Markus Schubnell

Validation in Thermal Analysis

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Hanser Publishers, Munich

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Distributed by:
Carl Hanser Verlag
Postfach 86 04 20, 81631 Munich, Germany
Fax: +49 (89) 98 48 09
www.hanserpublications.com
www.hanser-fachbuch.de

Cover concept: Marc Müller-Bremer, www.rebranding.de, Munich
Cover image: METTLER TOLEDO GmbH
Cover design: Max Kostopoulos
Printed and bound by Hubert & Co. GmbH und Co. KG BuchPartner, Göttingen
Printed in Germany

ISBN: 978-1-56990-906-5
E-Book ISBN: 978-1-56990-907-2

Preface to the First Mettler-Toledo Edition

The validation of equipment, processes and methods is a basic requirement that nowadays has to be met in most industries. This handbook deals with the validation of computerized systems in general as well as with analytical method validation. The practical examples focus on thermal analysis.

The handbook is intended for newcomers interested in the theoretical and regulatory aspects of validation and for thermal analysis practitioners who have to validate their equipment and methods.

Many people have contributed to the preparation of this handbook. I am particularly grateful to Dr. Bob McDowall for providing a sound introduction into the field of computerized system validation, to Professor Wolfhard Wegscheider for providing valuable contributions on method validation, and to Dr. Manfred Schmid and Professor Samuel Affolter for the chapter on interlaboratory studies in thermal analysis.

Furthermore, I would like to thank my colleagues at METTLER TOLEDO Schwerzenbach for their help, discussions and support, and in particular Dr. Rudolf Riesen (for compiling standards relevant to thermal analysis), to Dr. Matthias Wagner (for the DSC validation example on purity measurements) and to Dr. Jürgen Schawe (for the TGA validation example). Special thanks also go to Dr. Klaus Fritsch for reviewing the manuscript and to Dr. Dudley May for translating the German sections of the original text into English and for many helpful suggestions.

Schwerzenbach, December 2008 Dr. Markus Schubnell

Preface to This Hanser Edition

Since the first Mettler-Toledo edition of this booklet in 2008, many new legislation and guidances have been published, such as e. g. EU Annex 11, effective since 2010, or regulatory guidance and enforcement actions regarding data integrity. In this Hanser edition, major changes and supplements in regulations and guidances and its impact on computerized system validation and analytical instrument qualification have been incorporated. This mostly affects the first part and appendix 1. Apart from some minor corrections, part two of this booklet is identical to the first Mettler-Toledo edition.

I am particularly grateful to Dr. Bob McDowall who brought up to date the first part and appendix 1.

Greifensee, October 2021 Dr. Markus Schubnell

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Introduction

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In an analytical laboratory, most analyses are nowadays performed using computerized measurement systems. Generally, the analyst has to follow an analytical method that details how to use the system to measure a particular sample. From a validation point of view, one therefore has to distinguish between the validation of the equipment and the validation of the analytical method itself.

The first part of this handbook deals with the validation of computerized systems in general. It first covers basic terminology followed by a discussion of the regulatory requirements for the validation of computerized systems. The process of computerized system validation is then discussed in detail. This begins with some general remarks followed by the different qualification steps (DQ, IQ, OQ, PQ, AIQ) and ends by covering some aspects of auditing vendors of computerized systems.

The second part of the handbook covers topics related to method development and validation. Method validation is nowadays a basic requirement to ensure the quality and reliability of results, i.e. to demonstrate that an analytical method is suitable for its intended purpose.

One of the most important aspects of validation has to do with assessing the quality of the measurement data. The second part therefore begins with a discussion about the concept of measurement error, the sources of measurement error and the uncertainty of measurement. This is illustrated with the aid of a number of examples. After discussing these basic concepts, the principles of method validation are outlined. Since interlaboratory studies are widely used to validate methods, we present the results of a number of studies performed using thermal analysis. After some general remarks regarding the development of analytical methods in thermal analysis, some practical examples are given that illustrate the process of method development and method validation in thermal analysis.

