Food Contaminants and Residue Analysis

by

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Chapter 3

Guidelines on quality implementation for analytical methods

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3.1. Introduction

The concept that no laboratory can survive in the long term without having a fit-for-purpose quality system in place is nowadays widely accepted by the international scientific community. Experimental information must be, in fact, supported by documented evidence to be valid, credible and comparable. To date, quality systems can be traced back basically to two distinct, yet complementary, approaches, *i.e.*, those adopting the criteria for accreditation, mostly those worked out by the International Standardisation Organisation (ISO) and those based on compliance with the principles of Good Laboratory

Practice (GLP), in particular as developed by the Organisation for Economic Co-operation and Development (OECD) (1 – 3). The rationale behind the latter roots in the need for assessing the integrity of experimental studies, while the former aims at evaluating the competence of a laboratory to perform measurements. In other words, in a GLP system the validity of a completed study is challenged. In so doing, necessarily all the phases of the study are reconstructed and the laboratory performance and facilities are checked. On the other hand, in the case of a quality system based on accreditation, the target is to gain confidence in the ability of the laboratory to generate defendable experimental data.

More in detail, a GLP system aims at providing the decision maker with reliable experimental information on new chemical substances so as to allow for a sound assessment of the benefit-to-risk ratio well before chemicals are produced and marketed. The cornerstone of this policy is the implementation of the OECD GLP principles whenever non-clinical safety studies on new chemicals are undertaken by test facilities. Such principles can be found in the Decision of the Council concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30(Final)], the Council Decision-Recommendation on Compliance with Principles of GLP [C(89)87(Final)] and the Council Needless to say, the GLP quality system is compulsory resorted to whenever there is, *e.g.*, a registration obligation for the commercialization of a new substance. Decision concerning the Adherence of Non-member Countries to the Council Acts related to the Mutual Acceptance of Data in the Assessment of Chemicals [C(97)114(Final)].

In turn, an accreditation-oriented quality system is governed by the ISO/IEC Standard 17025 and has to cover the administrative and technical issues specified in the Standard, including internal audits, job descriptions and responsibilities, procedures for equipment/instrument maintenance and calibration, document control, handling of reagents, chemicals and reference materials, sample delivery and storage, validation of test methods, traceability and uncertainty of the test results, training of personnel, client complaints and corrective and preventive actions. Several of these issues are also required for compliance with the OECD GLP principles either with a different emphasis or with additional requirements. Although the two systems have been designed to meet largely different needs, it is hoped that they can more and more support each other to minimize redundancy and to provide the end user with experimental information as trustable as possible.

3.2. The role of quality

3.2.1. General aspects

Important decisions are often taken on the basis of experimental data. Hence, it is crucial that such data be comparable, reliable and valid. No laboratory can in fact be run without a fit-for-purpose quality system in place. Quality has been defined by ISO as "*The totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs*". To date, quality systems are basically inspired either by the Good Laboratory Practice (GLP) principles or by the accreditation criteria.

Laboratory work may be of two different types: *i*) *the* outcome of the investigation are exact figures, to which precision and reproducibility are expected to be attached; *ii*) the outcome of the investigation is, in a general sense, complex information which should be credible, reliable and comparable. In the former case, what matters more are the experimental measurements. In this context quality is assessed in terms of precision and reproducibility of the numerical data obtained. The ability of the laboratory to generate such data is thus of primary importance. Quality systems based on accreditation criteria are ideal in this respect. In the latter case, the focus is on the overall study as such. Third parties should be enabled to reconstruct the whole course of the study and to check its integrity so that confidence can be gained in the way the study results have been obtained. Under such circumstances, quality systems based on the GLP principles do apply. Which approach is to be preferred depends only on the scope and goals of the activities performed in the laboratory, although it should not be overlooked that accreditation is basically voluntary, whereas the GLP system is prescribed by law for those Test Facilities (TFs) undertaking non-clinical safety studies.

There is still some confusion surrounding the terms of accreditation and certification. As this may well misleading, consensus has been reached on the following definitions: *accreditation* is a means used to identify competent testing laboratories, whereas *certification* is the official approval granted by a given authority.

3.2.2. Key aspects of a quality system based on the accreditation criteria

As set forth by the IUPAC, "*The international scientific community recognizes that a laboratory must take appropriate measures to ensure that it is capable of providing*

data of the required quality. Such measures include: i*) internal quality control procedures;* ii*) participation in proficiency testing schemes;* iii*) validated methods of analysis;* iv*) accreditation to an international standard.*" (4).

Accreditation-based quality systems are governed by the international Standard ISO/IEC 17025 (5). This standard exploits the extensive experience gained in implementing the ISO/IEC Guide 25 and EN 45001 norms and replaces them both. The ISO/IEC Standard sets forth the requirements a laboratory has to meet to be recognized as competent to carry out tests and/or calibrations, including sampling. The pillars of an accreditation system are listed in Table 1.

