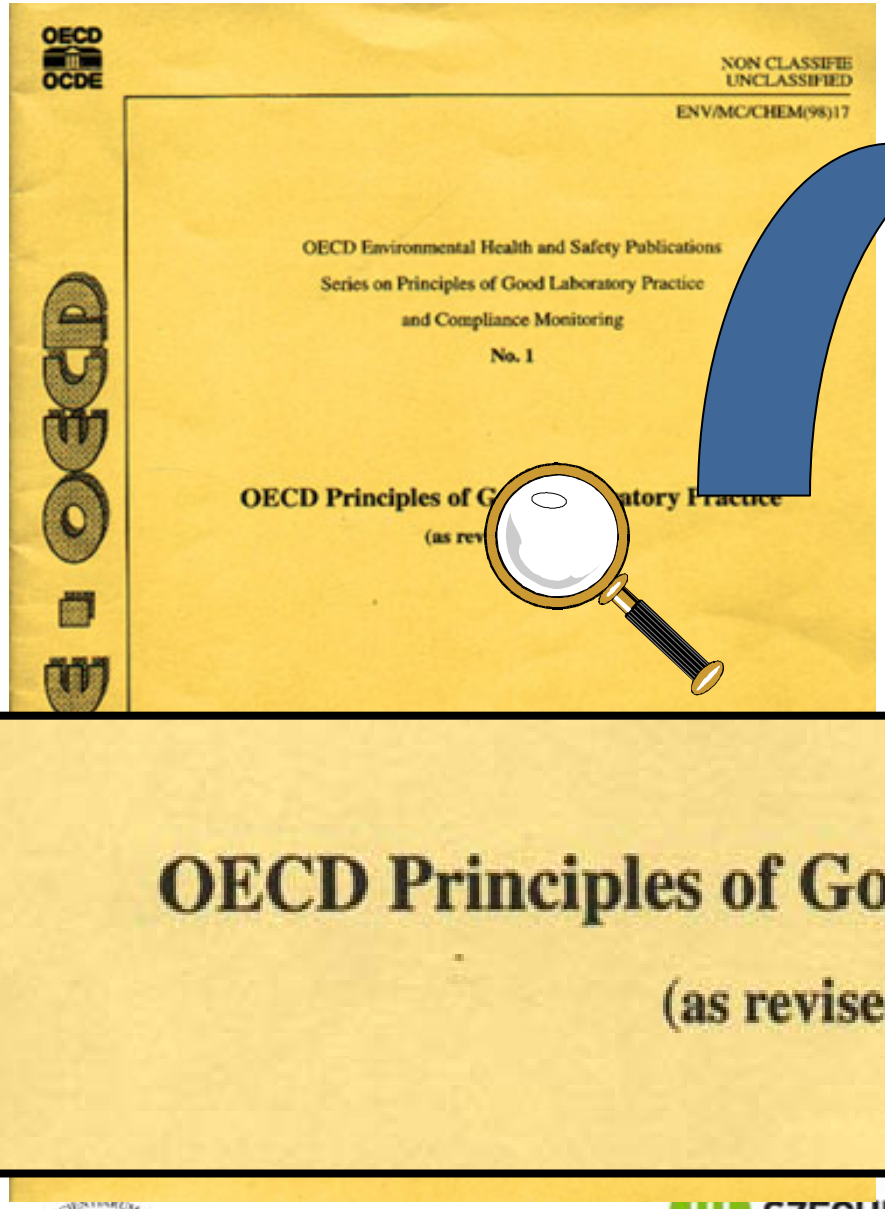

OECD Principles of Good Laboratory Practice

(as revised in 1997)

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OECD Series on the Principles of GLP (1/4)

No. 1, OECD Principles of Good Laboratory Practice

No. 2, Revised Guides for Compliance Monitoring Procedures for Good Laboratory Practice (1995)

No. 3, Revised Guidance for the Conduct of Laboratory Inspections and Study Audits (1995)

No. 4, Quality Assurance and GLP (as revised in 1999)

No. 5, Compliance of Laboratory Suppliers with GLP Principles (as revised in 1999)

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OECD Series on the Principles of GLP (2/4)

No. 6, The Application of the GLP Principles to Field Studies (as revised in 1999)

No. 7, The Application of the GLP Principles to Short-term Studies (as revised in 1999)

No. 8, The Role and Responsibilities of the Study Director in GLP Studies (as revised in 1999)

No. 9, Guidance for the Preparation of GLP Inspection Reports (1995)

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OECD Series on the Principles of GLP (3/4)

No. 10, The Application of the Principles of GLP to Computerised Systems (1995)

No. 11, The Role and Responsibilities of the Sponsor in the Application of the Principles of GLP (1999)

No. 12, Requesting and Carrying Out Inspections and Study Audits in Another Country (2000)

OECD Series on the Principles of GLP (4/4)

No. 13, The Application of the OECD Principles of GLP to the Organisation and Management of Multi-site Studies (2002)

No. 14, The Application of the OECD Principles to Alternative Studies (2004)

No. 15, Establishment and Control of Archives That Operate in Compliance with the Principles of Good Laboratory Practice (2007)

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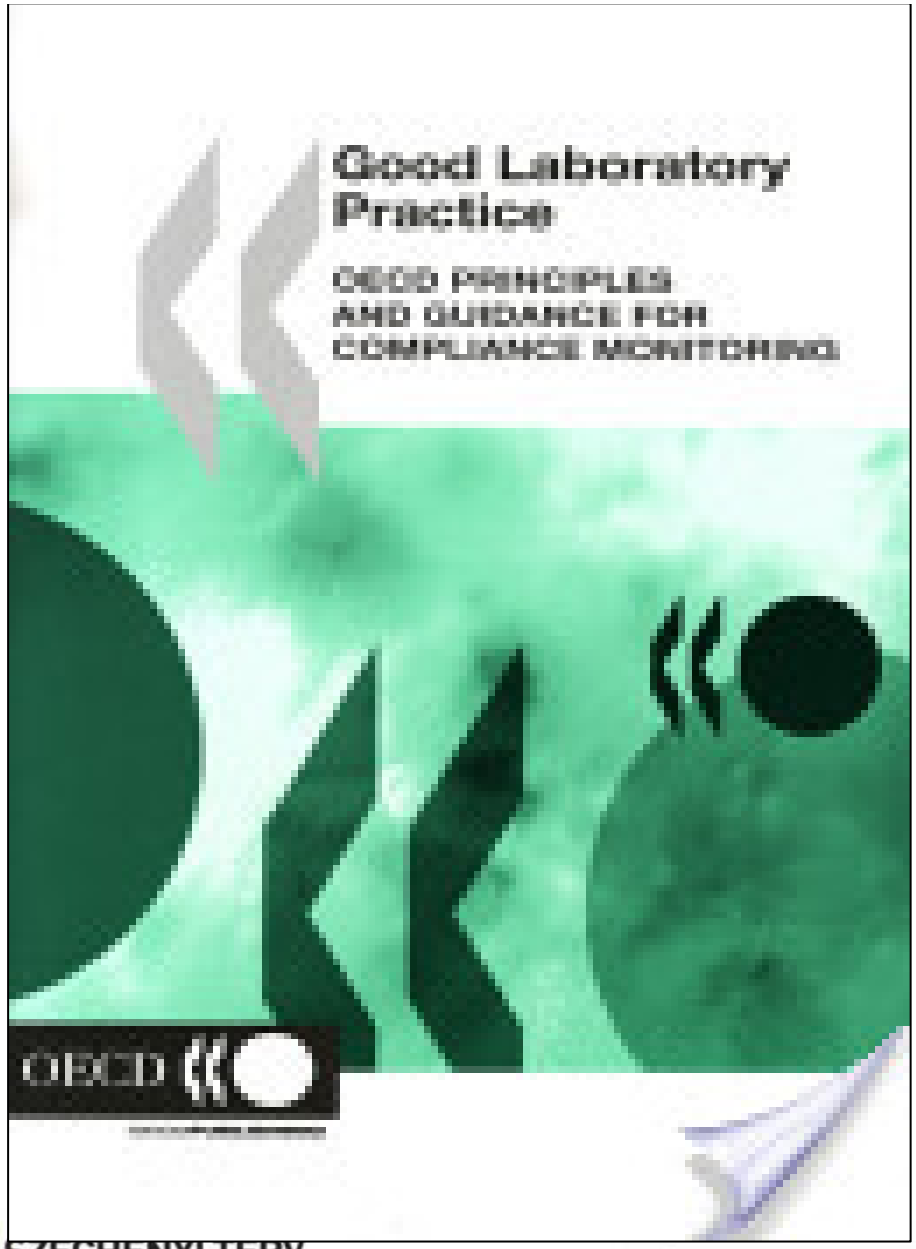
All of the 15 Guidance Documents are now collected under the same cover.



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Acronyms

FR	→	Final Report
MA	→	Monitoring Authority
MS	→	Master Schedule
PI	→	Principal Investigator
QAU/P	→	Quality Assurance Unit/Programme
RA	→	Receiving Authority
SD	→	Study Director
SP	→	Study Plan
SOP	→	Standard Operating Procedure
TF	→	Test Facility
TS	→	Test Site

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Definitions (1/7)

★ TF management means the person(s) who has (have) the authority and formal responsibility for the organisation and functioning of the TF according to the Principles of GLP.

★ Sponsor means an entity which commissions, supports and/or submits a non-clinical health and environmental safety study.

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Definitions (2/7)

- TF means the persons, premises and operational unit(s) that are necessary for conducting the non-clinical safety study.
- SD means the individual responsible for the overall conduct of the non-clinical health and environmental study.

