Validation in Thermal Analysis
Collected Applications

METTLER TOLEDO
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This does not however absolve you from personally assessing the concepts discussed here regarding their applicability to your own laboratory, methods and processes. We do not take responsibility for any consequences that might arise from using the information presented in this handbook.

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Preface

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

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Introduction

M. Schubnell

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. Appendix 2 summarizes a number of basic statistical concepts needed for the presentation of data in the validation process. Appendix 3 gives an overview of international standards relevant to thermal analysis techniques.
Part 1: Validation of Computerized Systems

R. D. McDowall

1 Analytical Instrument Qualification, Computerized System Validation and Analytical Method Validation

1.1 Terminology

1.1.1 What is a Computerized System?

The key components of a computerized system are shown in Figure 1.1. It is important to realize early in your project that if you are validating a computerized system, you do not just concentrate on the computer hardware and software. Validation encompasses more, as we will now discuss.

![Figure 1.1. Elements of a Computerized System [1].](image-url)

The elements comprising a computerized system consist of a computer system and controlled function working within its operating environment.

The **computer system** consists of:

- **Hardware**: The elements that comprise this part of a computerized system are the computer platform that the computerized system application software runs on such as workstation or server plus clients etc. Any network components such as hubs, routers, cables, switches and bridges. The system may run on a specific segment of the whole of a network and may have peripheral devices such as printers, plotters with the associated connecting cables.
Software: This comprises several layers such as:
- Operating systems of the workstation clients and networked server
- Network operating system in the switches and routers of the network
- General business applications such as Word and Excel
- Computerized system application software and the associated utility software such as a database or reporting language

The controlled function comprises:

- **Equipment** linked to the computerized system e.g. the thermal analysis system itself (including firmware). Ideally the equipment connected to the data system should be qualified as part of the overall validation of the software otherwise how do you know that you are generating quality results?

- **Trained Staff and Written Procedures**: Trained staff should follow written SOPs as well as the manuals to operate the equipment and the data system software.

Validation is not just a matter of testing and calibrating the computerized system. There is a greater range of items to consider under the scope of validation. You could be subjected to regulatory action if you only qualify your instrument and do not validate the computerized system software.

### 1.1.2 Equipment Calibration and Adjustment

This is a vendor service function where according to Parriott [2]:

> “The term calibration implies that adjustments can be made to bring a system into a state of proper function. Such adjustments generally cannot be performed by analysts and are best left to trained service engineers who work for, or support, the instrument manufacturers.”

A calibration shows that an instrument supplies you with the correct values. Depending on the numbers of sensors in your instrument, you will have to perform different calibrations. Derived from the definition above, equipment calibration can be subdivided into

- **Calibration**: determination of the deviation of an instrument parameter, and
- **Adjustment**: change of an instrument parameter to meet specification.

Calibration and adjustment require reference materials or standards. These are substances with known literature values needed for calibration or traceable to recognized international standards. Calibration and adjustment are therefore inextricably linked to preventative maintenance and then to analytical instrument qualification. Whenever calibration involves adjustments of the type described above, it is important to document the activity. It is important to realize that this term can be confused with analytical instrument qualification.

### 1.1.3 Analytical Instrument Qualification (AIQ)

Analytical Instrument Qualification (previously Equipment Qualification, EQ) is to demonstrate that an item of equipment is fit for purpose. This implies that all the parameters (e.g. temperature accuracy, linearity of response etc) utilized by the methods that will run on the instrument are within accepted limits. Ideally, but not always, these parameters will use recognized or internationally accepted standards. Since many methods can be specific to a single laboratory, the instrument parameters to be qualified can vary from organization to organization. This is an essential requirement for equipment working in a regulated environment and is the basis for all subsequent analytical method validation work.

The term qualification was introduced by the Pharmaceutical Manufacturers Association (PMA). From the user’s point of view, the qualification of an analytical instrument or system comprises four main phases. Table 1.1 summarizes the most important responsibilities and activities for the user.
Table 1.1. Overview of the different phases relevant for the user in the qualification of an instrument.