Three appendices provide further information relevant to the main chapters: Appendix 1 discusses electronic records and electronic signatures based on 21 CFR Part 11 and EU Annex 11. Appendix 2 summarizes a number of basic statistical concepts needed for the presentation of data in the validation process. Appendix 3 provides a link to international standards relevant to thermal analysis techniques.

Part 1: Validation of Computerized Systems

R. D. McDowall

1 Changes in Regulations and Regulatory Guidance Since the First Mettler-Toledo Edition

Since the first Mettler-Toledo edition of this validation book was written, there have been major changes in regulations impacting computerized systems, qualification of analytical instruments and validation computerized systems plus regulatory guidance and enforcement action regarding data integrity in regulated analytical laboratories.

There is also a new approach for method validation where new USP general chapters and ICH guidance documents advocate a lifecycle approach. To support this, there will be an update of ICH Q2(R1) method validation, and text and new guidelines ICH Q14 and a new USP <1220> on Analytical Procedure Lifecycle Management (APLM).

This section outlines the major changes in regulations and regulatory guidance since publication of the first Mettler-Toledo edition.

1.1 Data Integrity

Data integrity is the major problem in the pharmaceutical industry today, impacting all pharmaceutical companies, contract manufacturing and research organizations (CMO and CRO) and active pharmaceutical ingredient (API) suppliers. Investigation of computerized systems found that companies had been testing into compliance by deleting results that did not pass, turning the system clock back and retesting the samples until they passed. This was coupled with poor records management practices such as defining paper as raw data and ignoring the underlying electronic records from analysis, failing to back up electronic records. Other issues were having all users either sharing the same account or allowing all users to have application administration privileges. As a result, several regulatory agencies have issued guidance documents and this has been followed by industry associations as shown in Figure 1.1.

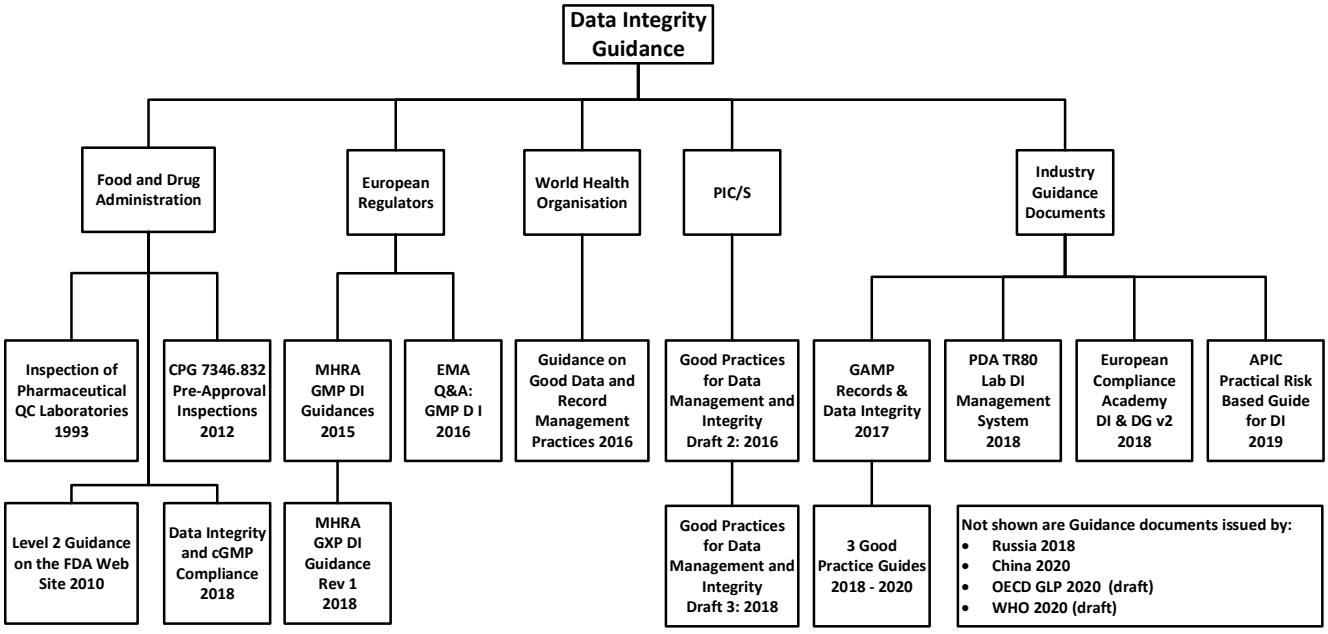

Figure 1.1: Data Integrity Guidance Documents Issued by Regulatory Authorities and Industry Associations

1.1.1 Regulatory Authority Data Integrity Guidance Documents

In response to the data integrity violations and poor data management practices, regulatory authorities have issued draft and final versions of data integrity guidances.