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Definitions (3/7)

QAP means a defined system, including personnel, which is independent of study conduct and is designed to assure TF management of compliance with the Principles of GLP.

SOPs are documented procedures which describe how to perform tests or activities normally not specified in detail in study plans or test guidelines.

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Definitions (4/7)

- Non-clinical health and environmental safety 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 for subsequent submission to the appropriate RA.
- Test system is any biological, chemical or physical system or a combination thereof used in a study.

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Definitions (5/7)

- Reference (or control) item means any article used to provide a basis for comparison with the test item.
- TS means the location at which a phase of a study is conducted.
- SP means a document which defines the objectives and experimental design for the conduct of the study and includes any amendments.
- FR should be prepared for each study.

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Definitions (6/7)

★ PI means an individual who, for a multi-site study, acts on behalf of the SD and has defined responsibility for delegated phases of the study.

★ MS means a compilation of information to assist in the assessment of workload and for the tracking of studies at a TF.

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Definitions (7/7)

★Archivist is an individual responsible for the archive facilities where study plans, raw data, final reports, samples of test items and specimens are securely stored and retrieved.

[Definition based on that of Archive Facilities]

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The proper conduct of a GLP study requires that:

- there is a sufficient number of qualified personnel (with documented evidence of training and experience as well as with job descriptions);
- the SD has been appointed and procedures for replacement have been established;
- an MS is in place;

(to be continued)

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(continued)

- QAP and QAU have been set up;
- appropriate facilities, equipment and materials are available;
- test and reference items are appropriately characterised;
- TF supplies are duly delivered;
- SOPS are available;
- all study-relevant documents and supporting material are archived;
- waste disposal is carefully planned.

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Note 1

- In the GLP context, test systems are the tools through which safety data on the effects caused by test items can be generated.
- Hence, in order to ensure the scientific validity of the studies undertaken, the properties of test systems should be well known, and documented evidence on their suitability and integrity should be available.

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Note 2

- Records including test item and reference item characterization, date of receipt, expiry date, and quantities received and used in studies should be maintained.
- Handling, sampling, and storage procedures should be identified so that the homogeneity and stability can be assured to the highest possible degree and contamination or mixup are precluded.

Note 3

- Storage container(s) should carry identification information, expiry date, and specific storage instructions.
- Each test and reference item should be appropriately identified, *e.g.*, by code, Chemical Abstracts Service (CAS) Registry Number, name, and biological parameters.

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Note 4

- For each study, the identity, including batch number, purity, composition, concentrations, or other characteristics to appropriately define each batch of the test or reference items should be known.
- In cases where the test item is supplied by the sponsor, there should be a mechanism, developed in co-operation between the sponsor and the TF, to verify the identity of the test item subject to the study.

Note 5

- The stability of test and reference items under storage and test conditions should be known for all studies.
- If the test item is administered or applied in a vehicle, the homogeneity, concentration and stability of the test item in that vehicle should be determined. For test items used in field studies (*e.g.*, tank mixes), these properties may be determined through separate laboratory experiments.

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Note 6

- A sample for analytical purposes from each batch of test item should be retained for all studies except short-term studies.
- Technical personnel should be properly trained and highly motivated to fully master the highly sophisticated instruments available nowadays. The TF management should be well aware of the crucial role played by instrumental techniques in performing GLP-compliant studies.

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Test systems may be of two basic types:

- physical-chemical;
- biological.

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Physical-chemical test systems (1/3)

Apparatus used for the generation of data should be suitably located and of appropriate design and adequate capacity. The integrity of such systems should be ensured.

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Physical-chemical test systems (2/3)

As a rule, physical-chemical tests are short-term studies, meaning by this that they are of short duration and are highly standardizable. Their nature can be extremely variable.

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Physical-chemical test systems (3/3)

Key issues in this context are:
- test item identification;
- routine maintenance and validation;
- QAU audits.

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Biological test systems (1/7)

Biological test systems require that proper conditions be established and maintained for storage, housing, handling and care in order to ensure the quality of the data.

Newly received animal and plant test systems should be isolated until their health status has been assessed.

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Biological test systems (2/7)

Key issues in this context are:

- design and construction of animal facilities;
- entry of staff, animals, diet, bedding , test items into the animal house;
- ease of cleaning;
- state of repair, cleanliness and good order;
- separation between clean and dirty materials
- barrier unit with service corridors;
- separation in time (tidal flow system);

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Biological test systems (3/7)

- control of movement between different animal rooms or units;
- protective clothing;
- storage of diet;
- supply of drinking water (bottles or automated systems);
- control and monitoring of animal room temperature and humidity;
- checking of flow rate (room changes per hour);
- checking of lighting cycle;

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Biological test systems (4/7)

- observation of routine animal husbandry activities;
- acclimatisation of animals to the test environment before the first administration of the test item;
- proper identification of animals at all stages of experimentation;
- cleaning and sanitation of animal housing;
- absence of contaminants in all material in contact with animals;

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Biological test systems (5/7)

- purchase of animals from reputable suppliers;
- records of vaccinations (*e.g.*, for primates, dogs and cats);
- check of health status upon arrival and during the acclimatisation period;
- observation of routine animal husbandry activities;

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Biological test systems (6/7)

- routine and emergency care (animals on
  study may require veterinary treatment
  during the study);
- information on housing (study number,
  cage number, treatment group, number of
  animals in cage or pen);

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Biological test systems (7/7)

- dosing (nature of the test item and physical
  state);
- administration of test item (infusion,
  suspension, diet);
- necropsy (collection of tissues).

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Facilities (2/4)

Primary requisites
- safe storage of data and substances used in
  studies to support validity of test results;
- minimization of deterioration;
- limited access (only personnel authorized
  by TF Management should have access);
- retention period (final disposition of any
  study materials should be documented);

Archives (2/4)

- storage of the records of all QAU inspections and master schedule (under the responsibility of the QAU);
- information on personnel (records of qualifications, training, experience, job description);
- storage of records and reports of instrument maintenance and calibration;

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Archives (3/4)

- storage of supporting electronic data;
- storage of reports of validation;
- storage of records of electronic system maintenance (*e.g.*, addition or deletion of hardware and software);
- storage of historical SOPs;
- security (movement of material in and out of the archives should be carefully recorded);

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Archives (4/4)

- raw data archived at an independent archive;
- data archived at the sponsor's archive;
- location of archives in another country;
- transfer of archived data to a legal successor or sponsor in the event of TF closure.

Waste Disposal

Not a minor aspect in the conduct of GLP studies is handling and disposal of wastes which should be carried out in such a way as not to jeopardize the integrity of studies.

This calls for appropriate collection, storage, and disposal
facilities as well as for decontamination and transportation procedures.

National GLP monitoring systems (1/3)

As prescribed by Directive 2004/9/EC, each Member State (MS) must have a GLP Monitoring Programme (MP) aimed at verifying the compliance of TFs with the GLP principles in conducting non-clinical health and environmental safety studies to be submitted to RAs.

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National GLP monitoring systems

The scope and working procedures of the GLP MP must be documented. In particular, such information include: (I/II)

- scope and extent of the GLP MP;
- mechanism whereby TFs enter the GLP MP;
- provisions for TFs inspections and study audits (also upon request of RAs);

National GLP monitoring systems (3/3)

(II/II)

- powers of Inspectors for entry into TFs;
- procedures for the verification of TFs inspections and study audits;
- follow-up to TFs inspections and study audits.

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Major components of a national GLP monitoring system (1/8)

- GLP Monitoring Authority
- GLP Inspectorate

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Major components of a national GLP monitoring system (2/8)

GLP Monitoring Authority (I/IV)

- Each MS must establish at least one GLP MA to cover non-clinical safety studies on test items contained in pharmaceuticals, pesticides, cosmetics, veterinary drugs, as well as food additives, feed additives and industrial chemicals.

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Major components of a national GLP monitoring system (3/8)

GLP Monitoring Authority (II/IV)

- The GLP MA must be a properly constituted and legally identified body adequately staffed and working within a defined administrative framework.
- The GLP MA is directly or ultimately responsible for an adequate team of Inspectors having the necessary technical/scientific expertise.

Major components of a national GLP monitoring system (4/8)

GLP Monitoring Authority (III/IV)

- The GLP MA publishes documents detailing the adoption of the GLP principles within its territories, including the relevant legal or administrative framework.
- The GLP MA maintains records of TFs as well as of studies audited.

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Major components of a national GLP monitoring system (5/8)

GLP Monitoring Authority (IV/IV)

- The GLP MA makes provisions for the maintenance of the confidentiality of all information gained in the context of its monitoring activities.
- It is the responsibility of the GLP MA to ensure that an adequate number of Inspectors is available.

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Major components of a national GLP monitoring system (6/8)

GLP Inspectorate (I/III)

The number of Inspectors depends on:

- the number of TFs covered by the GLP MP;
- the frequency of verification of the GLP compliance of TFs;
- the number and complexity of studies undertaken by TFs;

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Major components of a national GLP monitoring system (7/8)

GLP Inspectorate (II/III)

- Inspectors should have qualification and practical competence in the scientific disciplines relevant to the testing of chemicals;
- training programmes should be set up to the benefit of Inspectors;

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Major components of a national GLP monitoring system (8/8)

GLP Inspectorate (III/III)

- whenever the need arises, Experts in specific fields can be appointed to assist Inspectors in conducting inspections and/or study audits;
- Inspectors may be on the permanent staff of the GLP MA, of a body separate from the GLP MA or contracted on a case-by-case basis.

Note!

