STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies of the USPC or the USP Council of Experts

A Life Cycle Approach to the Calibration and Qualification of Analytical Instruments and Systems to Establish "Fitness for Purpose" for Pharmacopeial Purposes

Christopher Burgess,[a] Rose Rae[b]

Correspondence should be addressed to: Lucy L. Botros, Scientific Liaison, General Chapters, United States Pharmacopeial Convention, 12601 Twinbrook Parkway, Rockville, MD 20852-1790; email: LYB@usp.org.

ABSTRACT

This *Stimuli* article presents the principles contained in *Analytical Instrument Qualification* ⟨1058⟩ extended to cover the analytical procedure life cycle. In addition, it recommends revisions to the *USP–NF* to establish consistent requirements and acceptance limits in below ⟨1000⟩ general chapters ensuring analytical instruments are "fit for purpose". Verifying the operation and performance of an analytical instrument is a critical part of a robust quality management system and is required in a current good manufacturing practice (GMP) environment. In pharmacopeial applications, the performance of an instrument directly impacts the data reported in establishing the quality of a drug substance or product. As part of instrument qualification procedures, the accuracy of the measurement and operating parameters are tested and verified against specifications. To do this, certified reference materials (CRMs) are often used and required in below ⟨1000⟩ chapters. A CRM is a material that has been characterized by a metrologically valid procedure for one or more specified properties, accompanied by an RM certificate that provides the most probable true value of the specified property, its associated uncertainty, and a statement of metrological traceability. Since all measurements are subject to error, the associated uncertainty is critical to confirming whether a significant bias in the measurement or operating parameter exists, thus verifying the accuracy of the instrument and ensuring it is fit for its intended purpose. Many *USP–NF* analytical instrument chapters have been revised to include concepts that align with ⟨1058⟩, yet they are inconsistent in their use of CRMs, in their acceptance limits for accuracy and precision, and in their position on the use of user-prepared reference materials for the purposes of instrument qualification.

This article has been shared with the General Chapters—Chemical Analysis Expert Committee, who have expressed their agreement with the principles and the recommendations presented herein. The author seeks the feedback from stakeholders particularly on the following topics:

1. The proposed approach to expanded and metrological uncertainties
2. The proposed generic process flow for the calibration and qualification life cycle
3. The use of user-prepared solutions for the purposes of instrument qualification
4. The potential revision of ⟨1058⟩ to include life cycle concepts of ICH Q12 and established conditions

INTRODUCTION

All analytical instruments and systems need to be subject to qualification as described in *Analytical Instrument Qualification* ⟨1058⟩. This general chapter focuses primarily on the extent of all calibration and qualification activities that need to be performed rather than a life cycle approach. The details of calibration and qualification requirements are given in instrument-specific general chapters; for example, UV spectroscopic systems are covered in general chapter *Ultraviolet-Visible Spectroscopy* ⟨857⟩. These chapters specify the installation qualification, operational qualification, and performance qualification requirements and acceptance criteria needed for compliance for use within the pharmacopeia. The companion above ⟨1000⟩ general chapters, such as *Ultraviolet-Visible Spectroscopy—Theory and Practice* ⟨1857⟩, support the mandatory below ⟨1000⟩ chapters with recommendations and suggestions for best practices.

The primary purpose of this *Stimuli* article is to propose a generic calibration and qualification process with the intent of defining and harmonizing activities in a uniform structured manner within the *USP–NF* and within the context of the analytical procedure life cycle. In addition, some inconsistencies regarding the use of user-prepared and externally certified calibration standards within general chapters will be discussed.

CALIBRATION, QUALIFICATION, VERIFICATION, AND VALIDATION

The lack of agreement about the meaning of the terms *calibration*, *qualification*, *verification*, and *validation* is an important issue. Agreement on a technical glossary is necessary for consistency throughout the *USP–NF*. In addition, 21 CFR §211.68 creates a challenge in that the requirement refers to routine calibration, inspection, or checking of equipment, so FDA citations include calibration deficiencies involving issues with instrument qualification.

Calibration

It is accepted that *calibration* forms part of *qualification*. Calibration is about metrology. Calibration is that part of qualification relating to measurement integrity of the ordinate response and abscissa functions, i.e., ensuring that all measurements from the instrument/system are within defined acceptance limits of a true or certified value.

The foundation for assurance of metrological "fitness for purpose" lies with the correct use of either a certified reference material (CRM) and/or a reference standard (RS). In a pharmacopeia, calibration is a comparison between a known or accepted value of a CRM or RS and its measured value on a specific laboratory analytical instrument or system being used for a pharmacopeial purpose. The difference between these two values is compared with an acceptance criterion, which may be an acceptable range or a tolerance interval.

Qualification

Qualification is about overall "fitness for purpose" of an instrument or system; it's not just about good numbers. For this reason, compliance with the below ⟨1000⟩ general chapter in its entirety is needed for overall "fitness for purpose". Hence *USP–NF* requires qualified instruments and systems.

Verification

Currently, *verification* relates to the "fitness for purpose" of analytical procedures as required by *Verification of Compendial Procedures* ⟨1226⟩. However, verification is also used in the American National Standards Institute (ANSI) sense for software, demonstrating that each individual step is mathematically or procedurally correct (1).

Therefore, some aspects of modular calibration (see *Modular or Holistic Calibration*) may be regarded as parts of a verification process.