- Medicines and Healthcare products Regulatory Authority (MHRA) issued two versions of a GMP data integrity guidance for industry in 2015 [1-2], then a draft GXP guidance for industry comment in 2016 with the final version being published in 2018 [3]. All versions had a section where key terms are defined coupled with a regulatory expectation underneath, this is a good place to start reading the key definitions. The exception is the definition of raw data which is incorrect and should encompass all data and records generated from sampling to generation of the reportable result.
- World Health Organization (WHO) in 2016 published the final version of their guidance document entitled Guidance on Good Data and Record Management Practices [4]. This is the most encompassing data integrity guidance with Appendix 1 having a comprehensive explanation of the ALCOA principles with expectations for paper and electronic records plus special risk management issues.
- Pharmaceutical Inspection Cooperation Scheme (PIC/S) PI-041 have the third draft of their data integrity guidance called Good Practices For Data Management And Integrity In Regulated GMP/GDP Environments issued in 2018 for industry comment [5]. When finalized this document will be one of the most encompassing for data integrity.
- European Medicines Agency (EMA) has a data integrity question and answer section on their website [6].
- Food and Drug Administration (FDA) has four publications that impact data integrity. The first, issued after the Barr Laboratories court case in 1993, is Inspection of Pharmaceutical Quality Control Laboratories [7] that requires control of blank forms used in laboratories and is a pointer to working electronically. Following the 2005 Able Laboratories fraud case, the FDA published a discussion on their web site on why electronic records are the key GMP records and not paper printouts that must be retained [8].

  In addition, the Agency have updated Compliance Program Guide (CPG) 7346.832 for Pre-Approval Inspections (PAI) that became effective in 2012 and again in 2019, data integrity theme runs throughout the document including Objective 3 – Data Integrity Inspection [9, 10]. The new version of the CPG presents more information on possible data integrity breaches that an inspector could find.

  The FDA has also issued a draft (2016) and then a final version (2018) of a guidance for industry entitled Data Integrity and CGMP Compliance [11]. This is in a question and answer format and is a good starting point to understand how data integrity is built into existing regulations.

- The data integrity guidances issued by the Russian and Chinese regulatory authorities are not discussed here as the Russian guidance adds little to existing guidance documents, and there is not an official English translation of the Chinese guidance which makes citing any clause difficult. WHO published a draft data integrity guidance document for comment in 2020 that omitted the extensive explanation of the ALCOA criteria and needs extensive revision to be useful.

1.1.2 Industry Data Integrity Guidance Documents

There are several data integrity guidance documents available that have been issued by industry associations as follows:

- GAMP Forum have issued a Records and Data Integrity guide in 2017 and is a companion to GAMP 5 [12]. In addition, Good Practice Guides (GPGs) on Data Integrity – Key Concepts (2018) and Data Integrity by Design (2020) [13, 14].
- Parenteral Drug Association (PDA) have issued Technical Report 80 entitled Data Integrity Management System for Pharmaceutical Laboratories which provides advice for laboratories implementing data integrity projects [15]. This document provides good and unacceptable data integrity practices for chromatographic and microbiological analysis.
- European Compliance Academy (ECA) issued the second edition of the Data Integrity and Data Governance Guide, however this publication is for ECA members only.
- Active Pharmaceutical Ingredients Committee (APIC) issued a publication entitled Practical Risk-Based Guide for Managing Data Integrity in 2019 [16]. There is a very useful appendix on data process mapping to identify data integrity vulnerabilities and a checklist for assessments of systems.