It is not mandatory that a national GLP MA has its own Inspectorate.

Inspectors can be hired from another national MA.

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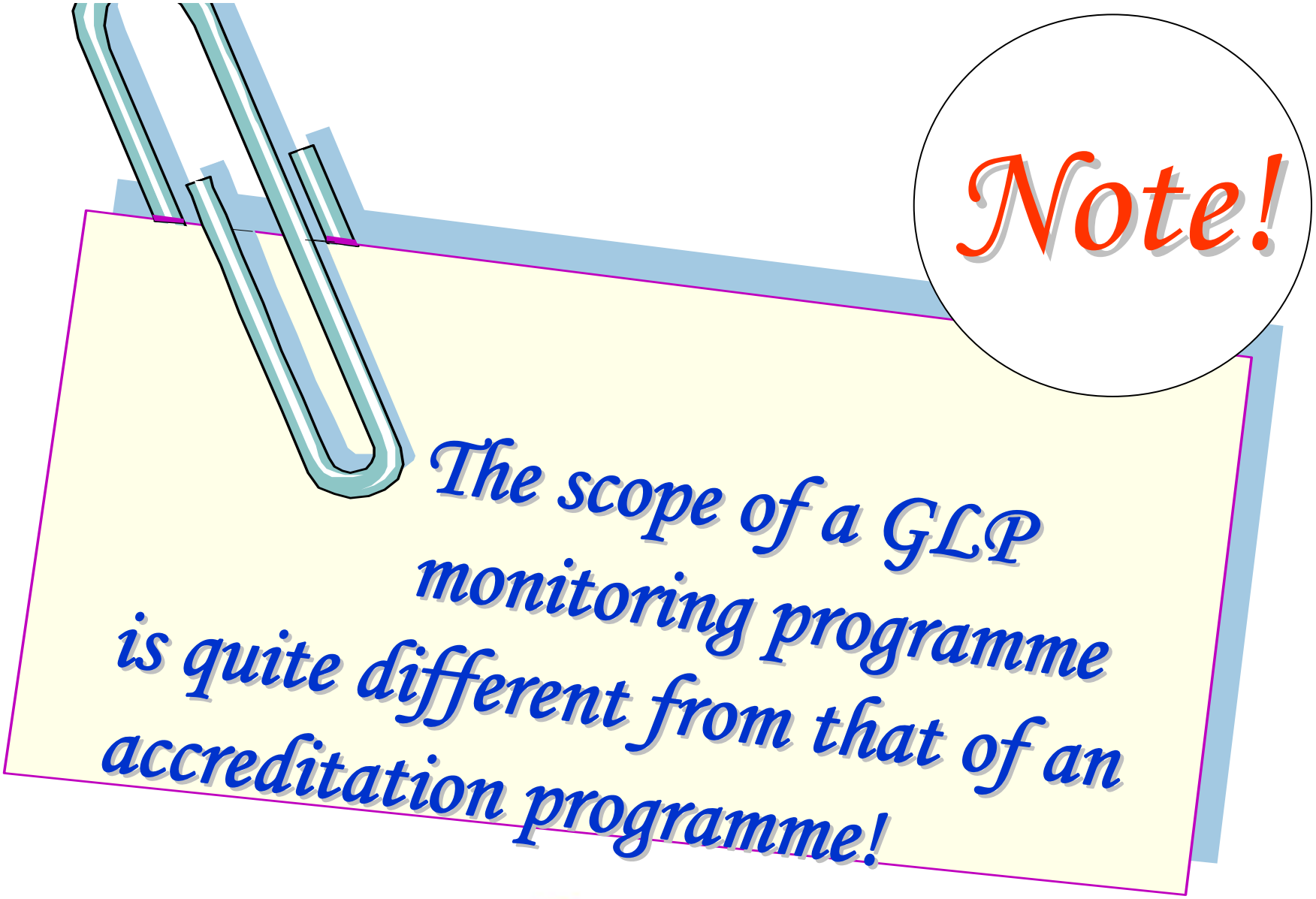

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Note!

Validated analytical methods must be in place, although validation can be performed in the context of other quality systems.

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The Case of Italy

The Italian MA has fully implemented the EU Directives on GLP (which in turn stem from the OECD Decisions and Recommendations on GLP) with a number of legal provisions, the most recent of which is the Legislative Decree 50 of March 2nd, 2007.

The Italian MA discharges its duties by means of a National Board for GLP where the TF applications are examined, GLP inspections assigned, inspections reports assessed and final decisions on compliance status made.

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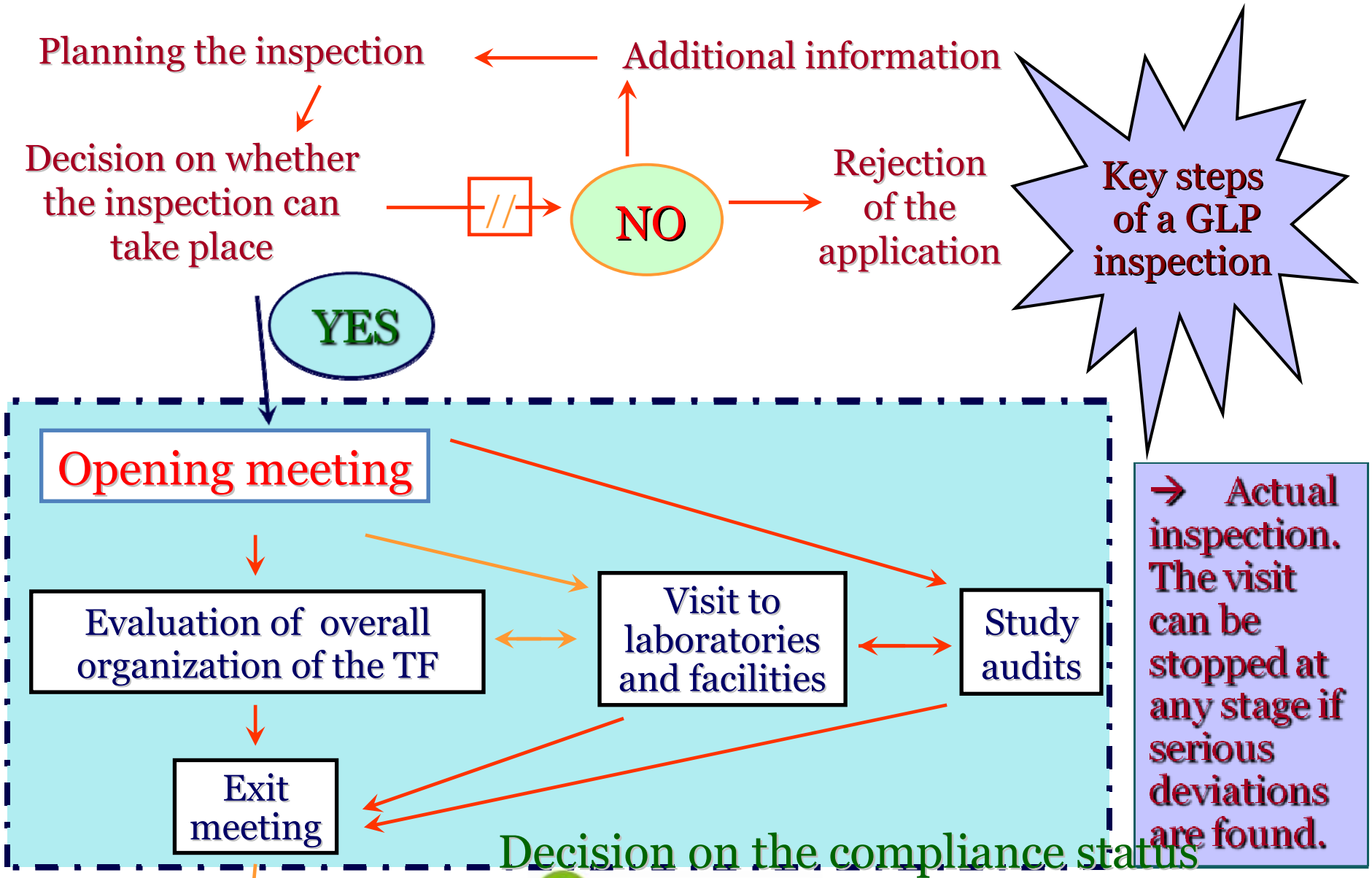

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Pre-inspection phase

First GLP inspection

Information on the (TF) should be reviewed, in particular as regards:

- management structure
- facility layout
- types of studies conducted
- CVs of staff members
- organizational chart

Re-inspection

Information should be gained as above, plus

- outcome of previous inspections

In both cases, the pre-inspection can be limited to the plain examination of documents and other informative material submitted by the TF

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The Opening Meeting (OM) (also called starting conference)

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Comment 1

At this stage, the Inspectors should be familiar with the overall layout and organization of the TF and also be able to check whether the activities performed actually fall within the scope of GLP or whether another quality system would better fit them.

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Preliminary steps

The exchange of information between the Inspection Team (IT) and the TF management should cover:

- purpose and scope of the inspection
- identification of the areas of the TF to be inspected
- request of documentation and specimens, as necessary
- details on the approach adopted to conduct the inspection, Exit Meeting (EM) included

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Comment 2

All potentially controversial issues should be mentioned and clarified at this point in time. Particular attention should be devoted to the spatial and temporal criteria used to identify GLP areas and to check the proper allocation of functions to staff members. The GLP Inspectors should also illustrate in full detail their mandate to the TF management.

