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Validation of Analytical Methods and Instrumentation for Beryllium Measurement: Review and Summary of Available Guides, Procedures, and Protocols*

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Abstract

This document provides a listing of available sources which can be used to validate analytical methods and/or instrumentation for beryllium determination. A literature review was conducted of available standard methods and publications used for method validation and/or quality control. A comprehensive listing of the articles, papers, and books reviewed is given in the Appendix. Available validation documents and guides are listed therein; each has a brief description of application and use. In the referenced sources, there are varying approaches to validation and varying descriptions of the validation process at different stages in method development. This discussion focuses on validation and verification of fully developed methods and instrumentation that have been offered up for use or approval by other laboratories or official consensus bodies such as ASTM International, the International Standards Organization (ISO) and the Association of Official Analytical Chemists (AOAC). This review was conducted as part of a collaborative effort to investigate and improve the state of validation for measuring beryllium in the workplace and the environment. Documents and publications from the United States and Europe are included. Unless otherwise specified, all referenced documents were published in English.

INTRODUCTION

Method Validation

Method validation is the process of evaluating whether an analytical method is acceptable for its intended purpose. For pharmaceutical methods, guidelines from the United States Pharmacopeia (USP), International Conference on Harmonisation (ICH), and the United States Food and Drug Administration (USFDA) provide a framework for performing such validations. In general, methods for regulatory compliance must include studies on specificity, linearity, accuracy, precision, range, detection limit, quantitation limit, and robustness. Elements of these guidelines are readily adapted to the issue of validation for beryllium sampling and analysis.

Benefits of Validation

Validation is used to establish the validity of use of a new or revised method or instrument to provide accurate data for a specific analyte or group of analytes in a given sample matrix (for example, the determination of total beryllium in soils). Although a thorough validation cannot rule out all potential problems, the process of method development and validation should address the most common issues such as analytical recovery, matrix interferences with the analyte determination, inadequate sample preparation procedures, sampling errors, stability of materials, and general robustness. In addition, the specified parameters of detection limits, precision, accuracy, bias, and quantitation limits can also be verified. Validation also provides the appropriate quality assurance documentation for the method.

Requirements for Validation

Normally either the supplier (e.g., a laboratory or organization that developed a new method or instrument) or the end user requests validation of an instrument and/or method. Accrediting organizations may require the use of validated methods in subject laboratories, possibly in accordance with applicable consensus standards. Validation usually requires setting up a test bed that is composed of a specified number of laboratories capable of performing the validation tests. The supplier and the test bed

participants define the scope of work, test conditions, types of samples, and specify the criteria for success. The supplier will specify the capabilities and limitations of the instrument or method. Minimum quality and performance objectives (success criteria) for the instrument or method must be specified. This information is communicated to the test bed participants. Performance evaluation samples, which are blind for the laboratories performing the analyses, are prepared and submitted to the participating laboratories for evaluation.

Specificity

Specificity is the ability to specifically and accurately measure the analyte(s) of interest in the presence of other components that may be expected to be present in the sample matrix and may potentially interfere with the measurement. Specificity is a measure of the freedom from interference from such potential contributors as other active ingredients, other analytes, impurities, and degradation products, thereby ensuring that a measured response is due to a single component analyte only (or analytes if multi-species analysis is of interest).

Accuracy

The accuracy of a method, the closeness of the measured value to the true value for the sample, can be assessed in a number of ways. Most commonly, accuracy is assessed by analyzing a sample of known concentration and comparing the measured value to the true value. National Institute of Standards and Technology (NIST) Standard Reference Materials (SRMs), NIST-traceable standards, and other certified reference materials (CRMs) are often used for this purpose. Another approach is to compare test results from the new method with results from an existing reference method that is known to be accurate. Spike recovery, involving measuring the recovery of known amounts of analyte spiked into sample matrix, is also used for method confirmation purposes. The fourth approach is the technique of standard addition, which can also be used to determine recovery of spiked analyte. This approach is used if it is not possible to prepare a sample matrix that is chemically and physically representative of the samples that the method is designed to process, but without the presence of the analyte (e.g., beryllium). This can

occur, for example, when there is interaction among constituents in a sample so that the resultant signal is significantly different when the analyte is absent or when there is a high background signal in the range where the analyte is being measured

Sensitivity

For an analytical method, sensitivity refers to the ability of the method to detect small amounts of, or small changes in the amount of, the analyte of interest. Sensitivity is both a function of the method detection limit (such as 1 microgram versus 1 milligram in a sample) and of how well the method detects small changes.