<table>
<thead>
<tr>
<th>Qualification</th>
<th>Phase</th>
<th>Responsibility of</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DQ</strong> Design Qualification</td>
<td>Evaluation of the instrument</td>
<td>User</td>
<td>Documented evidence that proves that the instrument meets the requirements with regard to functional and operational specifications.</td>
</tr>
<tr>
<td><strong>IQ</strong> Installation Qualification</td>
<td>Installation of the instrument</td>
<td>User</td>
<td>Documented evidence that verifies that the instrument has been properly installed in the selected environment. Functional check.</td>
</tr>
<tr>
<td><strong>OQ</strong> Operational Qualification</td>
<td>Putting the instrument into operation</td>
<td>User</td>
<td>Documented evidence that verifies that the instrument functions according to its operational specifications in the selected environment. Performance check.</td>
</tr>
<tr>
<td><strong>PQ</strong> Performance Qualification</td>
<td>Routine operation of the instrument</td>
<td>User</td>
<td>Documented evidence that the instrument performs consistently as intended in routine use in its normal operating environment. Periodic checks of: Specifications Specific system suitability tests Analysis of control samples.</td>
</tr>
</tbody>
</table>

**1.1.4 Computerized System Validation (CSV)**

The aim of computerized system validation is to show that the system works and is fit for its intended purpose. As in the analytical instrument qualification, one also distinguishes within the context of computerized system validation IQ, OQ, and PQ. However, the meaning of these terms slightly differs to the analytical instrument qualification and this is the major problem with using the qualification terminology. Even the FDA has acknowledged the confusion this causes in the Guidance for Industry on the General Principles of Software Validation [3] and do not mention this approach in this document. A comparison of the qualification steps in AIQ and CSV, respectively, is given in Table 1.2. To minimize confusion, Figure 1.2 further illustrates the differences between the way these terms are used in AIQ and CSV.

Table 1.2. Differences in qualification terminology between Analytical Instrument Qualification and Computerized System Validation.

<table>
<thead>
<tr>
<th>Term</th>
<th>Analytical Instrument Qualification</th>
<th>Computerized System Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design Qualification (DQ)</td>
<td>DQ or User Requirements Specification (URS) that documents the functional requirements of the instrument and any software features including 21 CFR Part 11 and predicate rule compliance.</td>
<td>Documented evidence that all key aspects of hardware and software installation adhere to appropriate codes and the computerized system specification [5].</td>
</tr>
<tr>
<td>Installation Qualification (IQ)</td>
<td>Assurance that the intended equipment is received as designed and specified [4].</td>
<td></td>
</tr>
<tr>
<td>Operational Qualification (OQ)</td>
<td>Confirmation that the equipment functions as specified and operates correctly [4].</td>
<td>Documented evidence that the system or subsystem operates as intended in the computerized system specifications throughout representative or anticipated operating ranges [5].</td>
</tr>
<tr>
<td></td>
<td><strong>Operational Release of Equipment</strong></td>
<td></td>
</tr>
</tbody>
</table>
Table 1.2: Differences between Analytical Instrument Qualification and Computerized System Validation terminology.

<table>
<thead>
<tr>
<th>Term</th>
<th>Analytical Instrument Qualification</th>
<th>Computerized System Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance Qualification (PQ)</td>
<td>Confirmation that the equipment consistently continues to perform as required [4]. (Requires periodic testing and calibration)</td>
<td>Documented evidence that the integrated computerized system performs as intended in its normal operating environment [5].</td>
</tr>
</tbody>
</table>

**Operational Release of System**

| On-Going Validation Activities | Change control and configuration management (maintenance). | Change control and configuration management. Periodic reviews to ensure that the system is still validated and under control. |

As part of the computerized system includes the measurement instrument itself, this also has to be qualified. Therefore, a user will be undertaking both AIQ on the instrument (IQ and OQ) plus CSV on the software (IQ, OQ and PQ). Your validation plan should therefore make it clear how this problem will be tackled. Will you be qualifying the instrument separately from the software or adopting an integrated approach? Typically, since most thermal analysis instruments cannot operate without the computer and acquire and process data, the integrated approach may be the only option you have.

![Diagram](Figure 1.2.png)

Figure 1.2: Differences between Analytical Instrument Qualification and Computer System Validation terminology.