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Assessment of the organization and capabilities of the TF (1/2)

The evaluation is based on the stepwise obtainment of detailed information on:

- qualification of staff resources
- ongoing and completed studies
- SOPs
- QAP
- indoor and outdoor areas of the TF
- study plans and reports
- retention of records

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Assessment of the organization and capabilities of the TF (2/2)

Existence, adequate capacity and proper functioning should be checked in particular for:

- instrumentation and ancillary apparatuses
- materials, chemical reagents and test and reference substances
- biological test systems, if applicable, in particular as regards care, housing and containment
- archives
- computerized systems
- any outdoor and indoor facilities relevant to the studies being undertaken

The overall organization should enable adequate management of the activities of the TF.

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Comment 3

The evaluation does not take place at a given point in time. Rather, it is an ongoing process beginning already during the OM and continuing throughout the visit. The IT may find desirable to use a check list from this moment on.

Comment 4

The GLP Inspectors should always have an impartial mental attitude and refrain from blaming when detecting omissions, deviations and inadequacies.

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Comment 5

The OM may well require the active involvement of Experts. Their presence in the inspection team should therefore be planned beforehand on the basis of the outcome of the preinspection phase.

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Note 1

The OM is crucial to set the stage for the remainder of the GLP inspection.

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Note 2

The inspection unavoidably interferes with the activities in progress at the TF. The IT should be fully aware of this and inform the TF Management that all necessary measures should be taken to minimize potentially detrimental effects.

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Note 3

Should extremely serious deviations in the GLP compliance of the TF be detected at this early stage of the inspection, it is anyhow recommended to proceed with the visit to obtain a full picture of the actual status of the TF.

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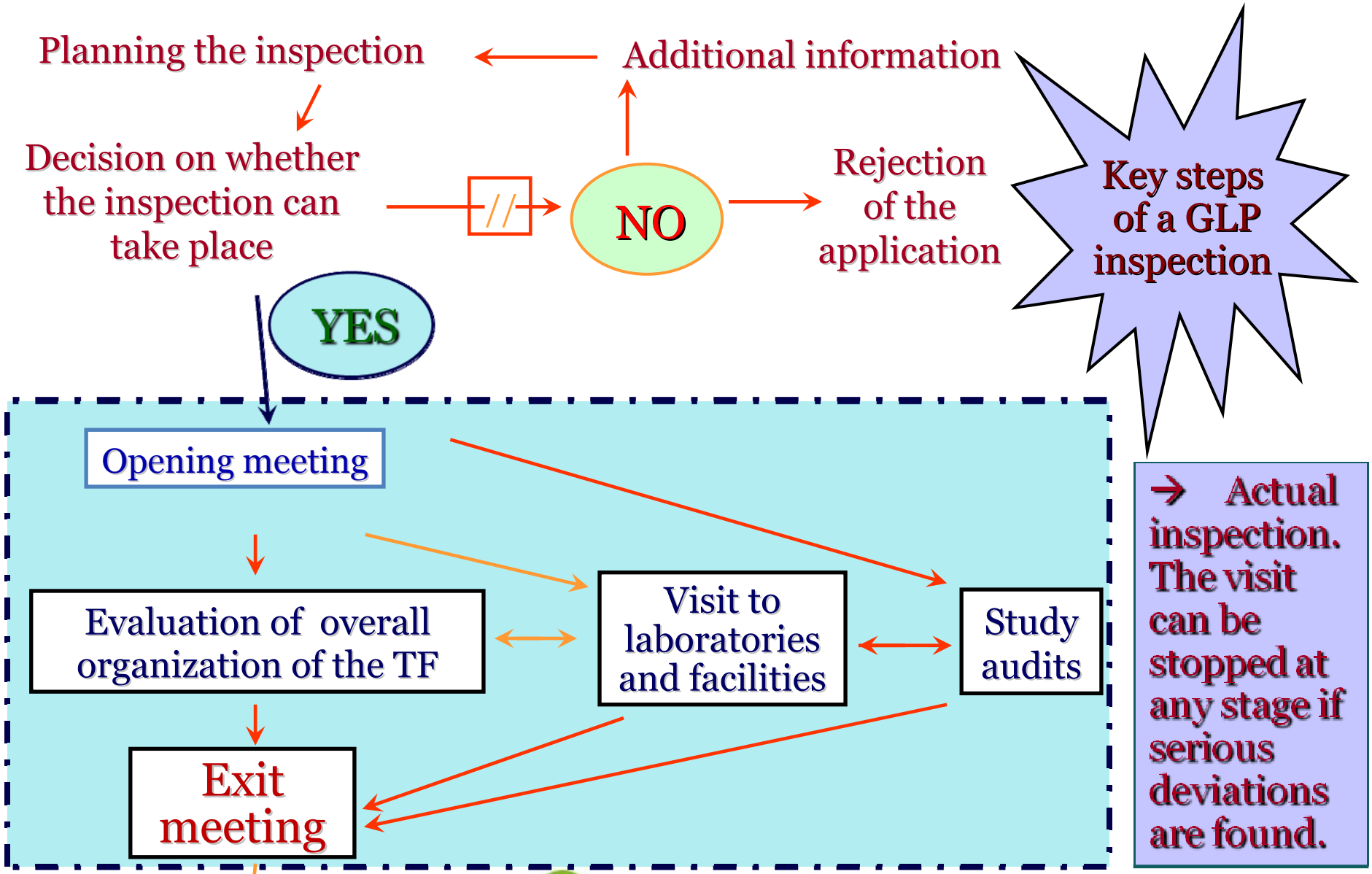

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Exit Meeting (1/4)

The key aspects of the Exit Meeting (EM) (also called closing conference) are outlined in the Guidance for GLP Monitoring Authorities - Revised Guidance for the Conduct of Laboratory Inspections and Study Audits *(Environment Monograph No. 111, OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 3).*

Exit Meeting (2/4)

At the end of an inspection and/or study audit, an EM should be held between the IT and the TF Management.

Deviations from the Principles of GLP found during the inspection/study audit are discussed.

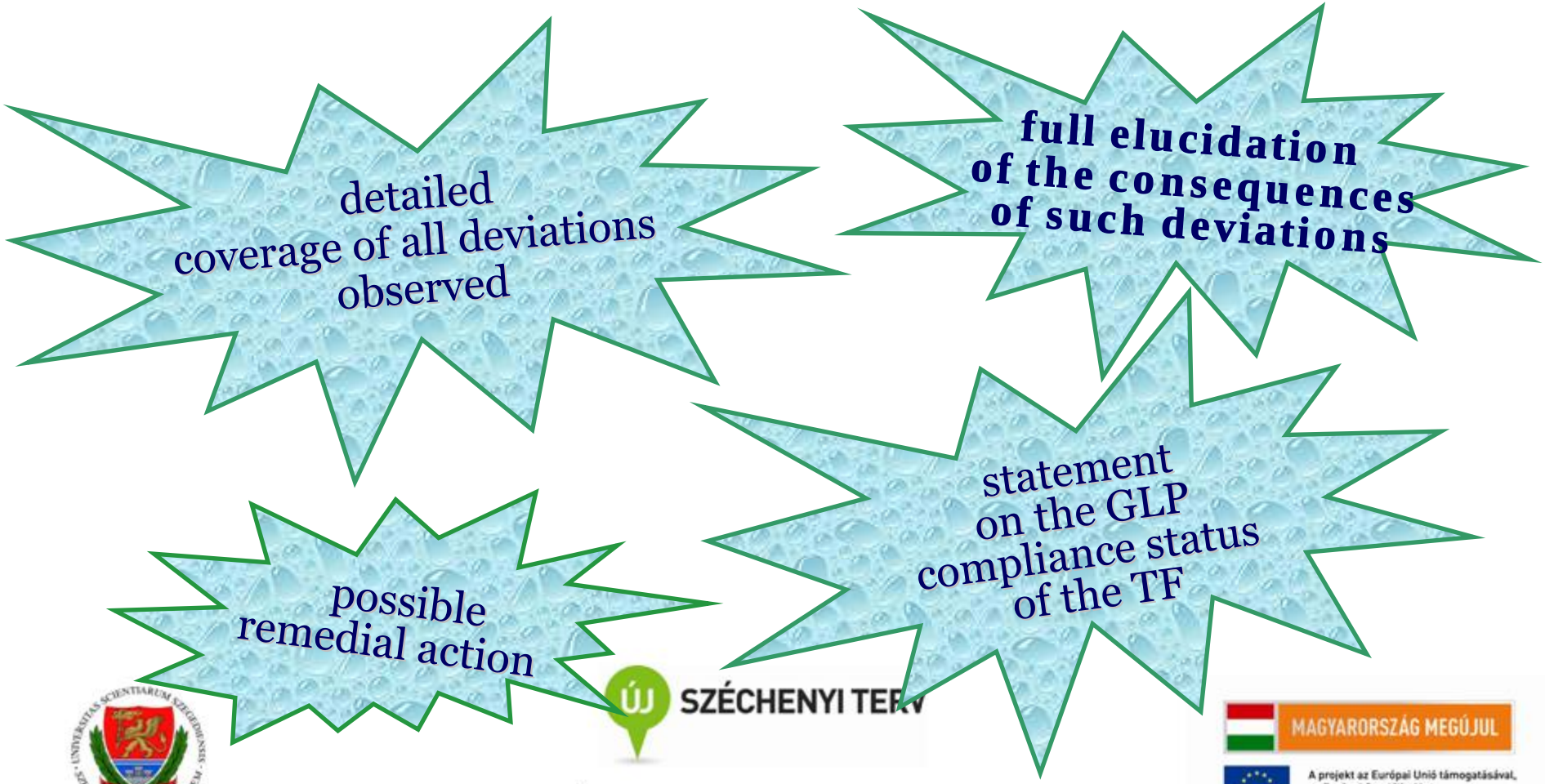
Exit Meeting (3/4)

As a rule, during the EM a written list of inadequacies should be presented describing the observed deviations, if any,

The discussion held during the EM should be summarized in the Inspection Report (IR).