Range and Detection Limits

The range of an analytical method is the concentration interval over which acceptable accuracy, linearity, and precision are obtained. In practice, the range is determined using data from linearity and accuracy studies. Assuming that acceptable linearity and accuracy (recovery) results will have been obtained as described earlier, the only remaining factor to be evaluated is precision. The precision data should be available from the *replicate* analyses (*triplicate* at a minimum) of spiked samples, certified reference materials (CRMs), or other suitable replicate samples in the accuracy study. The detection limit of a method is the lowest analyte concentration that produces a response that is detectable above the noise level of the system. A variety of methods can be used to establish the detection limits. One approach is to use three times the background noise level of replicate blank measurements. Precision data can be established through round-robin testing, for example in accordance with ASTM standard E691.

Test Beds

A test bed is a platform for experimentation for large development projects. Test beds allow for rigorous, transparent and replicable testing of scientific theories, computational tools, and other new technologies.

GENERAL SUMMARY OF GUIDANCE

Initially, minimum requirements or acceptance specifications for the method or instrument should be established and agreed upon by the developer and the entities conducting the validations. Such requirements or guidelines are often covered in applicable regulations or consensus standards (e.g., ASTM, ISO). The following is a general summary of parameters included in a typical validation protocol:

- Define Scope of Work – Analyses that involve multiple methods or process steps (such as digestion of the sample followed by spectrophotometric analysis) should have validation split into separate methods (one for each method or process step).
- Test conditions – The supplier should provide a detailed description of the method or instrument operating parameters.
- Types of samples – The supplier should provide a description of the initial samples to be analyzed. The supplier may provide the samples or provide detailed instructions on their preparation. The samples should be representative of media and analyte concentration that would be encountered in the field of study and submitted for analysis.
- What constitutes a difficult sample – The supplier should provide information as to the limitations and interferences that may affect data.
- Examine typical samples, worst case, and best case (standards) – Samples to be analyzed should be at or within twice the detection limit and ten times the minimum detection limit in both clean matrices (calibration standards) and challenging matrices.
- Supplier will describe the limitations and attributes of the instrument/method.
- Detection limits – Estimates of minimum detection limits and practical quantitation or reporting limits should be provided.
- Matrices – the supplier should specify what matrices are compatible or incompatible with the instrument and/or method.
- Minimum sample requirements – the supplier should specify the minimum required sample size (volume or mass).

- Limitations – The supplier should specify any limitations on the analysis or instrumentation.
- Instrument/method must meet minimum quality and performance objectives that have been specified by the supplier.
- Test (User) Labs – The testing is often split into two phases. In the first phase, the supplier sends standards or instructions on how to prepare standards to test bed labs and the labs perform the analyses. In the second phase, the test bed labs prepare blind standards using a specified protocol to be analyzed by the supplier at its facility. Criteria for success in accordance with applicable performance criteria will be defined prior to test initiation.
- Test instrument/method using stated supplier parameters/protocol.
- Must have appropriate number of labs (e.g., minimum of four for NIOSH, a minimum of six for ASTM). Inter-laboratory testing is described by ASTM standards E177 and E691.
- Tests on laboratory challenge parameters (e.g., high and low detection limits, matrix spikes and interferences, particulate samples).
- Report results to supplier/user (or other interested party).
- After receiving the data, the supplier will prepare a report detailing the results from all test-bed labs and how well the instrument or method performed.
- Data will be statistically evaluated to determine true precision, accuracy, and bias/overall uncertainty (e.g., as per ISO GUM).
- Labs will send blind standards to supplier for test evaluation.
- Standards must be representative and reproducible.
- The supplier will provide resulting data to one of the test bed labs for review. The data will be complied into a report detailing how well the instrument or method performed against the defined success criteria (see e.g., A. Agrawal et al., J. Environ. Monit. 8: 619-624 (2006); K. Ashley et al., Anal. Chim. Acta 584: 281-286 (2007)).