1.1.3 ALCOA+ Criteria for Integrity of Laboratory Data

Any record that is generated as during regulated laboratory analysis needs to have its data integrity assured as discussed above. This now raises the question how does an analytical scientist assess data integrity of regulatory records? In Table 1.1 the term ALCOA is mentioned as a means of assessing the integrity of data.

As a quick introduction to the basic criteria of laboratory data integrity we need to explain the acronym ALCOA mentioned in the previous section. This is a term developed in the 1980's by an FDA GLP inspector as a means of teaching his colleagues about the integrity of data and records generated during non-clinical toxicology studies. The five ALCOA terms are:

- Attributable
- Legible
- Contemporaneous
- Original
- Accurate

In addition, there are four more terms that were added by an EMA document on clinical trial electronic source data [17]:

- Complete
- Consistent
- Enduring
- Available

These nine terms are collectively called ALCOA+ or sometimes ALCOA-plus and are detailed in Table 1.1.

Although many of the regulatory guidance documents talk about ALCOA and claim that the four additional terms can be derived from the original five, in this book we will use ALCOA+ criteria for data integrity as there are differences. These terms will be discussed in more detail in Chapter 9 on the data life cycle.

Table 1.1 ALCOA+ Criteria for Data Integrity

Criterion	Meaning
Attributable	• Attributable means information is captured in the record so that it is uniquely identified as executed by the originator of the data (e.g. a person or a computer system). • Attributable to the person generating the data. • Who acquired the data originally or performed an action subsequently to it and when.
Legible	• The terms legible and traceable and permanent refer to the requirements that data are readable, understandable, and allow a clear picture of the sequencing of steps or events in the record so that all GXP activities conducted can be fully reconstructed by the people reviewing these records at any point during the records retention period set by the applicable GXP [1-3]. See also consistent and enduring. • Can you read the data together with any metadata or all written entries on paper? • Can you read and understand all audit trail entries?
Contemporaneous	• Contemporaneous data are data recorded at the time they are generated or observed. • Documented (on paper or electronically) at the time of an activity.
Original	• Original record: Data as the file or format in which it was originally generated, preserving the integrity (accuracy, completeness, content and meaning) of the record, e.g. original paper record of manual observation, or electronic raw data file from a computerized system. • True copy: An exact verified copy of an original record. • Original data include the first or source capture of data or information and all subsequent data required to fully reconstruct the conduct of the GXP activity. The GXP requirements for original data include the following: - original data should be reviewed - original data and/or true and verified copies that preserve the content and meaning of the original data should be retained As such, original records should be complete, enduring and readily retrievable and readable throughout the records retention period. • Written observation or printout or a certified copy thereof. • Electronic records including all metadata of an activity.
Accurate	• The term "accurate" means data are correct, truthful, complete, valid and reliable. • No errors in the original observation(s). • No editing without documented amendments/audit trail entries by authorized personnel.
Complete	• All data from an analysis including any data generated before a problem is observed, data generated after repeat part or all of the work or reanalysis performed on the sample.

	• For hybrid systems, the paper output must be linked to the underlying electronic records used to produce it.
Consistent	• All elements of the analysis such as the sequence of events follow on and data files are date (all processes) and time (when using a hybrid or electronic systems) stamped in the expected order.
Enduring	• Recorded on authorized media e.g. laboratory notebooks, numbered worksheets for which there is accountability or electronic media. • Not recorded on the backs of envelopes, laboratory coat sleeves, body parts, cigarette packets or Post-It notes.
Available	• The complete collection of records can be accessed or retrieved for review and audit or inspection over the lifetime of the record.

Analytical scientists need to understand these criteria and apply them in their respective analytical methods. The WHO guidance provides the best understanding of the ALCOA principles. In particular, in its Appendix 1 definition of each of the five ALCOA terms with side-by-side tables of expectations for paper and electronic records is given, followed by special risk considerations for each of the five terms [4]. This is a very useful source of information about ALCOA requirements for data integrity of records and to understand the issues associated with each term.

1.1.4 Static and Dynamic Data

Several of the data integrity guidances refer to the terms static data and dynamic data. The best definition of these two terms is found in the FDA Data Integrity Guidance for Industry.