Exit Meeting (4/4)

The Inspectors discuss their findings with the TF Management as regards, primarily:



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Key aspects of the EM (1/6)

- Participants: IT, TF Management, SDs, QAU, Archivist, PI (if applicable).
- Purpose: communication in writing of deviations found (brief report).
- Action: setting deadline for rectifying deviations.
- Announcement: re-inspection in the case of serious deviations.
- Additional issues: depending on circumstances.

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Key aspects of the EM (2/6)

In general, a number of deviations from the Principles of GLP will be detected during the inspection. The IT should inform in writing the National GLP MA on the nature and extent of their observations by means of an IR.

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Key aspects of the EM (3/6)

If deviations are minor, they probably will not affect the integrity of studies and the TF can be said to operate in compliance with the Principles of GLP. Assurance should be sought from the TF Management that remedial action will be taken within a prescribed deadline.

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Key aspects of the EM (4/6)

If serious deviations are identified which may affect the validity of studies performed at the TF, the action taken by the MA and/or the RA (as appropriate) will depend upon the nature and extent of the findings and the legal and/or administrative provisions within the national GLP Compliance MP.

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Key aspects of the EM (5/6)

Follow-up:

- the TF Management should submit a written reply to the List of Observations and corrective action should be taken within a given deadline;
- the findings discussed during the EM should be thoroughly illustrated in the IR;
- a decision on the compliance status is then made by the GLP MA.

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Key aspects of the EM (6/6)

The IT should try to have the consensus of the TF Management on the deviations observed and their commitment to solve problems within an agreed period of time.

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Example of form with remarks (1/2)

Annex to the GLP IR

Test facility: .....

Inspection date: .....

Exit meeting

1) □ No Remarks.

2) □ Remarks (with a deadline set to perform corrective action)

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Example of form with remarks (2/2)

Remark 1: .....
Remark 2: .....
....
Remark n: .....

The TF must confirm in writing that the necessary corrective action will be made within the prescribed deadline.

Copy handed over to the TF.

Date: .....

Signatures of the
GLP Inspectors
.....
.....
.....

Signatures of the
Representatives of TF
.....
.....
.....

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Deviations and more...

The conduct of GLP inspections and study audits poses some practical problems due to the wide variety of cases that can be encountered.

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Examples (1/6)

Problem. The archive of a TF located in the countryside was a small isolated building in the field. The risk that insects, small animals and dust could enter the archive could not be ruled out.

Solution. The TF installed physical barriers to minimize the above risk. In a supplemental visit two months later the IT checked that the corrective action was fit-for-purpose.

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Examples (2/6)

Problem. Unusual, often bizarre, terminology was used in the Final Reports of some GLP-compliant studies, this resulting at times rather confusing and misleading.

Solution. Harmonized terms and definitions were adopted. Thirty days after the GLP inspection the TF submitted documented evidence of the corrective action. No supplemental visit was thus necessary.

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Examples (3/6)

Problem. The description of the tasks and activities of the QAU was scattered throughout several SOPs, thus making difficult to have an overall view of the way the QAU discharged their duties.

Solution. The relevant SOPs were amended and submitted again to the MA. Their revision was found to be quite beneficial. Hence, no further inspections were necessary.

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Examples (4/6)

Problem. A TF was located in relatively small premises and both GLP and non-GLP activities were conducted under the same roof with a substantial risk for cross contamination.

Solution. The TF modified the conduct of BPL activities, in some instances also physically confining them in pre-assigned areas. The MA received photographic evidence of those changes and deemed them to be acceptable.

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Examples (5/6)

Problem. A TF conducted GLP studies in the framework of an integrated quality system covering both the Principles of GLP and the ISO/IEC 17025 Standard. This was in contrast with some specific requirements of the Principles of GLP.

Solution. GLP activities were made completely independent of the ISO/IEC 17025 Standard. Written assurance of this was given to the MA. A supplemental inspection was scheduled, anyhow.

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Examples (6/6)

Problem. In an acute toxicity study performed on rats it was noted that the total number of samples mentioned in the study plan was higher than that of the samples actually under test. The TF was unable to explain this fact during the inspection.

Solution. Two days after the inspection the TF provided sound evidence that a clerical error occurred in the transcription of numerical data. The said study was then considered to be GLP-compliant.

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Decision on the compliance status (1/2)

The GLP MA and/or RA will take action as appropriate depending on the nature and extent of the deviations found. The compliance status of the TF is reported in the annual overview of TFs inspected by each Member Country participating in the MAD programme. In the case of major deviations, the IT may need to return to the TF to verify that corrective actions have been taken as appropriate.

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Decision on the compliance status (2/2)

It should be always kept in mind that many minor deficiencies detected at a TF during a GLP inspection and/or study audit may point towards much more serious problems when taken on mass.

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Mind!

- Even if at first sight something seems useless or strange, inspectors should try to see what is behind it and what are the reasons for it being part of the system.

- Each TF may find their own way to implement GLP because there is room for flexibility in the Principles of GLP.

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Everything should be as simple as it is, but not simpler.

(Albert Einstein)

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Upon completion of the TF inspection and/or study audit the IT should prepare a written report of the findings.

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Inspection Report (1/2)

The key aspects of the IR are outlined in the Guidance for GLP Monitoring Authorities – Guidance for the Preparation of GLP Inspection Reports (Environment Monograph No. 115 of the OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 9).

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Inspection Report (2/2)

The IR should be a faithful and objective representation of facts. An overall assessment of the degree of compliance
of the TF with the Principles of GLP should be made to assist the GLP MA to make a decision.

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The Principles of GLP prescribe that "… details of the inadequacies or faults detected should be provided to the TF and assurance sought from its senior management that action will be taken to remedy them. The IT may need to revisit the facility after a period of time to verify that necessary action has been taken."

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It is also stated that "if a serious deviation from the Principles of GLP is identified during a TF inspection, … the Inspector should report back to the (National) GLP MA. The action taken by that Authority and/or the RA, as appropriate, will depend upon the nature and extent of the non-compliance…"

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Information required (1/6)

There are many different ways to organise an IR. All of them are acceptable, provided that the IR contains the required information and meets the requirements of the RA.

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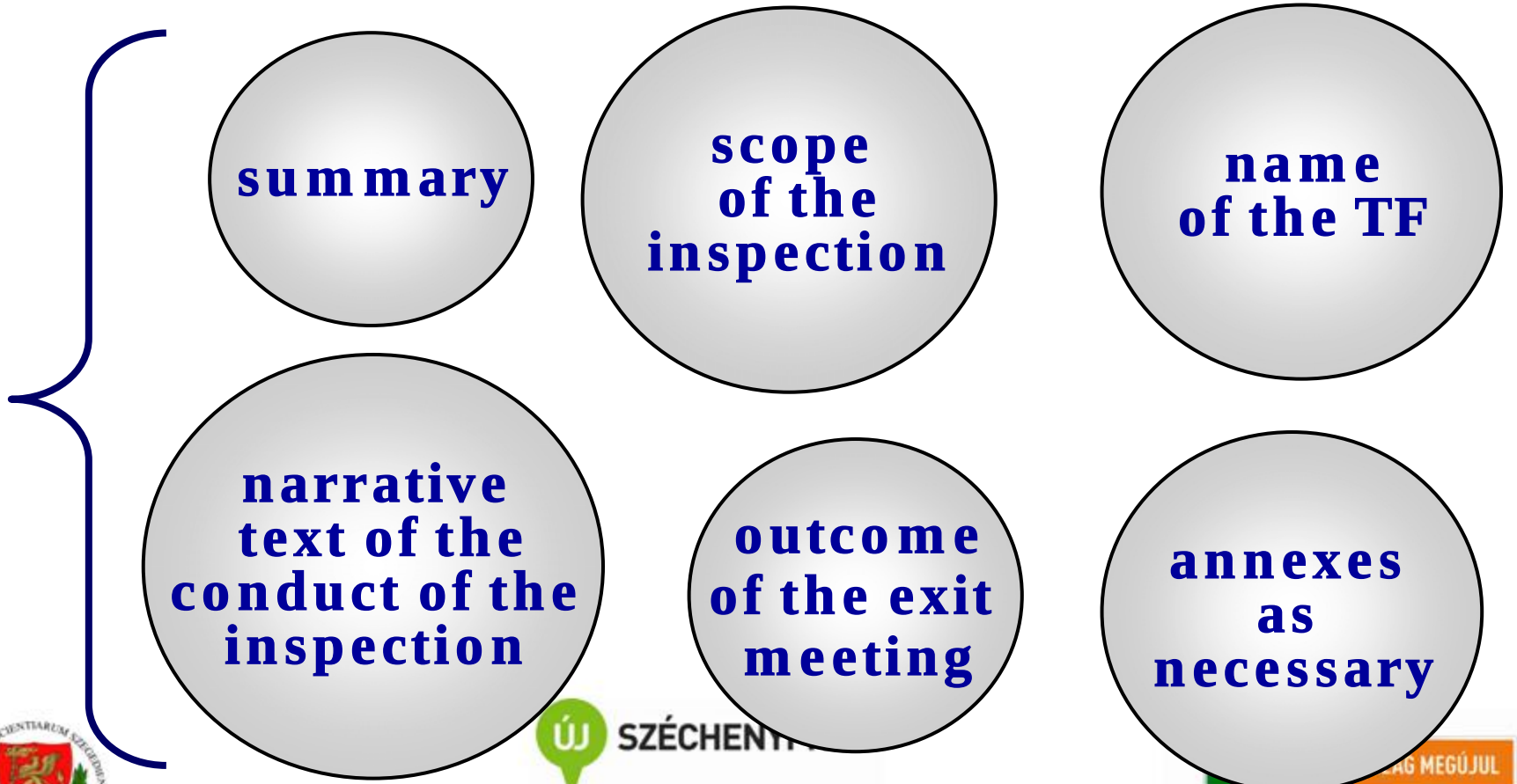
Information required (2/6)

The IR should contain:



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Information required (3/6)

In particular, as detailed in the OECD Guidance Number 9, the IR should record the date and time of the EM and the names of attendees. It should also give a brief summary of the GLP deviations noted by the IT. The responses of the TF representatives should be included.