Method validation is central to the accreditation process as reliability and comparability of data are crucial to perform experimental meaningful tests and to achieve credible results which can be profitably used by the client, *i.e.*, the end-user. It should be noted that the overall validation process covers all of the pivotal phases of an experimental measurement and not only the mere quantification step, as illustrated in Fig. 1. In turn, method validation as such should at least cover the parameters given in Table 2.

3.2.3. Key aspects of a quality system based on the principles of good laboratory practice

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 TFs for regulatory purposes were basically unreliable. Evidence was in fact provided of major adverse effects of such substances which had not been reported at the time when the authorization to production and commerce was granted. In the early 1970's the US Congress undertook the re-assessment of studies submitted by some TFs to Regulatory Authorities (RAs) and suspected to be fraudolent. Under such conditions thousands and thousands of safety studies on industrial chemicals, pesticides, herbicides, drugs, cosmetics, and food and feed additives were conducted for years (about 35 – 40 % of all toxicological studies authorized in the USA in that period). As an example, an article published by *The Washington* Post in 1997 is shown in Fig. 2.

Senator Edward Kennedy declared at the US Congress of January 20, 1976, that "*... unreliable, undocumented and fraudolent research is the most frightening menace to the health and safety of people. That research be wrong because of technical problems or*

because of the lack of competence or even due to criminal negligence is less important than the very fact that it is wrong…"

The principles GLP were conceived to harmonize the conduct of non-clinical safety studies and to minimize the risk of fraud. Since the early years, this matter became a priority for the Organisation for Economic Co-operation and Development (OECD) which set up the GLP principles in order to promote and manage the mutual acceptance of non-clinical safety studies in the Member Countries. According to OECD, the principles of GLP are a quality system concerned with the organizational process and the conditions under which safety studies are planned, conducted, controlled, recorded, reported and archived. In practice, they form a body of reciprocally dependent documented items that make the falsification of a study more time-consuming and expensive than its actual correct performance.

The three major acts of OECD in the field of GLP are as follows: *i*) Decision of the Council concerning the Mutual Acceptance of Data (MAD) in the Assessment of Chemicals [C(81)30(Final)]; *ii*) Council Decision-Recommendation on Compliance with Principles of Good Laboratory Practice; *iii*) [C(89)87(Final)] Council Decision concerning the Adherence of Non-member Countries to the Council Acts related to the Mutual Acceptance of Data in the Assessment of Chemicals [C(97)114(Final)]. As a part of the permanent activities of its *Environment, Health and Safety* Programme, the OECD also prepares and publishes Test Guidelines for Chemical Substances to be used when performing GLP studies and thus enhance their reliability.

The Series on the GLP principles and compliance monitoring consists at present of 14 monographs, as detailed in Table 3, whereas Table 4 details the pillars of a GLP system (6, 7). These guides form the core of the legal provisions of the European Union in the field of GLP (8, 9).

3.3. ***Conclusions***

The two quality systems have been conceived to meet quite different needs. In other words, the accreditation criteria are designed to manage activities in a laboratory where routine quantitative measurements (such as analytical determinations) are carried out, whereas the GLP principles are intended to guarantee the integrity of data generated in

non-clinical safety studies. Their respective fundamental characteristics are summarized in Table 5. From this standpoint, it is worth mentioning that, *e.g.*, the GLP system prescribes that the Director of the TF, the person responsible of the Quality Assurance Unit, the Study Director and the Archivist be all independent of each other to fully guarantee the fair conduct of the study, while in the case of the accreditation system the first two functions can coincide and the third one does not exist. On the other hand, in the accreditation system, it is imperative to have a quality manual, which in turn is not formally requested in the GLP system, although in the latter the Standard Operating Procedures play basically the same role. Moreover, a study plan, mandatory in the GLP system, is not needed in the accreditation one, not to speak of the fact that management of complaints and participation in proficiency testing is mandatory in the latter, but not necessary in the former. As regards validation of methods, the GLP system requires that validated methods are in place, but does not impose that such methods are set up according to the GLP principles, any other fit-for-purpose quality system being acceptable to this end.

All this provides clear evidence of the profound diversity in the approaches and goals of the two systems, although some common aspects are present. In this regard, in recent years, the OECD has established a dialogue group to verify where the two systems can actually interact, thus minimizing useless duplication of efforts. In conclusion, the selection of the quality system to be adopted should be carefully made on the basis of the prevailing activities carried out in the laboratory. Quality is inescapable, but it has a cost: a wrong decision can only lead to failure.

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9. Directive 2004/10/EC of the European Parliament and Council, 11 February 2004, *Off. J. EU*, **L50** (2004), 44 -59.