### 1.1.5 Reconciling Analytical Instrument Qualification and Computerized System Validation

In essence, the DQ and IQ stages outlined in Table 1.2 are similar between the AIQ and CSV terminology and answer the questions is the system specified and is the system installed correctly. The differences come in the OQ and PQ phases and are due, in part to the perceived complexity of a computerized system over an analytical instrument. The OQ stage for AIQ aims to show that the item is fit for purpose. This is the responsibility of the laboratory and after successful completion the instrument is released for operational use.

With CSV, there are two further stages to go through before the operational release. The OQ is to show that it works as the vendor says it should (anticipated operating ranges) and then the PQ in the user defined system’s actual operating...
environment. The latter stage is the responsibility of the laboratory. Now the computerized system, once it successfully completes its PQ, is ready for release into a regulatory environment.

What does this mean in practice for thermal analysis systems? Since thermal analysis systems nowadays are always controlled by computers, the validation of the computerized system will incorporate either explicit or implicit testing of the control of the thermal analysis instrument. Therefore, qualification of the thermal analysis equipment and validation of the software are closely linked and are usually done together.

1.1.6 Different Aims of Computerized System Validation IQ and OQ

Having defined the computerized system validation terms of IQ and OQ, what is the purpose of two phases of the system development life cycle? This is shown diagrammatically in Figure 1.3, at the top is the IQ of a computerized system; there is an IQ of each layer from the bottom up.

- Install and qualify the computer hardware.
- Install and configure the operating system (e.g. Internet Protocol address of the computer on the network and operating system functions do you want turned on or off).
- Install and qualify the database.
- Finally install and qualify the thermal analysis application software.

You cannot proceed to the next level up until you have successfully completed the layer below. This is an important concept.

![Figure 1.3. Differences between Installation Qualification and Operational and Performance Qualification.](image-url)
1.1.7 Analytical Method Validation (AMV)
This is demonstrating that an analytical method is fit for its intended purpose. This implies that the analyst knows why
the method is required and the acceptable values of key method validation parameters.
Building on these last three definitions, the differences and interactions between them will now be discussed.

1.1.8 AIQ, CSV and AMV Interrelationships
The relationships between analytical instrument qualification, computerized system validation and analytical method
validation are shown in Figure 1.4. The first three of the six blocks are the responsibility of the equipment vendor; the
remaining three are the responsibility of the laboratory or end user. The best way to describe the relationships is to use
an analogy of building a house.

![Figure 1.4. Relationship between Analytical Instrument Qualification, Computer System Validation and Analytical Method Validation.](image)

When building a house, you must have a firm foundation otherwise the structure overhead (building) will collapse. Therefore, the foundations in our analogy are to ensure that the analytical instrument or system has been designed, built and maintained correctly, this is where the instrument vendor comes in first. The instrument and any associated thermal analysis software must be designed correctly as shown in the first building block and the vendor is responsible for constructing and testing the instrument including the software elements as shown in the second block of the foundation. Maintaining the equipment and the thermal analysis software is also the responsibility of the vendor.

Implied, but not shown is the role of the user, who must select the right instrument and software for the right job. However, the third building part of the foundation is often missing: the laboratory must have selected the correct instrument. This means that they have a specification for the functions that the instrument will perform along with the software requirements including any issues on compliance with health authority regulations such as GMP and 21 CFR Part 11.

Once the foundations are successfully completed, the ground floor is now built. Here the responsibility turns over to the laboratory for analytical instrument qualification and computerized system validation.
The instrument is qualified against the range of operating parameters defined in the URS. This can be, for example, measuring the instrument’s set temperature with a digital thermometer that is calibrated to national standards to confirm that the temperature set is the temperature obtained.

Once the instrument is qualified and the software is validated, each analytical method needs to be validated (see Chapter 2).

### 1.2 Apply Validated Methods Using Qualified Instrumentation

Once the system has been qualified, you have the right system able to perform as expected, it can now be released for use in a regulated environment and be used to develop, validate and apply methods. The analyst is able to operate on a firm foundation knowing that the right system performs as expected and major variables are removed from an analysis.

### 1.3 Distinguishing between Analytical Instrument Qualification and Method Validation

Qualification of analytical instruments cannot be achieved through method validation. Analytical instrument qualification provides the foundation to develop, validate and run analytical methods within the operating range measured. If a method is developed using parameters outside of this range, then the analytical instrument needs to be requalified before method validation can proceed.

