Josef Künzle, PhD, Wolfgang Nedvidek, PhD

GMP Series

Qualification and Calibration of Laboratory Instruments in Pharmaproduction

Maas & Peither
GMP PUBLISHING

PDF Download

Excerpt from the GMP Compliance Adviser

Contents

Laboratory Instruments

Josef Künzle, PhD, Wolfgang Nedvidek, PhD

Here you will find answers to the following questions:
- What instruments have to be qualified?
- How is the qualification carried out?
- What qualification documentation has to be created?
- What scope of qualification is both useful and necessary?
- How is instrument software validated?
- What has to be done when the configuration of an instrument is changed?
- How are instruments managed?
- Which instruments have to be calibrated?
- How and how often is calibration carried out?
- What needs to be done if calibration is not successful?
- How is calibration documented?
- What level of maintenance is required for laboratory instruments?

1 Qualification of laboratory instruments

1.1 Introduction

Qualification of equipment is a basic GMP requirement. It does not only apply to production equipment, but also to laboratory equipment. Whereas instrument testing has always been carried out, a comprehensive qualification concept was only added at a later date. The specifications in the international requirements and guidelines regarding the qualification of equipment, premises and facilities used in production therefore also apply to analytical instruments. Qualification begins as soon as a decision has been made to purchase an instrument – and not when a particular instrument has been chosen, procured or even installed.

The stipulation to qualify laboratory instruments can be found in the USP General Chapter <1058> *Analytical Instrument Qualification* and in the Quality Management Document of the OMCL *Network of the Council of Europe* PA/PH/OMCL (08) 73, September 2008.

In contrast to the validation of analytical methods, for example, there are no specific directives or methods that apply to the qualification of analytical instruments. This means that a number of different approaches can be taken. The scope of qualification depends on the complexity of the instrument and its intended use (see chapter 1.3 *Scope of qualification*).

There are four critical components that support the generation of correct analytical results:
- The first component is the *qualification of the instrument*. This ensures that the instrument is suitable for its intended use.
- The second component is the *validation of the analytical method* which ensures that the analytical method is suitable for its intended use. Both components, the qualification of the instrument and the validation of the method, contribute to the quality of the result before the analysis is carried out.
- The third component is the *system suitability test* – SST (see chapter 1.11 *System suitability test (SST)*). This test ensures that the performance of the system meets the requirements during analysis, i.e. at the moment the SST is carried out, which is usually at the beginning of a test series.
- The fourth and final component that ensures the quality of the analytical result are *control samples* (see chapter 1.12 *Control samples*). These are samples with a known content that are analysed during the test series and are meant to prove the suitability of the analytical system for the duration of

the analytical series. The system suitability test and control samples contribute immediately before or during the analysis to the quality of the data.

The four components are shown collectively in figure 1:

Instrument qualification	Contributes to the quality of the data before the analysis is carried out
Method validation	
System suitability test	Contributes to the quality of the result immediately before or during the analysis
Control sample	

Figure 1 Components for reliable and consistent analytical data

The qualification of instruments is documentary proof that the respective analytical instrument is suitable for its intended use. This documentary proof must be produced in written form and can be divided into four logical phases.

DQ	Design qualification	Specification and selection of the instrument
IQ	Installation qualification	Installation of the instrument
OQ	Operational qualification	Functional testing of the instrument
PQ	Performance qualification	Suitability for use testing

Figure 2 Qualification – terminology

Carrying out a necessary action during qualification is more important than assigning it to the "correct" phase. For example, the operating instruction SOP can be created during the *installation qualification* or during the *operational qualification*. Important is that the SOP is actually created during the qualification.

Computer validation has been added in recent years as a fifth component because most analytical instruments are operated and controlled from a PC and the control software is often used to carry out evaluations (see chapter 1.8 *Validation of instrument software*).

Qualification should always be performed prospectively and in compliance with the requirements of Annex 15 to the EU GMP Guidelines.

1.2 Qualification documentation

In principle, a plan must be created for every step of the qualification that shows how testing is to be carried out. The analysis and evaluation of the data must be documented in a report. This approach – implementation – evaluation – report – is a general principle in a GMP-regulated environment and applies to all areas.