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Appendix – Literature Review: Method Validation

Guidance Documents

- OSHA Guidelines for Spectroscopy, available at http://osha.gov/dts/sltc/methods/spectroguide/spectroguide.html

These evaluation guidelines were developed to provide OSHA with a uniform and practical means for evaluating sampling methods that utilize spectroscopic analytical techniques. The guidelines define sampling and analytical parameters, specify required laboratory tests, statistical calculations, criteria for acceptance, and provide a detailed outline for preparation of written reports. Tests are described to evaluate sampler capacity, digestion efficiency, sampling interferences, cassette wiping, analytical detection limit, instrument calibration, analytical interference, detection limit of the overall procedure, reliable quantitation limit, precision of the overall procedure, and reproducibility of the method. Results of the evaluation tests are intended to be included in the written sampling and analytical methods. The overall goal of these guidelines is to provide OSHA with sampling and analytical methods that can clearly be defended with evaluation data. Other tests deemed necessary for any evaluation are permissible, and a description of these tests and the resultant experimental data shall be included in the back-up data section following the format prescribed in this document. Summary results of these tests shall be presented in the main body of the method. These guidelines are continually open to examination by OSHA and refinements are formally made on a

periodic basis. The resulting evolution in the guidelines is apparent when comparing early methods to more recent ones

- NIOSH Guidelines for Air Sampling and Analytical Method Development and Evaluation, available at http://www.cdc.gov/niosh/docs/95-117/pdfs/95-117.pdf

The objective of this protocol is to determine if a candidate method will provide results that are within ±25% of the true concentration at least 95% of the time. The experiments described in the protocol include determination of analytical recovery from the sampler, sampler capacity, storage stability of samples, and effect of environmental factors. Also included are evaluation criteria for the experiments, and an appendix to assist users in estimating method bias, precision, and accuracy. Other appendices are included that detail statistical equations, limits of detection and of quantitation, reports and methods, and other subjects of interest. The work described in the protocol can be summarized in five steps: 1) selection of analytes for testing; 2) development of the sampling and analytical method; 3) evaluation of the method; 4) preparation of a written method; and 5) preparation of a technical report on the development and evaluation.

- **Standard Practice for Applying Statistical Quality Assurance Techniques to Evaluate Analytical Measurement System Performance - ASTM D6299, available at** http://www.astm.org/Standards/D6299.htm

This ASTM practice is used to continuously demonstrate the proficiency of analytical measurement systems that are used for establishing and ensuring the quality of petroleum and petroleum products. The methods can be applied to other methods but are not approved as such (since they are beyond the present scope). Data accrued using the techniques included in this practice provide the ability to monitor analytical measurement system precision and bias. These data are useful for updating test methods as well as for indicating areas of potential measurement system improvement. This practice provides information for the design and operation of a program to monitor and control ongoing stability and precision and bias performance of selected analytical measurement systems using a collection of generally accepted statistical quality control (SQC) procedures and

tools. A complete list of criteria for selecting measurement systems to which this practice should be applied, and for determining the frequency at which it should be applied, is beyond the scope of this practice. However, some factors to be considered include (*1*) frequency of use of the analytical measurement system, (*2*) importance of the parameter being measured, (*3*) system stability and precision performance based on historical data, and (*4*) regulatory, contractual, or test method requirements. This practice is applicable to stable analytical measurement systems that produce results on a continuous numerical scale as well as laboratory test methods. This practice does not address statistical techniques for comparing two or more analytical measurement systems applying different analytical techniques or equipment components that purport to measure the same property, so it could not be used to validate a new analytical method by comparison with an existing standard method.