It is important to recognize the difference between analytical instrument qualification and method validation. In some analytical scientists’ minds, these are the same and therefore by validating a method, the equipment is considered qualified. This is wrong.

It should be realized that analytical instrument qualification assesses the performance of modules or the system over the complete operating range of the instrument that the laboratory anticipates using. For instance, if the operating range of a thermal analyzer is qualified over the range 100–300 °C then any method working over this temperature range can be run without any issues. This is shown in Figure 1.5, where methods 1 and 2 operate within the qualified range and are acceptable from a regulatory perspective.

However, if the analytical scientist now wants to use a temperature of 350 °C, which is outside of the qualified range, the instrument is not qualified and the analysis is jeopardized from a regulatory perspective. This is shown by method 3 in Figure 1.5, the upper end of the analysis is outside of the qualified range of the instrument.
The key to ensuring the parameters to qualify and the operating range is to specify your requirements before purchasing the thermal analyzer. Where a method exceeds the qualified operating range for a parameter, the instrument needs to be requalified and, where necessary, the user requirements specification updated.

### 1.3.1 What is Done in AIQ and What is Done in AMV?

The main question is now, what must be done when qualifying an analytical instrument and what done when validating an analytical method? Remember, the aim of PQ is that the instrument functions correctly according to the user’s requirements (not the vendor’s) and that the aim of the assay method validation is a method using the qualified instrument that is fit for intended purpose. Therefore, there are two different aims.

Analytical Instrument Qualification is intended to show that the instrument functions correctly, so AIQ goes up to the point where the system is producing correct measurement values and curves. Using independently certified materials and substances such as certified pure metals and inert materials, certified weights and gauges, the parameters critical to a user are calibrated such as:

- Temperature using pure metals.
- DSC heat flow: Enthalpy with the help of the enthalpy of fusion of pure metals.
- TGA weight: Internal and external calibrated weights.
- TMA/DMA force and displacement: Calibrated gauges.

### 1.3.2 Impact of AIQ on Method Transfer

Qualification of instrumentation is important for transferring methods between laboratories. Even if you have different models or different vendors’ instruments, if they are qualified over the same operating range there will be a higher probability that a given method will transfer with less problems than if the equipment were not qualified.
2 Regulatory Requirements for Computerized System Validation

2.1 Regulatory Agencies

Most countries have a healthcare agency to enforce regulations for the licensing, manufacture and sale of products subjected to regulations (e.g. pharmaceuticals, food, cosmetics, among others). Some of these agencies include:

- USA – Food and Drug Administration (FDA)
- Australia – Therapeutic Goods Administration (TGA)
- UK – Medicines and Healthcare products Regulatory Agency (MHRA)

There is also a collaboration of regulatory agencies entitled the Pharmaceutical Inspection Co-operation Scheme or Pharmaceutical Inspection Convention (PIC/S) which is a collaboration of most of the major regulatory agencies in the world (www.picscheme.org).

The most influential of all regulatory agencies is the FDA, which initiated the start of computerized system validation in the early 1980s under their mandate to protect public health. Part of the FDA structure is shown in Figure 2.1:

![FDA Commissioner](center_for_biology_evaluation_and_research_cber)
![Center for Devices and Radiological Health (CDRH)]
![Center for Drug Evaluation and Research (CDER)]
![Office of Regulatory Affairs (ORA)]

Figure 2.1. Simplified FDA structure (excluding food and veterinary products).

The centers cover the following areas of responsibility:

- CBER: biological products.
- CDRH: medical devices and products involving radiation and imaging.
- CDER: pharmaceutical products – ethical, generic and over-the-counter medications including license applications.
- ORA: enforcement activities – the field force officers and site inspections.

2.2 Responsibility for Computerized System Validation

The responsibility for validation of any computerized system rests with the system or business process owner. However, most of these individuals do not fully understand the regulations they work under or the risk mitigation strategies that need to be undertaken when validating a computerized system. Therefore, before discussing how to validate a computerized system, it is important to understand the regulatory requirements and their interpretation so that sufficient work is done to demonstrate fitness for intended purpose and no more.

The regulations and guidelines have a view on what is expected during the implementation and release of a computerized system as well as over the whole life cycle of the system. In general, the emphasis is concerned with generating the documented evidence to demonstrate that the computerized system is reliable and fit for purpose when validated and continues to be so when it is operational and that there is sufficient proof of management awareness and control. To obtain evidence of an action usually means that it must be documented, although the format and nature of the documented evidence (paper or electronic) is left open by all schemes.