It is possible to include more than one qualification phase in a plan or report. However, it has proven practical to dedicate a separate plan and report to the *design qualification* (DQ). The design qualification (see chapter 1.4 *Design Qualification (DQ)*) lasts from the decision to procure an instrument until the instrument is ordered and therefore represents a separate phase.

To what extent the other three qualification phases can be covered in a single plan or report can, for example, depend on whether the contents of the operational and performance qualification can be determined before the instrument is delivered. This must be assessed in each individual case.

If, for example, the qualification of the second HPLC system in a laboratory is being considered, the scope of testing required during the qualification can normally be determined before the system is delivered. In this case, the three phases can be included in one plan/report.

In the case of instruments with a relatively limited number of functions, e.g. stop watches, water baths or drying cabinets, all four phases can be included in a single plan/report, i.e. a single plan/report is created for the entire qualification (for an example of this, please refer to chapter 2.1 *Qualification of a drying cabinet*).

The qualification phases must be carried out consecutively, irrespective of the documentation form (separate or combined plans).

The plans should describe the activities carried out during the respective phase in detail and include acceptance criteria.

The raw data must be created as specified for GMP-testing. The approach taken during the qualification must be transparent. Evaluations and calculations must be traceable and checked in accordance with the general GMP requirements.

The reports contain the actions that were carried out, the comparison with the acceptance criteria and the subsequent evaluation.

The qualification documentation can be stored, for example, in the instrument folder (see chapter 3.5 *Instrument folder*).

1.3 Scope of qualification

An analytical laboratory normally contains a number of different instruments, from a simple water bath to complex analytical instruments connected to a PC, such as a HPLC. A uniform approach to the qualification of these different instruments would not make sense. When the scope of qualification is determined, the complexity of the instrument and its intended use must be taken into account. Because the intended use of an instrument is user-specific, it is obvious that the decision about the scope of qualification is ultimately the responsibility of the user.

The USP General Chapter <1058> suggests categorising the instruments into three groups. However, the actual assignment of an instrument to a group must be carried out by the user based on the instrument's intended use. Extracts from the USP General Chapter <1058> are reproduced and explained below.

Group A

This category includes standard equipment with no measurement capability and no calibration requirement. The manufacturer's specification with regard to the functionality of the instrument is accepted by the user. Compliance of the equipment with the user requirements may be verified and documented through visual observation of its operation.

Examples of equipment in this group include rotary evaporators, centrifuges and magnetic stirrers. However, if a specific stirring rate is a user requirement for a magnetic stirrer, it no longer belongs in Group A, but Group B. The stirring rate must then be calibrated.

Group B

This group includes standard equipment and instruments that provide measured values as well as physical parameters such as temperature, pressure or flow rate, and must be calibrated. The specification of the instrument manufacturer with regard to the functionality and operating parameters of the equipment are in accordance with the user requirements.

Examples of equipment in this group include balances, pH meters, variable pipettes, thermal sensors, refractometers, titrators, ovens, refrigerators and water baths. Compliance of the instrument with the user requirements is confirmed by operating the instrument according to the operating instructions and checking the relevant parameters.

Test points		1	2	3	4	5
O	Likelihood of failure occurring	low	→	medium	→	high
S	Severity of the failure	low	→	medium	→	high
D	Detection probability of the failure	high	→	medium	→	low

Figure 3 Assessment scheme for an FMEA risk analysis

The use of five rankings means the maximum risk priority number is 125. As soon as the risk priority number exceeds a defined value, e.g. 25, the instrument function is taken into account during the qualification. C. Wangnick[1] explains this using the example of a HPLC system qualification. The pump, autosampler, detector and column oven were evaluated based on a number of different functions (see figure 4).

Instrument function	O	S	D	Risk priority number RPN (O x S x D)
Pump				
Flow rate precision	2	5	3	30
Gradient precision	3	5	3	45
Leak test	4	4	2	32
Autosampler				
Vial position detection	2	5	5	50
Injection precision	3	5	3	45
Carry over	3	5	4	60
Detector				
Wavelength accuracy	2	5	5	50
Baseline noise	3	4	1	12*
Baseline drift	4	4	1	16*
Linearity	2	5	5	50
Column oven				
Temperature accuracy	2	5	3	30
* The risk priority numbers for baseline noise and drift are too low for a qualification because these failures can in practice be very easily recognised.				