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Information required (4/6)

As regards the QAU, the points that should be documented are:

- number of QAU auditors;
- type of inspection programme;
- process *vs.* study specific approach or both;
- frequency of audits;
- scope of audits.

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Information required (5/6)

Points that should be documented as regards the TF premises are:

- description of key areas;
- number of laboratories;
- use of individual laboratories;
- standard of housekeeping;
- space available.

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Information required (6/6)

The deficiencies reported should:

- be clear;
- stand up without further explanation;
- not be subjective or vague;
- be linked to the Principles of GLP.

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An example of IR

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Inspection Report (1/10)

MA: Ministry of Health
Inspection Report
(Legislative Decree nr. 50, March 2, 2007)

- Full postal address of the TF
- Full postal address of the TF headquarters
- GLP MA reference number
- Date of assignment to the GLP Inspectors
- Inspection type
- Inspection dates
- Signatures of the GLP Inspectors

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Inspection Report (2/10)

Background information

- TF name
- Location of the headquarters of the TF
- Location of laboratories
- Name of the TF manager
- Date of application
- Type of inspection
- Date of submission of the preliminary questionnaire
- Lead Inspector and members of the IT and their affiliation (Ministry of Health or National Institute of Health)
- Inspection starting date
- Inspection completion date

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Inspection Report (3/10)

Types of studies performed at the TF (OECD List)

OM

- ❑ Names of participants
- ❑ Scope of the GLP inspection
- ❑ Presentation of the TF
- ❑ Requests of the IT

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Inspection Report (4/10)

Inspection of functions, facilities and instrumentation

- SOPS and facilities for the receipt, labeling, handling, usage and storage of test and reference substances (*)
- Criteria for writing, distributing, applying and updating POS (*)

*(Date and participants for the GLP IT and the TF are given for all items marked *)*

Inspection Report (5/10)

- QAP (*)
- Instrumentation, materials, reagents (*)
- Test systems (*)

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Inspection Report (6/10)

- Test and reference substances (*)
- Apparatus, materials, reagents and specimens (*)
- Chemical tests (*)

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Inspection Report (7/10)

- Care, housing and containment of biological test systems (*)
- Information technology (*)
- Archive (*)

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Inspection Report (8/10)

Study audit

Study No. 1

- ❑ Name of the study
- ❑ Consistency of raw data with final results
- ❑ Availability of reports of the QAU
- ❑ Date
- ❑ Participants for the GLP IT and the TF

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Inspection Report (9/10)

Study No. 2

.....

.....

- o - o — o -

Study No. X

.....

.....

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Inspection Report (10/10)

EM

- List of findings
- Participants for the GLP IT and the TF
- Date

Assessment of the GLP IT

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Follow-up (1/7)

After the completion of a GLP inspection/study audit three different scenarios are possible, *i.e.*:

i. there are no deviations at all;

ii. only minor deviations are found;

iii. major deviations are encountered.

In practice, it is impossible that there are no deviations: a GLP inspector will always find in a TF some deviations from the Principles of GLP.

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Follow-up (2/7)

When there are only minor deviations, the TF should be requested to take immediate action to amend them and to inform the GLP MA when the corrections have been introduced. Another inspection of the TF can take place, if necessary.

Major deviations are, in their turn, incompatible with the Principles of GLP. Several actions are then possible which may be taken on a case-by-case basis.

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Follow-up (3/7)

Examples of major deviations:

- the QAU participated actively in the studies;
- falsification of data is detected;
- there is no separation between GLP and non-GLP activities;
- incompatible key functions assigned to the same individual.

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Follow-up (4/7)

In the case of major deviations, action to be taken may be:

- outright rejection of the TF application and withdrawal from the national GLP MP;
- recommendation to a RA that some studies be rejected;
- law suits, if applicable.

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Follow-up (5/7)

What the inspector mostly (and luckily) experiences is the occurrence of minor deviations, often quite unusual and unexpected.

"There are more things in heaven and earth, Horatio, than are dreamt of in your philosophy" (Hamlet, Act I, Scene V).

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Follow-up (6/7)

The GLP MA and/or RA will take action as appropriate depending on the nature and extent of the deviations found. The compliance status of the TF will be mentioned in the annual overview of TFs inspected by each Country participating in the MAD programme.

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Follow-up (7/7)

GLP status

In compliance

No or minor deviations, correctable in a short time.

Pending

Deviations found, not correctable within a short time. Reinspection and study audit needed after a few months.

Not in compliance

Major deviations found, validity of data questionable. Data are not accepted until the TF is reinspected at their own request.

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Note (1/3)

The final assessment of the degree of compliance with the Principles of GLP of a TF and of the studies conducted therein depends on the nature and number of deviations detected by the IT. Common sense plays no minor role.

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Note (2/3)

The promptness of the TF Management in properly amending the adverse findings along with the holistic evaluation of the outcome of all previous inspections should be duly considered by the MA before a final decision is made.

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Note (3/3)

The deviations found during a GLP inspection and the corrective actions adopted by the TF should be reassessed with the greatest attention on the occasion of the next GLP inspection.

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The inspection is over!

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Overview

- Background information
- Conduct of a GLP Inspection
- Final remarks

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The Principles of GLP do not formally address scientific issues. Yet, they can give rise to better science.

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The quest for harmonization(1/2)

The mutual acceptance of non-clinical safety studies and the ensuing social and economic benefits depend primarily on the extent to which a national GLP MA is able to properly discharge its duties.

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The quest for harmonization(2/2)

The current programme of On-site Evaluation Visits to the national GLP MPs, managed by the OECD in cooperation with the European Commission, will further promote the harmonization of national approaches to GLP compliance monitoring.

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Summary (1/3)

The Principles of GLP constitute one set of rule applicable to a variety of situations.

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Summary (2/3)

The conduct of GLP studies require proper management of laboratory facilities, test and reference items, archives and waste disposal.

Flexibility and judgement are always required.

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Summary (3/3)

The GLP Inspectors are well advised to identify those aspects that are characterised by the highest risk for the integrity of the studies so as to concentrate on them.

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Stick to the GLP Principles!

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Tribute to experimental animals (Shenjang)

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MANY THANKS FOR YOUR KIND ATTENTION

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Time for questions...

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Part II
The Organization of a Test Facility in Compliance with the Principles of Good Laboratory Practice

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Overview

- Background information
- Key features of a Test Facility
- Final remarks

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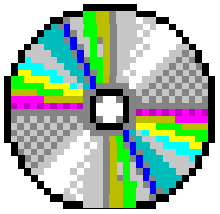
Overview

- **Background information**
- Key features of a Test Facility
- Final remarks



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Test Facilities (I/III)

Each TFM should ensure that the GLP principles are complied with in terms of:

- TFM
- principal investigator
- equipment
- qualified personnel
- Standard Operating Procedures
- study director
- quality assurance unit
- archive
- motivation
- master schedule

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Test Facilities (II/III)

It is the responsibility of the GLP MA to submit annually the list of TFs inspected and studies audited to the European Commission and to the OECD.

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Test Facilities (III/III)

In the European Union all this matter is basically managed through two GLP Directives, *i.e.*:

- Directive 2004/9/EC of 11 February 2004 (on the inspection and verification of the principles of GLP);
- Directive 2004/10/EC of 11 February 2004 (on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of GLP).

Overview

- Background information
- **Key features of a Test Facility**
- Final remarks

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The pillars of a Test Facility are:

- the Test Facility Manager
- the Quality Assurance Unit
- the Study Director
- the Archive

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The Standard Operating Procedures (SOPs) play a pivotal role in the management of a Test Facility and are in practice its quality manual.

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Guidance on SOPs

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SOPs are basically dealt with in two guidance documents of the OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, *i.e.*:

- No. 1, OECD Principles of Good Laboratory Practice (1997);
- No. 3, Revised Guidance for the Conduct of Laboratory Inspections and Study Audits (1995).

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Definition

SOPs are documented procedures describing how to perform tests or activities normally not specified in study plans or test guidelines.

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In practice

- SOPs are documents illustrating how activities are carried out in a TF.
- SOPs play the role of the Quality Manual typical of other quality systems.

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The rationale behind (1/2)

- The TF management is held responsible for ensuring that SOPs are produced, issued, distributed, revised and archived.
- SOPs are intended to ensure the quality and integrity of data.

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The rationale behind (2/2)

- SOPs are of extreme importance to GLP Inspectors in order to audit and reconstruct GLP studies.
- SOPs can be thought of as the institutional memory of the way a TF performs its activities and ensure self-consistency and traceability even in the case of replacement of staff members.

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Key aspects to be checked

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The GLP Inspector is well advised to check that all SOPs are available to the interested personnel and fully implemented.

