Quality Assurance in Toxicology

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Abstract

Reliable data are essential for the assessment and evaluation of the toxicological characteristics of chemical substances and of safe exposure levels for man and the environment. Data reliability is closely linked with the exclusion or minimization of errors and mistakes in the generation of data. These objectives can be reached by the implementation of appropriate Quality Assurance (QA) systems as an

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important part of the Quality Management (QM). The major characteristics and differences of the more important quality assurance systems are presented in this chapter.

Keywords

Quality Management · Quality Assurance · GxP · Accreditation · Certification · "Codes of Conduct"

Introduction

Quality must be defined in advance: The quality of a finished product or of a service function at the end of a value creation chain is determined by a number of factors – the basic elements of quality first described by Kaoru Ishikawa (1968) and linked by him into a "fishbone" or "cause-and-effect" diagram. These factors include management, environment, methods, machines, materials, measurement, and – last but not least – people. "Quality" in this context is so defined that any activity, performance, or technical product should meet specific, predefined requirements and characteristics on completion. In order to reach and maintain such quality requirements, specific prerequisites and boundary conditions on the road to the finished product must be defined in advance. These will include quality criteria and quality control procedures applicable not only to the end product but also for all critical initial parameters and intermediate steps. In the case of reproducible or frequently repeated activities, such prerequisites and boundary conditions are often defined in Standards, Guidelines, or Directives according to the specific legal and administrative systems. This applies to the majority of physical, chemical, and biological-medicinal measurement systems and to methods for the generation of data relating to chemical substances and their properties.

Quality of Data

Relevant and reliable data are required to assess and evaluate the toxicological characteristics of chemical substances or of exposure levels. The quality of the available data is of decisive importance and thus has to be carefully considered during the human health risk assessment process. Good quality means not only that the data provide an important or significant contribution in the sense of providing new insights or filling a previous gap of knowledge but also that the data is reliable, in the sense that both the probability of errors occurring and the extent of any which may occur are as small as possible.

Practically, every measurement (no matter how accurate) or other form of experimental or epidemiological data collection implies some risk of random or systematic errors, which then result in a deviation from the "true" value (which is – in general – not known). An important aim of any institution generating such data must thus be

to implement appropriate general conditions and control procedures so that there is a high probability that the data obtained approach the "true" value and can be confirmed – either by repeating the process or by some other method. Given a certain process or method, the probability of approaching the "true" value can thus only be improved by systematically eliminating all known sources of error and – gradually – identifying and eliminating unexpected or previously unimaginable sources of random and systematic error. Data quality in terms of reliability thus depends on the systematic elimination of sources of error. This necessitates a Quality Management approach with a suitable Quality Assurance system.

Quality Management (QM) and Quality Assurance (QA) (QM/QA Systems)

The aim of *Quality Management* systems is firstly to ensure that errors in ongoing processes are excluded as far as possible. As part of a continuous learning and improvement process, any remaining errors should be identified, documented, and avoided in the future. This can be achieved by the choice and implementation of a QA system with appropriate boundary conditions, methods, and controls. The international standard ISO 9001:2015 is the most prominent approach to quality management systems, specifying requirements for QM systems.

The aim of every *Quality Assurance* system is to generate credibility and confidence in the reliability of the data internally and externally – that is within the organization, toward direct clients, and all others who may be interested in the data concerned. In practice, two different strategies can be identified, neither of which alone is sufficient but which supplement each other in various QA systems with varying degrees of emphasis on individual features.

First Strategy: Traceability and Transparency of Studies

Data are usually generated in the course of experimental or in silico studies and any kind of projects. Many such studies cannot be easily repeated, should doubt about the reliability of the data arise. Reasons may be ethical grounds, cost grounds, or the huge workload involved. Examples of such studies are long-term experimental studies in animals (often with large numbers of animals), studies in human beings, and field studies with crop protection agents. Any attempt to reconstruct such studies shortly or long after they have been conducted requires extensive and detailed recording of all initial conditions, methods, working steps, and the results obtained. In such cases, an extensive documentation and archiving system is required, such as that particularly described in the *Good Laboratory Practice* (GLP) system. The workload for the testing facilities and test sites involved with such systems is significant, even for relatively small or short-term studies.

Second Strategy: Reproducibility and Comparability of Data

Ideally, experimental toxicological research produces statistically significant effects that can be interpreted as causal effects. Naturally, every single experiment is a singular observation. In order to assume a generally valid causality, individual observations should be reproducible. The requirements to obtain reproducible data in toxicological studies have been intensively discussed in recent years (e.g., Miller 2014; Briner and Kirwan 2017). Many studies to determine, e.g., physicochemical properties of substances such as melting or boiling point or the presence of substances in biological matrices can be fairly easily and quickly repeated under the same methodological conditions or can be easily checked by other means. This applies to the majority of chemical-bioanalytical and many other physicochemical determinations. The stringent application of the International System of Units (SI) facilitates comparison of data. This implicates increased requirements regarding technical expertise, calibrations, and comparison measurements (e.g., participation in inter-laboratory tests) for data validation and quality management procedures in the laboratories concerned. However, the documentation effort is then reduced and more flexible. Quality assurance systems of this type include accreditation and – for products and services – certification.