Figure 4 Example for a risk analysis of a HPLC system (according to Wangnick, 1997)

The risk priority numbers can also be used, if during calibration, the test points are to be derived from the critical parameters (see chapter 4.2 *Calibration programme*).

1. Wangnick C.: Gerätequalifizierung am Beispiel von HPLC-Anlagen. In: Pharma Technologie Journal "Aktuelle Anforderungen an die pharmazeutische Qualitätskontrolle", Art. No. 1076, No. 3/1997, p 127.

Regular requalification – Report ***Company name***

Instrument designation: _____

Operator: _____

Plan: SOP XXX Version 01 - Plan for the regular requalification

Implementation:

Test point in accordance with SOP XXX Version 01	**Acceptance criterion in accordance with SOP**	**Result**	**Acceptance criterion met?**	**Initials/Date**
Examination for mechanical damage	must be carried out.			
Examination for electrical damage	must be carried out.			
Calibration in accordance with SOP _____	must be successful.			

Date of the last (re)qualification: _____

Test point in accordance with SOP XXX Version 01	**Result**	**Initials/Date**
Malfunctions and incidents since the last re(qualification)		
Evaluation of the malfunctions and incidents		
Measures from the retrospective analysis and evaluation of the malfunctions and incidents		
Requalification successful?		

Signature/Date:

Implementation: _____

Test: _____

QA: _____

Instrument has been released for further use: Yes No (delete if not applicable)

Release: _____

Figure 5 Periodic requalification (form)

To compare the peak areas of standard solutions 1 and 2 for the system suitability test or calculate the spread, they must first be converted to a uniform weight which is generally the prescribed weight. The procedure is shown in figure 7.

Target weight	10 mg
Actual weight standard solution 1	10.08 mg
Actual weight standard solution 2	9.92 mg
The peak areas are calculated as follows: adjusted peak area = [measured peak area × target weight] / actual weight	
Adjusted peak areas for standard solution 1	10243 x 10 mg / 10.08 mg = 10162 10218 x 10 mg / 10.08 mg = 10137 10298 x 10 mg / 10.08 mg = 10216 **Average value: 10172**
Adjusted peak areas for standard solution 2	10167 x 10 mg / 9.92 mg = 10249 10191 x 10 mg / 9.92 mg = 10273 10173 x 10 mg / 9.92 mg = 10255 **Average value: 10259**

Figure 7 Calculation of the peak areas for the SST

The adjusted areas are now checked to see if they meet the requirements of the SST.

- Requirement 1: The averaged area for standard solution 2 (10259) must be 98 to 102% of the averaged area for standard solution 1 (10172). This condition is met with 100.9% (10259 / 10172 x 100%).
- Requirement 2: The variation coefficient of the areas for the six standard solutions may not exceed a maximum of 2.0%. This condition is met with 0.54%.

The areas of the control samples are then tested and compared with the peak areas for standard solution 1. The measured average value comes into effect here if the individual values do not differ greatly. The sample weight does not require adjustment, because standard solution 1 was also used as a control sample.

The areas of the control samples must be 98 to 102% of the (measured) area for standard solution 1 (10253). As the calculation shown in figure 8 proves, this condition is met by both control samples.

Control sample	Area control sample	Area standard solution 1	% value
Row 8	10294	10253	100.4
Row 11	10277	10253	100.2

Figure 8 Calculation of peak areas for control samples

The control samples are used to check whether the calibration carried out at the start of the test series was valid for the entire test series. In an ideal situation, they provide proof. This also indirectly proves the suitability of the analytical system for the entire test series.

4.4 Sample calibration SOP

The calibration of an instrument must be described in a specific SOP for the instrument.
A sample SOP for the calibration of a stop watch is shown below.