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Checking SOPs (1/3)

Inspectors should check the "SOP of SOPs" and verify whether:

- the system is logical and usable;
- everything is covered;
- the system is consistently used for all SOPs.

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Checking SOPs (2/3)

Inspectors should check whether:

- the historical file of SOPs is complete;
- the Quality Assurance Unit (QAU) maintains copies of the SOPs;
- the QAU verifies that SOPs are updated.

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Checking SOPs (3/3)

Inspectors should check whether:

- the personnel use the SOPs thoroughly and appropriately;
- there are SOPs properly dealing with deviations from the study plan.

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What else?

- Published material, *e.g.*., papers, text books, manuals, can be attached to the SOPs as supplements.
- Relevant documentation should be retrievable at any time.

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Cornerstones (1/8)

A general SOP (the SOP of SOPs) should be in place to manage the entire SOP system of a TF, as regards, in particular:

- role of the QAU;
- index system;
- preparation of new versions and removal of old ones;
- distribution.

Cornerstones (2/8)

The GLP principles do not define who should write the SOPs. However:

- it goes without saying that SOPs should be set up by somebody well familiar with the procedures, *i.e.*, quite often, the Study Director (SD);
- by no means SOPs should be written by the QAU (with the only exception of the QAU SOP).

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Cornerstones (3/8)

Key steps in managing the SOPs are:

- ❑ review by the QAU;
- ❑ approval by TF Management;
- ❑ use by personnel;
- ❑ check by the QAU that SOPs are being followed;
- ❑ acknowledgement of deviations by the SD.

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Cornerstones (4/8)

If deviations from SOPs occur:

- the SD and (if applicable) the Principal Investigator (PI) should be timely informed;
- the SD should react promptly and describe deviations occurred and corrective actions taken;
- the impact on the study integrity should be assessed in the Inspection Report (IR) of the Inspectors.

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Cornerstones (5/8)

Role of the TF Management:

- the overall quality and integrity of data is the responsibility of the TF Management;
- the Management approves all SOPs and their revisions;
- the Management ensures that SOPs are produced, issued, distributed and stored.

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Cornerstones (6/8)

The role of the QAU:

- the SOPs are reviewed (but not formally approved) by the QAU to check their compliance with the Principles of GLP;
- a copy of the full set of SOPs is kept by the QAU;
- the availability of SOPs to the interested personnel is monitored.

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Cornerstones (7/8)

The role of the study personnel:

- each SOPs should be always available where it is needed;
- the personnel should promptly inform the SD (and /or the PI, if applicable) of any deviations from the approved SOPS.

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Cornerstones (8/8)

Management of SOPs:

- ❑ preparation and approval;
- ❑ role of the QAU;
- ❑ index system;
- ❑ preparation of new versions and removal of old ones;
- ❑ distribution.

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Typical SOPs for test and reference items

- Reception of materials
- Identification
- Labelling
- Handling
- Sampling
- Storage

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Typical SOPs for apparatuses

- Use
- Maintenance
- Calibration
- Cleaning

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Typical SOPs for materials, reagents and calibrants

- Preparation
- Labelling

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Typical SOPs for computerised systems

- Validation
- Operation
- Maintenance
- Security
- Change control
- Back-up

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Typical SOPs for studies

- Coding of studies
- Data collection
- Indexing systems
- Handling of data
- Reporting
- Archiving

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Typical SOPs for test systems (I/II)

- Receipt, transfer, placement, characterisation, identification, care
- Setting of environmental room conditions
- Preparation, observation and examination at all study phases

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Typical SOPs for test systems (II/II)

- Handling of animals found moribund or dead during the study
- Collection, identification and handling of specimens (including those from necropsy and histopathology)

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Typical SOPs for inspections performed by the QAU as regards

- Planning
- Scheduling
- Performing
- Documenting
- Reporting

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How does all this apply to multisite studies?

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Note (1/2)

- It is recommended that TS personnel follow the TS SOPs.
- When this is not the case, the use of other SOPs should be mentioned in the study plan.

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Notes (2/2)

- SOPs revised by the TF should be sent also to the TS and the superseded versions should be removed.
- The PI should ensure that all TS personnel are aware of the revised SOPs.

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Typical SOPs for multisite studies

- Storage, return of disposal of test and reference items
- Foreign language translation of study plans and/or SOPs (if applicable)
- Selection of TSs
- Appointment and replacement of the PI
- Transfer of data, specimens and samples between sites

Major types of technical equipment (1/5)

- General-purpose devices
- Physical-chemical apparatuses
- Analytical instrumentation

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Technical equipment (2/5)

General-purpose devices are those used for operations independently from the specific study, such as:

- balances;
- thermostatic baths;
- pH-meters;
- electronic multichannel pipettes;
- potentiometric titration workstations;
- cell culture incubators.

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Technical equipment (3/5)

Physical-chemical apparatuses are used to measure physical-chemical quantities (parameters useful to characterize test items and to predict their possible adverse effects), *e.g.*:

- melting and boiling points;
- vapour pressure, density;
- water solubility;
- lipid solubility;
- *n*-octanol-water partition coefficient;
- viscosity.

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Technical equipment (4/5)

Analytical instrumentation:

- essential to identify and quantify chemical entities quite often involved in GLP studies;
- basically chromatographic, electrophoretic, electrochemical and spectrochemical apparatuses.

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Technical equipment (5/5)

Test Facilities may well be equipped with analytical techniques as diverse as, *e.g.*:

▪ ASV ▪ CZE ▪ ELISA ▪ ETA-AAS ▪ FAAS ▪ FIAS ▪ FTIRS ▪ GC ▪ HPLC ▪ ICP-AES ▪ ICP-MS ▪ NMR ▪ PIXE ▪ SEC ▪ SEM ▪ SPE ▪ UVS ▪ XRFS

Two or more techniques are often combined to form a hyphenated system.

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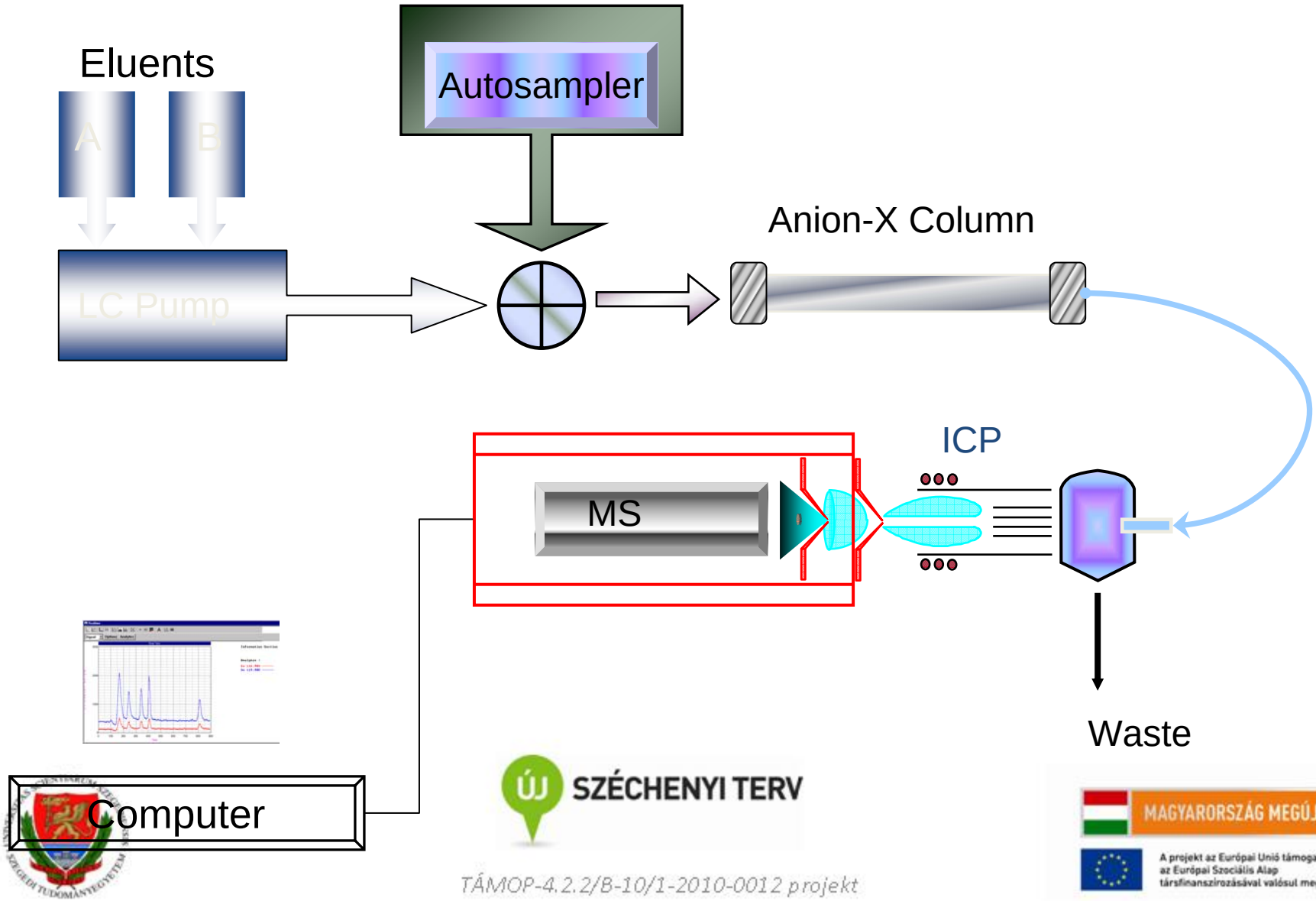
Scheme of an LC-ICP-MS system. Example (1/3)



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LC unit of the LC-ICP-MS system. Example (2/3)

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ICP-MS unit of the LC-ICP-MS. Example (3/3)

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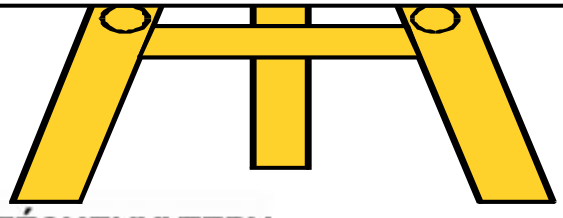
Note!