Good Laboratory Practice (GLP) and Other "GxP" Systems

Some quality assurance systems are required in relevant laws and regulations and thus fall under legal controls, for example, those for *Good Laboratory Practice* (GLP). The first GLP regulations were issued by the US Food and Drug Administration (US FDA) in the late 1970s after irregularities were discovered in the planning, conduct, and reporting of animal safety studies submitted in the registration dossiers for medicinal products (U.S. FDA 1978). Similar regulations were subsequently issued by the US Environmental Protection Agency (US EPA) covering studies conducted with pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and other chemical substances under the Toxic Substances Control Act (TSCA) (U.S. EPA 1983). The need to comply with these regulations acted as a nontariff barrier to international trade in such substances, which led the *Organisation for Economic Co-operation and Development* (OECD) to develop internationally harmonized "Testing Guidelines" and "Principles of GLP" which were then recommended for worldwide use to ensure the Mutual Acceptance of Data (MAD) generated according to the Testing Guidelines and GLP Principles (OECD 1981). The GLP Principles were recommended for use within the European Communities in 1987. The GLP Principles represent general quality requirements for the conduct of studies, and the OECD Testing Guidelines form the basis for the scientific or methodological approach. Both the GLP Principles and the OECD Testing Guidelines are the common basic concept to ensure the data quality of studies, for trust building and for the Mutual Acceptance of Data worldwide. At the end, it is up to the competent authorities to evaluate the study data with regard to

reliability, relevance, and adequacy. The latter term is used for the comparison of studies. Evaluation criteria for these three terms have been developed (Klimisch et al. 1997) and refined. For a recent overview, see, for instance, Beronius et al. (2018).

The GLP Principles (and the Testing Guidelines) are reviewed on an ad hoc basis by OECD Expert Groups and – where appropriate – revised to ensure best scientific practices. The last revision of the GLP Principles took place in 1995–1996, and the Revised Principles were formally adopted by the OECD in 1997. The Revised Principles were adopted in the European Communities in 1999 and are now binding within all Member States (in Germany, e.g., as Annex 1 to the Chemicals Law (Chemikaliengesetz)). The OECD Testing Guidelines have also been implemented into the European legislation and are being continuously updated according to the technological progress (Regulation (EC) No 440/2008). The European Regulations and Directives relating to biocides, chemical substances, cosmetics, detergents, feeding stuffs, foodstuffs, medicinal products, medical devices (where applicable), novel foods, and veterinary products all require that at least some of the test data required for the registration or regulatory approval of such products for use within the European Union be generated in compliance with the GLP Principles or with equivalent standards (EC website 2020).

The OECD has also developed procedures for governments on the inspection and verification of good laboratory practice in order to monitor the compliance of testing facilities with the GLP Principles (first adopted 1983, first revision 1989, second revision 1995). These documents have also been implemented by the individual Member States within the European Union (Directive 88/320, now replaced by Directive 2004/9 of March 2004). In addition, the OECD has sponsored the preparation and publication of a series of *Guidance Documents for Compliance Monitoring* (No. 2, 3, 9, 20), *Consensus Documents* (No. 4, 5, 6, 7, 8, 10, 13), and *Advisory Documents* (No. 11, 12, 14, 15, 16, 17, 19) providing further comments and explanations on certain specific items of the GLP Principles (for instance, quality assurance, laboratory supplies, field studies, short-term studies, computerized systems, full listing available on OECD website (OECD 2020)). These documents have no legal force but are – in practice – regarded as "state of the art" and are widely used by test facilities and test sites as well as by compliance monitoring authorities. The OECD Position Paper No. 18 *Regarding the Relationship between the OECD Principles of GLP and ISO/IEC 17025* states that laboratory accreditation (see below) is not applied to non-clinical health and environmental safety testing because ISO/IEC 17025 does not contain all of the requirements of the OEDC GLP Principles. Nevertheless, laboratory accreditation can make a valuable contribution within the GLP compliance structure. Although common rules and more detailed regulations exist, there may be differences in their interpretation, application, and enforcement between countries and even between monitoring authorities in the same country. For instance, whereas Seiler (2005) describes the implementation and application of the GLP Principles from a more "European" point of view, the same GLP Principles may be in part differently interpreted and applied in the United States and even between the two monitoring authorities US FDA and US EPA (Weinberg

2003; U.S. FDA 2020). The European Commission provides support under https://ec.europa.eu/growth/sectors/chemicals/good-laboratory-practice_en.