- **Huber, L.: *Validation and Qualification in Analytical Laboratories*: Informa Health Care, Interfarm/CRC, 1998**

This validation reference book provides a guide for all validation and qualification processes to comply with Good Laboratory Practices (GLP), Good Clinical Practice (GCP), Current Good Manufacturing Process (cGMP) and ISO 17025. It covers qualification of equipment, reference materials, people and validation of analytical procedures and systems. The book contains the following:

- Overview on regulations, quality standards and related guidelines on validation and qualification (Food and Drug Administration (FDA), Environmental Protection Agency (EPA), cGMP, GLP, GCP, ISO9000, United States Pharmacopeia (USP), ISO 17025
- How to deal with multiple regulations and Quality Standards
- Developing an overall validation strategy (Terminology, validation needs, strategy for implementation)
- Risk based validation and qualification, calibration, verification and validation of equipment
- Analytical instrument qualification
- Validation of software and computer systems

- Validation of analytical routine, non-routine and standard methods

- **Bansal S.K., Layloff T., Bush E.D., Hamilton M., Hankinson E.A., Landy J.S., Lowes S., Nasr M.M., St. Jean P.A., Shah V.P.: Qualification of Analytical Instruments for Use in the Pharmaceutical Industry: A Scientific Approach.** ***AAPS PharmSciTech*****; 5(1): (2004)**

The pharmaceutical industry relies on the precision and accuracy of analytical instruments to obtain valid data for research, development, manufacturing, and quality control. Through published regulations, regulatory agencies require pharmaceutical companies to establish procedures assuring that the users of analytical instruments are trained to perform their assigned tasks. The regulations also require the companies to establish procedures assuring that the instruments that generate data supporting regulated product testing are fit for use. The regulations, however, do not provide clear and authoritative guidance for validation/qualification of analytical instruments. Consequently, competing opinions abound regarding instrument validation procedures and the roles and responsibilities of the people who perform them. The American Association of Pharmaceutical Scientists sponsored a workshop entitled, "A Scientific Approach to Analytical Instrument Validation," which the International Pharmaceutical Federation (FIP) and International Society for Pharmaceutical Engineering (ISPE) cosponsored from which this paper was generated. The conference's objectives were to:

- Review and propose an effective and efficient instrument validation process that focuses on outcomes, and not only on generating documentation.
- Define the roles and responsibilities of those associated with an instrument's validation.
- Determine whether differences exist between validations performed in laboratories that adopt Good Laboratory Practice (GLP) regulations vs those that adopt Good Manufacturing Practice (GMP) regulations. Establish the essential parameters for performing instrument validation.
- Establish common terminology
- Publish a white paper on analytical instrument validation that may aid in the development of formal future guidelines, and submit it to regulatory agencies.

- **Chung Chow Chan, Herman Lam, Y. C. Lee, Xue-Ming Zhang: *Analytical Method Validation and Instrument Performance Verification.* John Wiley & Sons, 2004.**

Validation describes the procedures used to analyze pharmaceutical products so that the data generated will comply with the requirements of regulatory bodies of the US, Canada, Europe and Japan. This book provides a thorough explanation of both the fundamental and practical aspects of biopharmaceutical and bioanalytical methods validation. It teaches the proper procedures for using the tools and analysis methods in a regulated lab setting including appropriate procedures for calibration of laboratory instrumentation and validation of analytical methods of analysis.

- **Fitness for Purpose of Analytical Methods - A Laboratory Guide to Method Validation and Related Topics, available at** www.eurochem.org

Method validation is an important requirement in the practice of chemical analysis. However, information concerning its importance, why and when it should be done, and the tasks involved, is lacking. The purpose of this guide is to discuss the issues related to method validation and increase readers' understanding of how it can be achieved. The guide is expected to be of most use to a) laboratory managers who are responsible for ensuring the methods within their responsibility are adequately validated and b) the analysts responsible for carrying out studies on methods for validation purposes. Other staff may find the guidance of use as a source of background information - senior staff from a management point of view and junior staff from a technical point of view. The guide is aimed at laboratories needing to validate methods but working in isolation, with no immediate possibility of participation in collaborative trials. Those personnel with a working knowledge of simple statistics will find the method validation process easier to understand and implement. Where appropriate, formulae were included.