SOP no. Version 01 Replaces SOP/Version	**Standard Operating Procedure** Calibration of stop watches	(Part 1 of 3) Number of attachments: 0 Valid from: XX.XX.2009
Scope of application	Quality Control/Production	
Authorised copies	Quality Control Production	
Approval		
Created:	Checked:	Approved:

Figure 17 Sample SOP for the calibration of a stop watch

Testing the function of the diluter

The following potassium dichromate solutions are required when carrying out this test:

Stock solution A	Weigh 24 to 26 mg of potassium dichromate p.a. to the nearest 0.1 mg, and dilute in 0.01 N sulphuric acid p.a. to 100.0 ml
Stock solution B	Weigh 245 to 255 mg of potassium dichromate p.a. to the nearest 0.1 mg, and dilute in 0.01 N sulphuric acid p.a. to 100.0 ml

Figure 1

The diluter is used along with a 250-ml sample syringe, a 1-ml dilution syringe and a standard sample tube to produce dilution series A from stock solution A (see figure 19):

Dilution	Stock solution A	0.01 N sulphuric acid
1 + 1	250 µL	250 µL
1 + 3	125 µL	375 µL
1 + 7	75 µL	525 µL
1 + 15	62 µL	930 µL

Figure 19 Testing the function of the diluter: Dilution series A

The diluter is used along with a 250-ml sample syringe, a 1-ml dilution syringe and a standard sample tube to produce dilution series B from stock solution B (see figure 20): The solutions are tested using a UV/VIS spectrophotometer at 350 nm in 0.5-cm semi-micro cuvettes with 0.01 N sulphuric acid.

Dilution	Stock solution B	0.01 N sulphuric acid
1 + 19	250 µL	4750 µL
1 + 39	125 µL	4875 µL
1 + 79	62.5 µL	4940 µL
1 + 159	31.25 µL	4970 µL
1 + 199	25 µL	4975 µL

Figure 20 Testing the function of the diluter: Dilution series B

Acceptance criteria: fulfilment of the Lambert-Beer law is tested for each dilution series by determining the linearity ($y = mx + b$) and the regression lines (correlation coefficient r^2), e.g. using Excel. The tolerances in figure 21 must be observed.

Tolerances for the functional test of the diluter	
Linearity	The b intercept may not exceed 1% of the measured maximum value of absorbance.
Correlation	$r^2 \geq 0.99$

Figure 21 Tolerances for the functional test of the diluter

Contributors

Josef Künzle, PhD
josef.kuenzle@basilea.com

Chemist
Basilea Pharmaceutica International Ltd, Basel

Josef Künzle joined Basilea in 2007. In August 2015, he was appointed Head of Global Quality Management and is responsible for all GxP departments. He had previously worked in the pharmaceutical industry for 18 years in the areas of analytical R&D, quality control and quality management. He has taken part in official inspections and global supplier audits.

After graduating in Chemistry, receiving a PhD in Organic Chemistry from the University of Zurich and working as a post-doctoral scholar at Stanford University, he began his professional career in 1989 as Head of Laboratory in analytical R&D at Sandoz Pharma AG. Upon transfer to QC, he was responsible for the blockbuster Sandimmune, including a successful FDA inspection for Sandimmune Neoral. He was responsible for the Sandoz peptide products at Novartis Pharma AG.

In 1998, he joined the Carbogen group where he held a senior position and supported the development and strengthening of all aspects of quality.

From the end of 2003, he was Technical Manager and Head of QM for the Quality department of Permamed AG.

He works as a GMP trainer and shares his expert knowledge at GMP training events on a regular basis.

Wolfgang Nedvidek, PhD

Wolfgang Nedvidek completed studies in food chemistry at the University of Erlangen-Nuremberg and earned a doctorate in Stuttgart, and was initially entrusted as GLP study director with the testing of pesticide residues and the analysis of textiles and leather as well as the analysis and assessment of objects with food contact. After that, he switched to pharmaceutical quality control, where he analysed starting materials and finished products over 11 years, and conducted stability tests as well as method validations. Since 2009, Nedvidek has been active for PTS Training Service in the continuing education sector and responsible for the planning and implementation of in-house training and events. Wolfgang Nedvidek is a lecturer in the Faculty of Life Science at Albstadt-Sigmaringen University.

Index