For the purposes of this handbook, **static is used to indicate a fixed-data record** such as a paper record or an electronic image, and **dynamic means that the record format allows interaction between the user and the record content**. For example, a dynamic DSC record may allow the user to change the baseline and reprocess the DSDC curve so that the resulting peaks areas may appear smaller or larger.

The majority of thermal analysis records are dynamic data.

1.1.5 Data Integrity Guidance Summary

The key data integrity issues for computerized system validation are:

- Has the application been configured to protect the electronic records?
- Are records vulnerable to deletion via the operating system?
- Are the data records backed up and can they be recovered in case of a failure?
- Do all users have unique user identities?
- Do users have appropriate access privileges?
- Do any users have application administration privileges (e.g. conflict of interest)?

The application validation must include tests to demonstrate these points. Furthermore, analysts must be trained in ethics and data integrity to ensure that the results generated can be supported by the underlying data.

1.2 Updating EU Good Manufacturing Practice (GMP) Regulations

Since 2010 eight of the nine chapters of EU GMP Regulations Part 1 have been updated as well as two Annexes. Of these the key regulations with an impact on the content of this handbook are:

- Chapter 1: Pharmaceutical Quality System (PQS) [18]
  Clause 1.9 (iv) for Quality Control states:
  - Records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;
  - The requirement for ensuring that analytical work has been actually carried out is a direct response to the data integrity problems that have been plaguing the industry.
- Chapter 4: Documentation [19]
  This outlines the requirements for records and data and the controls required to ensure their integrity. Documents consist of instructions (procedures, protocols, analytical procedures etc.) that when executed generate records or reports. There are three clauses each for good documentation practices and record retention requirements.
- Chapter 6: Quality Control [20]
  The key requirement is for a second person to review the data including any deviations
- Annex 11: Computerized Systems [21]
  Revised in 2011 in parallel with Chapter 4, it is important to realize that to fully understand Annex 11, you need to understand the requirements of Chapter 4. The requirements for validation and maintaining the validation are contained in this Annex.
- Annex 15: Qualification and Validation [22]:
  This covers qualification of equipment, validation of analytical methods, and validation of computerized systems. The key points are:
  - Ability to merge qualification documents where appropriate e.g. IQ and OQ.
  - A user requirements specification (URS) is written first followed by the Design Qualification (DQ) to confirm that the selected system is acceptable compared to the laboratory URS.

1.3 USP <1058> Analytical Instrument Qualification

USP <1058> on Analytical Instrument Qualification (AIQ) had not been issued when the first edition of this handbook was published. The general chapter originated at a conference organized by the AAPS (American Association of Pharmaceutical Scientists) in 2003 entitled Analytical Instrument Validation. The first change was removal of validation and replacement by qualification as the attendees agreed that instruments are qualified and processes, methods and computer systems are validated. Thus, Analytical Instrument Qualification was born. Prior to this, the term used for the same activities was Equipment Qualification (EQ). AAPS published a white paper in 2004, its incorporation as a potential USP general chapter came about in 2005 and review cycles followed until it was finally adopted in the second supplement of USP 31 in 2008 [23].

The first version has a number of gaps such as the supplier was responsible for defining requirements and it treated software too simplistically by placing the requirement for validation on the supplier. Both of these tasks are the responsibility of the user. An updated version was published in 2017 that integrated instrument qualification and computerized system validation and introduced more granularity into the three instrument groups as shown in Table 1.1.

Table 1.1: USP <1058> Instrument Group Classification and Qualification Approach [24]

Category	Classification Criteria	Qualification Approach
A	Standard equipment or apparatus with no measurement capability or requirement for calibration	• Specification: manufacturer • Conformance with requirements verified by observation of the operation
B	Standard instruments with measurement values or control physical parameters	• User requirements specification to document intended use • Typically requires calibration and/or qualification • Firmware validated indirectly during qualification • Conformance to requirement via SOPs and IQ/OQ • Sub Types of the Group: Type 1 Instrument only Type 2: Instruments with inbuilt calculations Type 3: Instruments with the ability to write user defined programs
C	Complex instruments with a computerized system	• Full instrument qualification integrated with software validation required • Specific function, compliance, data integrity and performance tests in software validation • Sub Types of the Group: • Type 1: Systems with GAMP category 3 software • Type 2: Systems with GAMP Category 4 software • Type 3: Systems with GAMP category 4 software plus category 5 additions

Thermal analysis instruments controlled by S**TA**R^{e} software are classified as USP <1058> Group C, type 2 systems with GAMP category 4 software (commercially available configurable software).