A complicating factor is the current approach of the United States Food and Drug Administration (FDA) who are currently reviewing its approach to the Good Manufacturing Practice regulations for pharmaceutical products (21 CFR Part 211) [6]. One strand of this approach is the development of a risk-based approach to compliance and another is the review of the electronic records and electronic signatures final rule (21 CFR Part 11) [7].
2.3 Regulations and Guidelines Impacting a Computerized System

This section will give an overview of the regulations and guidelines that a computerized system will have to meet in its operation in a pharmaceutical or medical device laboratory. The aim in this section is to present the main principles of control required under the main regulations and guidance documents.

More detailed requirements and guidance will be presented in each of the main chapters dealing with the validation of the computerized system application so that the regulatory requirements governing the approaches suggested in this book can be clearly linked with the regulations and understood in context.

2.3.1 FDA Good Manufacturing Practice (GMP) 21 CFR Part 211

There are four specific sections that should be focused on within 21 CFR Part 211 [6] covering the current Good Manufacturing Practice regulations and how these impact the design of the overall validation of any computerized system.

The first is §211.63 and deals with equipment design, size and location, that requires the computerized system to be validated:

“Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.”

Interpreting this for a computerized system:

• Appropriate design …for its intended use:
   The system requirements need to be defined in a document, usually called a user requirements specification.
   To show that the appropriate design matches the installed system, it must be tested against the documented requirements.

• Adequate size … for its intended use:
   As part of the requirements specification, the size of the system for its intended use needs to be documented.
   “Size” can be defined in a number of ways such as number of users, the number and nature of the thermal analysis being controlled by the computer system.

• Suitably located …for its intended purpose:
   The location of all the components of the system need to follow the respective manufacturer or vendor recommendations. This will either be documented in vendor documentation or in the installation plan for the system. It will be demonstrated by the successful execution of the system installation and operational qualifications, where appropriate.

The second requirement under GMP is §211.68(b) that covers automatic, mechanical, and electronic equipment and has several issues to consider when dealing with computerized or related systems:

“Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.”

Therefore, a change control procedure must be operational so that authorized individuals can initiate approved changes with records of the change that can be inspected. Where necessary approved changes must be tested and validated.

“Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system.”

If you use the computerized system with manual input, transcription error checking will need to be undertaken for every analytical run. However, if you work electronically, validate once and use the process automatically until changes are made to the system. Therefore, it makes sense to eliminate paper and to work electronically wherever practicable.

“A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances, a written record of the program shall be maintained along with the appropriate validation
Data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.”

Data needs to be protected with implementation of effective backup measures (Note: the phrasing used above is from the 1970s – ensure that the methods used to backup are current and reflect today’s requirements and good IT practices).

The third is under the section dealing with Laboratory Controls, §211.160 (a):

“The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specification, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit.”

If you purchase vendor validation or qualification materials, there needs to be an approval stage before you use the documentation to demonstrate that the material is fit for purpose and to review and approve the documentation after the work has been carried out.

Furthermore, “The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.”

The fourth is §211.160 (b) “Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures ….”

Here you need to think of the tests that you have used in the performance qualification (PQ) testing to show that the computerized system is fit for purpose and if the design is scientifically sound.

### 2.3.2 Quality System Regulation for Medical Devices: 21 CFR Part 820

The medical device regulations, 21 CFR Part 820 [8], were written in the 1990s when computerization was more extensive than in the 1970s when the GMP and GLP regulations were drafted. Therefore, references to computers and their validation are far more explicit and encompassing.

Software used in device, production of the device or implementing the quality management system (QMS) must be validated.

- 820.30(g): Design Validation: “Each manufacturer shall establish and maintain procedures for validating the design device. … Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions. Design validation shall include software validation and risk analysis, where appropriate…..”

- 820.70(i): Automated Processes: “When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities will be documented.”

Note some common features:

- Defined user needs and intended use: document requirements in a specification.
- Risk analysis determines how much effort is necessary in the validation.
- Established protocol: written and approved plan and testing instructions.
- Changes must be validated before the change is made operational.
- All activities must be documented to show they have taken place.