- **Guidelines for Collaborative Study Procedures to Validate Characteristics of a Method of Analysis – Appendix D, AOAC International, 2002 available at** http://www.aoac.org/vmeth/Manual_Part_6.pdf

These guidelines incorporate symbols, terminology, and recommendations accepted by consensus by the participants at the IUPAC Workshop on Harmonization of Collaborative Analytical Studies, Geneva, Switzerland, May 4–5, 1987 [*Pure Appl. Chem*. **60**, 855–864 (1988); published as "Guidelines for Collaborative Study of Procedure to Validate Characteristics of a Method of Analysis," *J. Assoc. Off. Anal. Chem*. **72**, 694–704 (1989)]. The original guidelines were revised at Lisbon, Portugal, August 4, 1993, and at Delft, The Netherlands, May 9, 1994, *Pure Appl. Chem*. **67**, 331–343 (1995). These revised, harmonized guidelines have been adopted by AOAC International as the guidelines for the AOAC Official Methods Program, *J. AOAC Int*. **78**(5), 143A–160A (1995). Although the directions were developed for chemical studies, some parts may be applicable to all types of collaborative studies, including those involving beryllium determination.

- **Validation Of Analytical Procedures: Methodology (Cpmp/Ich/281/95) - ICH Harmonized Tripartite Guideline, The European Agency for the Evaluation of Medicinal Products, Step 4, Consensus Guideline, 6 November 1996.**

This guideline is complementary to the parent guideline, which presents a discussion of the characteristics that should be considered during the validation of analytical procedures. Its purpose is to provide some guidance and recommendations on how to consider the various validation characteristics for each analytical procedure. The document considers the various validation characteristics in distinct sections. The arrangement of these sections reflects the process by which an analytical procedure may be developed and evaluated.

- **Guideline for Industry – Text on Validation of Analytical Procedures – FDA Guidance Document, ICH-Q2A, March 1995, available at**

http://www.fda.gov/cder/Guidance/ichq2a.pdf

This document presents a discussion of the characteristics for consideration during the validation of the analytical procedures included as part of registration applications submitted within the European Union, Japan, and the United States. The document provides a collection of terms and their definitions which serve to bridge the differences

that often exist among various compendia, and regulators of the European Union, Japan, and the United States. A tabular summation of the characteristics applicable to identification, control of impurities and assay procedures is included. The discussion of the validation of analytical procedures is directed to the four most common types of analytical procedures:

- Qualitative identification tests,
- Quantitative tests for impurities' content, and
- Limit tests for the control of impurities if applicable.

- **Guide to Quality in Analytical Chemistry – CETAC/Eurochem Guide, 2002**

The aim of this guide is to provide laboratories with guidance on best practice for the analytical operations they carry out. The guidance covers both qualitative and quantitative analysis carried out on a routine or non-routine basis. A separate guide covers research and development work (CITAC/EURACHEM Guide reference A1 on page 43). The guidance is intended to help those implementing quality assurance in laboratories. For those working towards accreditation, certification, or other compliance with particular quality requirements, it will help explain what these requirements mean. The guidance will also be useful to those involved in the quality assessment of analytical laboratories against those quality requirements. Cross-references to ISO/IEC 17025, ISO 9000 and OECD Good Laboratory Practice (GLP) requirements are provided.

Journal Articles

- Taverniers, I., M. De Loose, and E. Van Bockstaele: **Trends in Quality in the Analytical Laboratory II. Analytical Method Validation and Quality Assurance.** *Trends Anal. Chem.,* 23(8): 535-552 (2004)

  This article places validation of analytical methodologies in the broader context of quality assurance (QA). It deals with the concepts of single-laboratory or in-house validation, inter-laboratory or collaborative study, standardization, internal quality

control (IQC), proficiency testing (PT), accreditation and, finally, analytical QA (AQA).

- Feinberg, M., B. Boulanger, W. Dewé, and P. Hubert: **New Advances In Method Validation And Measurement Uncertainty Aimed At Improving The Quality Of Chemical Data.** *Anal. Bioanal. Chem*., 380(3): 502-514 2004

  This paper discusses the effects of quality systems on the development of an analytical procedure. It emphasizes the importance of method validation and how validation must be fully integrated into the basic design of the method.

- Van Zoonen, P., R. Hoogerbrugge, S. M. Gort, H. J. Van de Wiel, and H. A. Van't Klooster: **Some Practical Examples of Method Validation in The Analytical Laboratory.** *Trends Anal. Chem.,* 18(9): 584-593 (1999)

  In this article, validation is put in the context of the process of producing chemical information. Two practical examples are given.