The GLP inspector does not need to be an expert in any instrumental technique, but only be able to assess whether apparatuses are properly installed, calibrated, used, and maintained.



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Scope of method validation (1/4)

Reliability and comparability of experimental data are crucial:

- to perform meaningful studies;
- to achieve credible results which can be profitably used by the decision maker.
- Validation is a scientific issue under the responsibility of the Study Director (SD).

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Scope of method validation (2/4)

- Validation refers to analytical systems, not only to analytical methods.
- An analytical systems comprises a defined method protocol, a defined concentration range for the analyte, and a specified type of test material.

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Scope of method validation (3/4)

- Each system has a specific field of application.
- It should be suitable for the particular purpose.
- It should be validated against the laboratory's own specifications.
- The laboratory should ascertain the measurement range and the correct functioning of the entire system.

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Scope of method validation (4/4)

Validation procedures
and their documentation should be elaborated and kept on file for later control and possible renewal.

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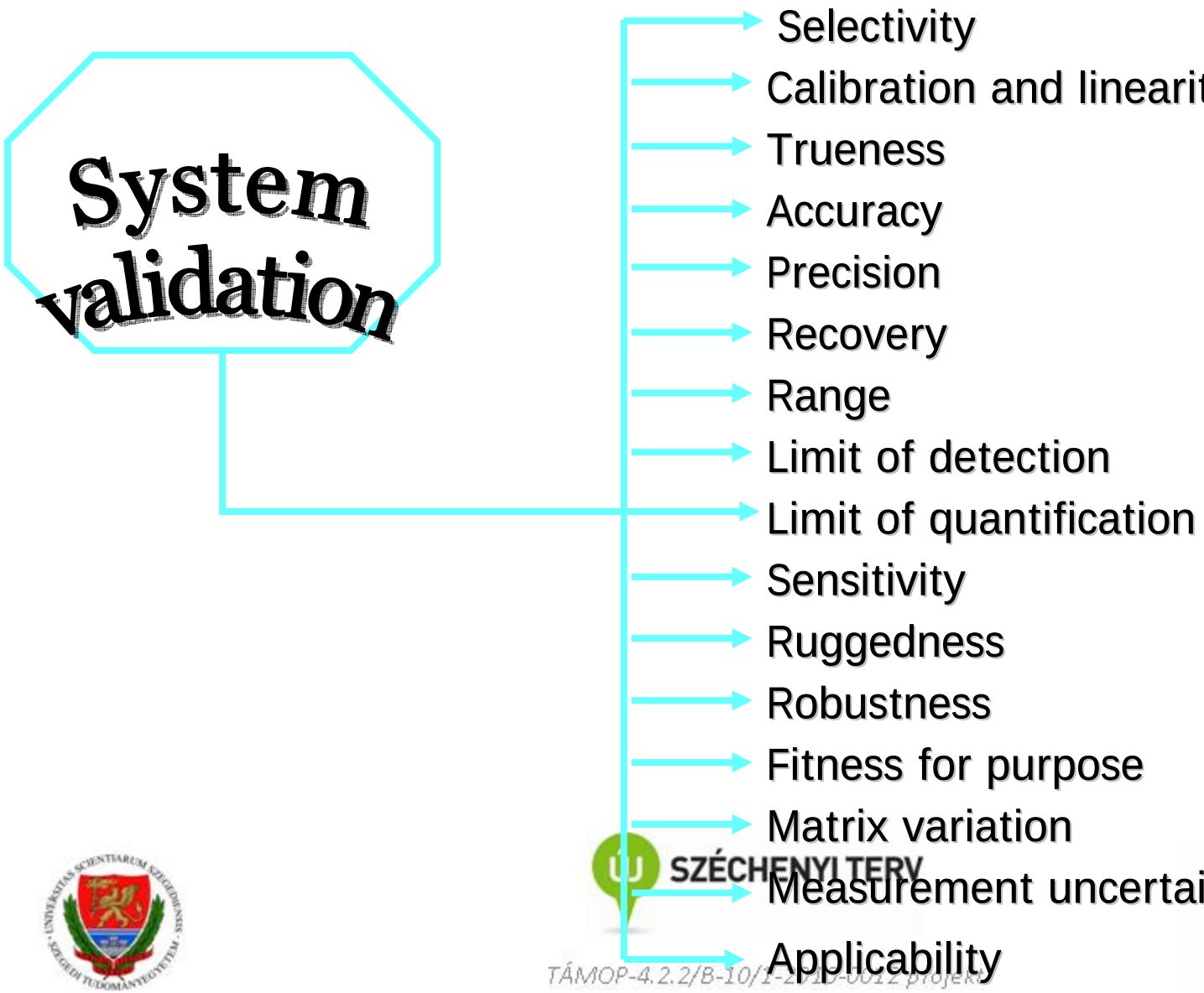
Method performance characteristics



System validation and GLP inspections (1/3)

- The GLP inspector should identify the key aspects of the experimental sysems in use at the Test Facility.
- This can be done on the basis of the information gained during the pre-inspection phase.

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System validation and GLP inspections (2/3)

- Prior to the actual visit to the laboratory, the GLP inspector is well advised to set up a check-list of validation items that would deserve in-depth examination.

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System validation and GLP inspections (3/3)

The GLP inspector should ask for documented evidence that validation was properly achieved, *e.g.*:

- vendor's documents;
- records of maintenance
- procedures for calibration.

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The ultimate goal of validation (1/4)

- Validation starts well before an instrument
  is placed on-line and continues long after method development and transfer.
- A well-defined and documented validation process provides regulatory agencies with evidence that the analytical systems are suitable for their intended use.

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The ultimate goal of validation (2/4)

- Suitability of equipment must be continuously assessed.
- A plan for the systematic control of the entire system or of parts thereof should be established.

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The ultimate goal of validation (3/4)

Efforts should be concentrated on aspects where the sources of errors are greatest, *i.e.*:

- control of adjustment and calibration of the analogue components ;
- verification and maintenance of procedures to ensure the safekeeping of data.

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The ultimate goal of validation (4/4)

By approaching method development, optimization, and validation in a logical, stepwise fashion, laboratory resources can be used in a more efficient and productive manner.

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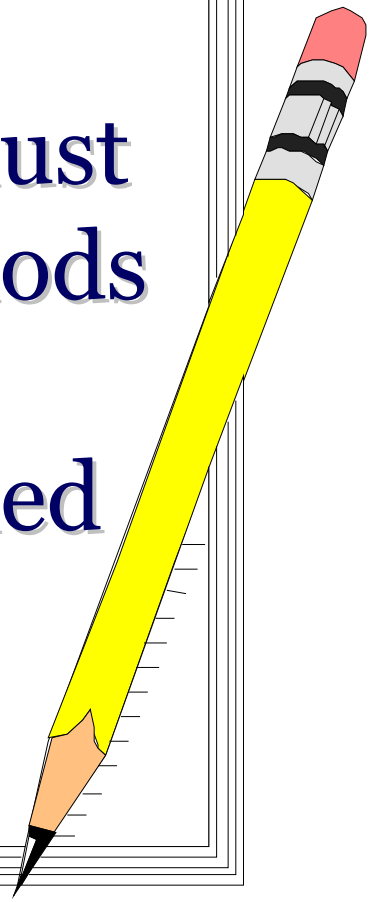
Note!

The GLP inspector must check that validated methods are in place, although validation can be performed in the context of other quality systems.



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Validation according to the GLP principles is more expensive!

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Remarks (1/4)

The validity of a GLP study greatly depends on the reliability of the experimental information obtained through instrumental techniques.

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Remarks (2/4)

Technical personnel should be properly trained and highly motivated to fully master the highly sophisticated instruments available nowadays.

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Remarks (3/4)

The TFM should be fully aware of the crucial role played by instrumental techniques in performing GLP-compliant studies.

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Remarks (4/4)

The GLP inspector should gain a thorough understanding of the policy of the TFM as regards the use and maintenance of instruments.

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Overview

- Background information
- Key features of a Test Facility
- **Final remarks**

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Conclusion (1/3)

SOPs are the working tool which allows a study to be reliably conducted. Hence, their constant updating and their correct use are of prime importance.

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Conclusion (2/3)

Agreed procedures for GLP compliance monitoring as well as for the conduct of laboratory inspections and study audits play a crucial role to substantiate mutual confidence.

SOPs are of paramount importance in this context.

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Conclusion (3/3)

A Test Facility can successfully carry out experimental activities intended for regulatory purposes only if all the key functions are properly in place and SOPs are carefully maintained, updated and archived.

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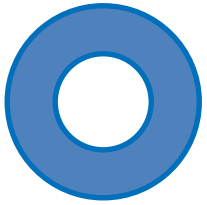
The Case of Hungary

http://www.ogyi.hu/lists/

List of the Hungarian Test Facilities (updated: 2012)



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Are there queries?

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