Table 1. Key aspects of a laboratory compliant with an accreditation system.

Service to the client	Motivation of personnel
Policy for complaints	Laboratory setting
Control of non-conformities	Validation of methods
Quality manual	Equipment
Management of records	Management reviews
Internal audits	Test and calibration items
Measurement traceability	Report of results

Table 2. Parameters to be ascertained to validate an analytical method.

Applicability	Limit of detection
Selectivity	Limit of quantification
Calibration and linearity	Sensitivity
Trueness	Ruggedness
Accuracy	Robustness
Precision	Fitness for purpose
Recovery	Matrix variation
Range	Measurement uncertainty

Table 3. The OECD series on the GLP principles and compliance monitoring.

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).
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).
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).
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 GLP Principles to *in vitro* Studies (2004).
No. 15. Establishment and Control of Archives That Operate in Compliance with the Principles of Good Laboratory Practice (2007)

Table 4. Key aspects of a Test Facility compliant with a GLP system.

Director of the Test Facility	Study plan
Study Director	Final report
Quality Assurance Unit	Standard Operative Procedures
Archivist	Test Site (if applicable)
Sponsor	Principal Investigator (if applicable)
Test and reference items	

Table 5. Key elements of the accreditation and GLP system.

Accreditation quality system	*GLP quality system*	*Overlapping aspects*
Management of complaints	Master schedule	Management
Uncertainty of measurements	Study director	Motivation
Proficiency testing	Archivist	Training
Preventive actions	Quality assurance unit	Reference materials
Service to the client	Study plan	Equipment and maintenance
Sampling	Test article	Method validation
	Reports	Chain of custody
		Quality control procedures
		Corrective action
		Audits
		Sample reception

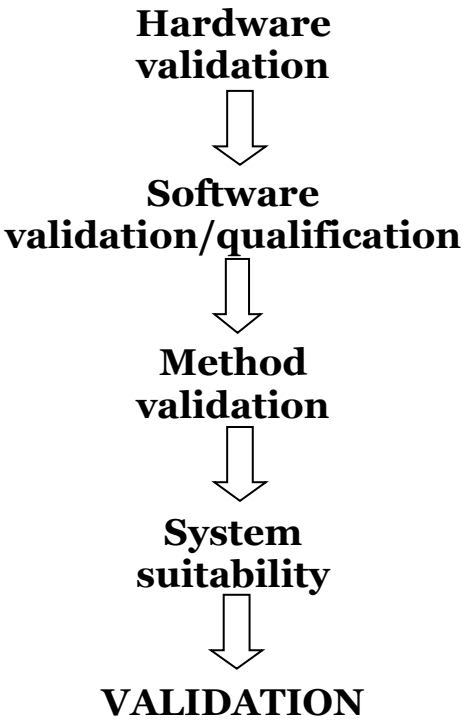

Fig. 1. Major steps of the validation process.

Ex-Officials of Chemical-Testing Lab Found Guilty of Falsifying Results
By Kevin Klose Washington Post Staff Writer
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By Kevin Klose
Washington Post Staff Writer

CHICAGO, Oct. 21—Three former officials of Industrial Bio-Test (IBT) Laboratories, once widely used by government and industry to test thousands of new chemicals for safety, were convicted today of falsifying results of four chemical tests.

A U.S. District Court jury found them guilty of mail fraud and making false statements to the government, ending a protracted federal investigation into the efficacy of toxicological tests peformed by the Northwood, Ill., firm.

IBT once was considered one of the nation's most reliable authorities for determining potential cancer and other hazards from new chemicals and compounds.

animals died of thirst or drowned in their water troughs.

Convicted were Dr. Moreno L. Keplinger, 53, former head of toxicology at IBT; Paul Wright, 48, former chief of IBT's rat toxicology section; and James B. Plank, 39, former assistant toxicology manager. A fourth defendant, Joseph C. Calandra, former IBT president, was granted a mistrial last summer after undergoing open-heart surgery. Federal prosecutors today said they have not decided whether to retry Calandra.

The three are expected to appeal the verdicts. U.S. District Court Judge John A. Nordberg set no sentencing date. He set Feb. 17 as the date for hearing defense motions for acquittal.

cor, a herbicide; Nemacur, a pesticide, both made by Chemagro; and trichlorocarbanilide (TCC), a Monsanto Corp. antibacterial agent.

No evidence of complicity by any of the manufacturers in the falsified tests was presented at the trial.

The studies were supposed to cover between 18 and 24 months of dosing segregated groups of rats and mice with the chemicals. Careful examination of the animals would determine if dangerous genetic or other changes had occurred as a result of the dosages.

Federal prosecutors said IBT now employs a skeleton staff chiefly to compile documentation on past tests.

Fig. 2. Article published by *The Washington Post* in 1974 on the falsification of experimental data