- Boulanger, B., W. Dewé, A. Gilbert, B. Govaerts, and M. Maumy-Bertrand: **Risk Management For Analytical Methods Based On The Total Error Concept: Conciliating the Objectives of the Pre-Study and In-Study Validation Phases.** *Chemometrics and Intelligent Laboratory Systems*, 86(2):198-207, (2007)

  This paper is a part of selected papers presented at the Chemometrics Congress "CHIMIOMETRIE 2005" in Lille, France, 30 November - 1 December 2005. It discusses two methods of checking the validity of a measurement method at the pre-study level. The first checks whether a tolerance interval for hypothetical future measurements lies within given acceptance limits; the second calculates the probability of a result lying within these limits and computes whether it is greater than a given acceptance level. The properties and respective advantages and limitations of these methods are investigated. A crucial point is to ensure that the decisions taken at the pre-study stage and in routine use are coherent. This paper shows how a laboratory can prevent its method from being rejected by choosing compatible validation parameters at both pre- and in-study levels.

- Moser, J., W. Wegscheider, and C. Sperka-Gottlieb: **Quantifying the Measurement Uncertainty Of Results From Environmental Analytical Methods.** *Fresenius J. Anal. Chem. 370*(6): 679-689 (2001)

  The Eurachem-CITAC Guide Quantifying Uncertainty in Analytical Measurement was put into practice in a public laboratory devoted to environmental analytical measurements. Consideration was given to the provisions of ISO 17025 and an attempt was made to base the entire estimation of measurement uncertainty on available data from the literature or from previously performed validation studies.

  This paper describes ways and means of quantifying uncertainty for frequently practiced methods of environmental analysis. It was shown that operationally defined measures are no obstacle to the estimation process as described in the Eurachem/CITAC Guide if it is accepted that the dominating component of uncertainty comes from the actual practice of the method as a reproducibility standard deviation.

- **Reports by the Royal Society of Chemistry Analytical Methods Committee on Evaluation of Instrumentation**.

  This series of six reports provides guidance on how to evaluate different instrumentation and make comparisons between different instruments. Instrument criteria evaluation forms are provided which list features of interest and how those features are evaluated. The experimental sections provide tests to be performed and the appropriate treatment of data. The reports are as follows:

  - Report by the Analytical Methods Committee: Evaluation of Analytical Instrumentation Parts III: Polychromators for Use in Emission Spectrometry with ICP Sources, Analytical Methods Committee, Royal Society of Chemistry, *Analytical Proceedings*, April 1986, Vol 23
  - Report by the Analytical Methods Committee: Evaluation of Analytical Instrumentation Parts IV: Monochromators for Use in Emission Spectrometry with ICP Sources, Analytical Methods Committee, Royal Society of Chemistry, *Analytical Proceedings*, January 1987, Vol 24

- Report by the Analytical Methods Committee: Evaluation of Analytical Instrumentation Parts V: Inductively Coupled Plasma Sources for Use in Emission Spectrometry, Analytical Methods Committee, Royal Society of Chemistry, *Analytical Proceedings*, September 1987, Vol 24
- Report by the Analytical Methods Committee: Evaluation of Analytical Instrumentation Parts VI: Wavelength Dispersive X-Ray Spectrometers, Analytical Methods Committee, Royal Society of Chemistry, *Analytical Proceedings*, December 1990, Vol 27
- Report by the Analytical Methods Committee: Evaluation of Analytical Instrumentation Parts VII: Simultaneous Wavelength Dispersive X-Ray Spectrometers, Analytical Methods Committee, Royal Society of Chemistry, *Analytical Proceedings*, October 1991, Vol 28
- Report by the Analytical Methods Committee: Evaluation of Analytical Instrumentation Parts VIII: Instrumentation for Gas Liquid Chromatography, Analytical Methods Committee, Royal Society of Chemistry, *Analytical Proceedings*, July 1993, Vol 30

- Green, J. M.: **A Practical Guide to Analytical Method Validation.** *Anal. Chem. 68*, 305A – 309A (1996)

  This article gives a description of a set of minimum requirements for validation of an analytical method.

- **Development And Validation Of A Method For Determining Elements In Solid-Waste Using Microwave Digestion,** Binstock D. A., P. M. Grohse, A. Gaskill, C. Sellers, H. M. Kingston, and L. N. Jassie, *Journal of the Association of Official Analytical Chemists 74*(2): 360-366 (1991)
  A microwave-assisted method for preparing samples for determination of elements in solid waste has been developed (draft EPA Method 3051). Validation of the sample preparation method was performed through a collaborative study to determine its precision and accuracy.