Good Manufacturing Practice (GMP) is a QA system (also first developed in the United States) to control in particular the manufacture of medicines, veterinary medicines, and medical devices. GMP is also prescribed by law for the manufacture of food contact materials and cosmetic products. The application and monitoring of GMP requirements is also largely harmonized, within Europe initially (1989) as "Guidelines to Good Manufacturing Practice," subsequently by Commission Directives 91/356 and 91/412 and Directive 2003/94. For details, for example, see also the websites of the European Medicines Agency (EMA 2020) and the European Food Safety Authority (EFSA 2020).

Good Clinical Practice (GCP) provides a quality assurance system for planning, conducting, and reporting clinical studies carried out – for example – to provide data in support of applications for marketing authorizations for medicinal products. The requirements were first developed by an expert working group of the "International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use" (E6(R1) Step 4 version (ICH 1996), current update: E6(R2) Addendum Step 4 version (ICH 2016))) and adopted by the regulatory bodies in the European Union, Japan, and the United States. In 2015, ICH has renamed itself as the International Council for Harmonisation and has become a legal entity under Swiss law. Among other issues, the GCPs require that clinical studies be planned and carried out according to the ethical standards described in the World Medical Association "Declaration of Helsinki." Further information on GCP can be found, for example, on the website of the European Medicines Agency (2020).

Accreditation and Certification

Most accreditation and certification systems are based on voluntary participation and are not governed by legal requirements. However, the use of such systems is often a prerequisite before a facility or laboratory may conduct studies if the results should be used in legally controlled activities. This applies, for instance, to laboratories performing analyses for the control of foodstuffs, the monitoring of ambient air or drinking water quality, or measurements to be used as part of health and safety requirements in the working environment as laid down in ISO/IEC 17025. Both systems give high priority to the use of appropriate quality management procedures. *Accreditation* is a system to monitor and approve the competencies of testing laboratories and their Quality Management systems. The organizations issuing such approvals are – themselves – monitored and accredited by the so-called Accreditation Bodies, as laid down in the International Standards Organization (ISO) Standards ISO/IEC 17011 and – when appropriate – 17020–17025. For instance, in Germany, the *Deutsche Akkreditierungsstelle* (DAkkS) is the national Accreditation Body (since January 2010). Pursuant to Regulation (EC) No. 765/2008, DAkkS acts in the public interest and as the sole provider of accreditations in Germany. *Certification* according the international standard ISO 9001:2015 relates to the

quality of products and/or service functions in the sense of a guarantee that certain defined characteristics are provided by the product or function. ISO 9001:2015 is compatible with other management systems standards and specifications, such as ISO 45001 *Occupational Health and Safety* and ISO 14001 *Environmental*. Appropriate certification and the establishment of a quality management system according to ISO Standard 13485 for medical devices is – for example – a prerequisite for the use of the CE Mark on certain types of products to be placed on the market within the European Economic Area (EEA). Another example is ISO 22716 for the manufacture of cosmetic products.

"Codes of Conduct" and Quality Assurance

A number of scientific societies and professional associations (e.g., those for medical practitioners, pharmacists, or toxicologists) have developed codes of conduct which are binding on their members. These Codices contain certain elements which help toward a quality assurance but are – usually – directed to ensuring a responsible and ethical behavior in professional activities. Such elements, for example, a requirement for scientific honesty, are important but alone cannot be regarded as a quality assurance system. The concept of "Safeguarding Good Scientific Practice" has been developed by some major institutions for basic research in response to spectacular cases of scientific misbehavior or fraud. For example, the German Research Foundation (Deutsche Forschungsgemeinschaft) (2019) has recently updated its "Safeguarding Good Scientific Practice" with some 16 detailed recommendations and suggested their use in scientific institutions, particularly those in academia. Among the more important recommendations in the sense of quality assurance are those related to organizational structure of working groups and the need for complete documentation and long-term archiving of important primary data; however, it is unclear in how far these recommendations have been or are being followed by the institutions concerned.

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JSQA (Japan Society of Quality Assurance). www.jsqa.com
RQA (Research Quality Association). www.therqa.com
SoFAQ (Société Francaise d'Assurance de la Qualité). www.sofaq.fr
SQA (Society of Quality Assurance). www.sqa.org

Cross-References

► International Regulation of Toxicological Test Procedures
► National and International Collaboration in Regulatory Toxicology
► Principles of Analytical Chemistry for Toxicology
► Quality Criteria for Primary Literature in Toxicology

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Recommended Reading

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