The first stage in qualification of the instrument and validation of the software is to write a user requirements specification (URS) outlining what the overall system should do.

After writing the laboratory URS, there is a four phase model for instrument qualification:

- Design Qualification (DQ): DQ is the documented collection of activities that define the functional and operational specifications and intended purpose of the instrument. DQ states what the laboratory wants the instrument to do and shows that the selected instrument is suitable. This phase must be performed before purchase of a new instrument.
- Installation Qualification (IQ): IQ is the documented collection of activities necessary to establish that an instrument is delivered as designed and specified, is properly installed in the selected environment, and that this environment is suitable for the instrument. IQ applies to an instrument that is new or was pre-owned. To be performed at installation of the system on new as well as existing systems.
- Operational Qualification (OQ): OQ is the documented collection of activities necessary to demonstrate that an instrument will function according to its operational specification testing in the

selected environment. OQ demonstrates fitness for the selected use, and should reflect URS. If there is any software used to control the instrument, this needs to be configured to protect electronic records and set up user profiles before the OQ is performed.

- Performance Qualification (PQ): PQ is the documented collection of activities necessary to demonstrate that an instrument consistently performs according to the specifications defined by the user, and is appropriate for the intended use. The PQ verifies the fitness for purpose of the instrument under actual conditions of use. After IQ and OQ have been performed, the instrument's continued suitability for its intended use is demonstrated through continued PQ.

As seen above, there is a relationship between the URS and DQ, OQ and PQ. This emphasizes the importance of the URS. For commercially available instruments, USP <1058> states that requirements should be "minimal" but sufficiently detailed to ensure that parameters can be tested. However, this statement does not apply to the application software for the instrument for Group 4 systems where requirements must be sufficiently detailed to define the tests for the User Acceptance Testing (UAT) / Operational Qualification phase.

AIQ is a relatively simple process but 4Qs model is intended for instruments not computerized systems. The problem is software. Software is all pervasive in analytical instruments with firmware that that can vary from simple programs through to an operating system with a database and configurable software all on a chip. When a workstation is attached to a thermal analysis instrument, the software application will control the instrument, acquire, manipulate and interpret data, write the report then store results and data. Instrument qualification is better undertaken as a sub-set of a computerized system validation life cycle as we discuss later.

In the next USP cycle 2020 – 2025, USP <1058> will be updated into a three phase life cycle model, similar to the analytical procedure lifecycle management discussed in a later section. This will mean the end of the 4Qs model and should have three phases entitled:

- Stage 1: Specification and Selection
- Stage 2: Qualification and Validation
- Stage 3: Continued Performance Verification

1.4 GAMP 5 Guide and Validation of Laboratory Systems Good Practice Guide

A flexible risk-based approach CSV was published with GAMP 5 in 2008 [25]. Different GAMP software categories now have different life cycles making validation more risk-based and leveraging the work of the supplier into the laboratory CSV project. GAMP 5 is a general approach to computerized system validation. For laboratory systems there is the second edition of the GAMP Good Practice Guide for Risk Based Validation of Laboratory Computerized Systems issued in 2012 [26].

1.5 Validation of Analytical Procedures

Guidelines for validation of analytical procedures ignore the most important part of the process: method development. This is evident in ICH Q2(R1) for Validation of Analytical Procedures omits any mention of method development and also is focused mainly on chromatographic methods [27]. There are three parallel developments for updated guidance for method validation:

- A USP expert committee has produced a number of stimuli to the revision process that resulted in the issue of a draft general chapter USP <1220> on Analytical Procedure Lifecycle [28, 29] and an update was published for public comment in September 2020.