Standards & Guidelines

- **Validation of Analytical Chemistry Laboratories,** Federal Construction Regulations (4510), COE EM 200-1-1, 1994

- **Water Quality - Guide to Analytical Quality Control for Water Analysis:** BSI DD ENV ISO 13530**,** Date: 1999-02-15.

- **ISO GUIDE 35** Reference Materials - General and Statistical Principles for Certification, Third Edition, 72 pages (2006)
  This Guide gives statistical principles to assist in the understanding and development of valid methods to assign values to properties of a reference material, including the evaluation of their associated uncertainty, and establish their metrological traceability. Reference materials (RMs) that undergo all steps described in this Guide are usually accompanied by a certificate and called a certified reference material (CRM). This Guide will be useful in establishing the full potential of CRMs as aids to ensure the comparability, accuracy and compatibility of measurement results on a national or international scale.

- **Validation of Analytical Procedures: Definitions and Terminology,** Directive75/318/EEC, November 1994

- **Note for Guidance on Validation of Analytical Procedures Methodology**, ICH Topic Q2B, Step 4 Consensus Guideline, 6 November 1996

- **International Conference on Harmonization. Draft Guideline on Validation of Analytical Procedures: Definitions and Terminology,** Federal Register, Vol. 60, pp. 11260, March 1, 1995.
  This document was prepared by a Working Group to provide guidelines on the single-laboratory validation of methods of analysis. These guidelines provide minimum

recommendations on procedures that should be employed to ensure adequate validation of analytical methods

Books

- Swartz, M., and I. S. Krull (Eds.): ***Analytical Method Development and Validation.*** CRC, 1997.

  This book describes analytical methods development, optimization and validation, and provides examples of successful methods development and validation in high-performance liquid chromatography (HPLC) areas. The text presents an overview of Food and Drug Administration (FDA)/International Conference on Harmonization (ICH) regulatory guidelines, compliance with validation requirements for regulatory agencies, and methods validation criteria stipulated by the US Pharmacopia, FDA and ICH.

- De Bièvre, P., and H. Günzler (Eds.): ***Measurement Uncertainty in Chemical Analysis*****,** Springer, 2003.

  This volume collects 20 papers on the topic of measurement uncertainty, mostly published from 1999-2002 in the journal "Accreditation and Quality Assurance." They provide the rationale for why it is important to evaluate and report the uncertainty of a result in a consistent manner. They also describe the concept of uncertainty, the methodology for evaluating uncertainty, and the advantages of using suitable reference materials. The benefits to both the analytical laboratory and the user of the results are considered.

- Parkany, M.: ***Quality Assurance and Total Quality Management for Analytical Laboratories*****,** Royal Society of Chemistry, 1993.

  This book provides guidance, through the experience and expertise of professionals and academics, on how laboratories should proceed in implementing appropriate QA systems to enable accreditation in accordance with ISO 9000 series, the ISO/IEC Guide 25, EN 45000 and the ISO 14000 series. Examples from multiple laboratories

(food, medicine, oil, clinical, forensic, environmental, industry and university) are given. It also contains the selected list of the relevant ISO International Standards and the ISO/IEC Guides.

- De Bievre, P., and H. Günzler: ***Validation in Chemical Measurement,*** Springer; 1st ed., 2005.

  The validation of analytical methods is based on the characterization of a measurement procedure (selectivity, sensitivity, repeatability, reproducibility). This volume collects 31 outstanding papers on the topic, mostly published in the period 2000-2003 in the journal "Accreditation and Quality Assurance". They provide the latest understanding, and possibly the rationale why it is important to integrate the concept of validation into the standard procedures of every analytical laboratory. In addition, this anthology considers the benefits to both: the analytical laboratory and the user of the measurement results.

- Swartz, Me. E. and I. S. Krull: ***Analytical Method Development and Validation,*** Marcel Dekker, Inc. New York.

  This book provides basic guidelines to develop a reliable and valid analytical method as well as guidelines for the evaluation of the method. Validation is treated as a part of the overall method development and implementation process.