Chapter ⟨1058⟩ does not use the term "verification" in either sense.

Validation

Currently, *validation* relates either to the establishment of analytical procedures as required by *Validation of Compendial Procedures* ⟨1225⟩ or to "fitness for purpose" as described in ⟨1058⟩. For example, ⟨1058⟩, *Software Validation; Instrument Control, Data Acquisition, and Processing Software* states:

"At the user site, integrated qualification of the instrument, in conjunction with validation of the software, involves the entire system. This is more efficient than separating instrument qualification from validation of the software."

From an ANSI perspective, validation is a holistic process of evaluation of a system to ensure it works as intended and meets a customer's needs. Herein lies the need for a life cycle approach.

The idea of a nested hierarchy is not new and dates back almost 25 years. For example, in 1996, the UK's Valid Analytical Measurement Programme (VAM) focused on what was then called "equipment qualification" (2). Shortly afterward, in 2000, an instrument vendor created a diagrammatic representation of the VQC (validation, qualification, and calibration) "shell" as part of *total quality management* (TQM).

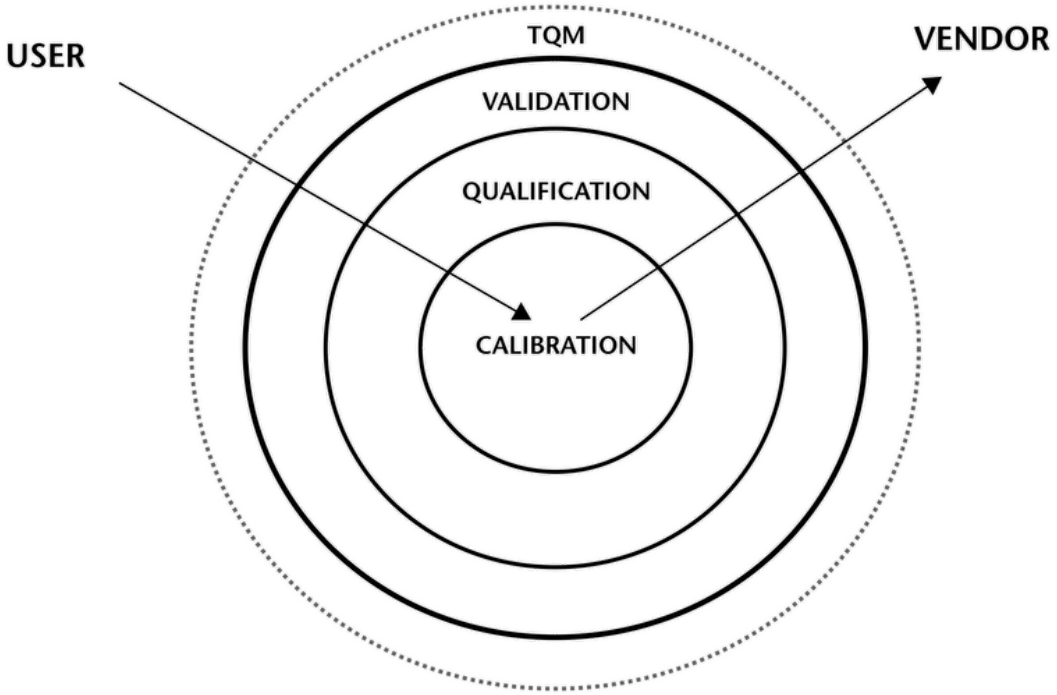

Figure 1. Validation, qualification, and calibration shell model.[1]

There are a variety of definitions for *calibration*, *qualification*, *verification*, and *validation* within the *USP–NF*, which need to be harmonized to assist understanding and prevent user confusion. An overall technical glossary would be highly desirable.

PROPOSED NEW GENERAL CHAPTER: ANALYTICAL PROCEDURE LIFECYCLE ⟨1220⟩

The concept of *validation* has changed radically since the publication of the FDA's revised Guidance for Industry on process validation in 2011 (3) and the European GMP *Annex 15: Qualification and Validation* update in 2015 (4), both of which require a validation life cycle approach. In addition, the International Council for Harmonisation has initiated the revision of ICH Q2(R1) *Validation of Analytical Procedures* and development of the new ICH Q14 *Analytical Procedure Development*. These developments were reinforced, in 2019, by a new guideline, ICH Q12 (5).

Established conditions (ECs) related to analytical procedures should include elements that assure performance of the procedure. The extent of ECs and their reporting categories could vary based on the degree of the understanding of the relationship between method parameters and method performance, the method complexity, and control strategy.

From 2011–2018, a USP Expert Panel was formed to develop a new general chapter on analytical procedure life cycle and published five *Stimuli* articles in the *Pharmacopeial Forum* (6–10). In 2019, a new Expert Panel was convened to carry on this work, and a new version of ⟨1220⟩ is planned for publication in the *Pharmacopeial Forum* in 2020.

The concept of an analytical life cycle process clearly requires, as a precursor, adequately calibrated and qualified instruments and validated systems.

EXPANDED UNCERTAINTY AND METROLOGICAL UNCERTAINTY

All measurements are subject to error. CRMs have an assigned most-probable value and an associated expanded uncertainty (approximately at 95% confidence with a coverage factor of k=2 [11]). In addition, this most-probable value is traceable to a primary standard. For example, a certified mass from NIST or any other national metrology institute (NMI) was traceable to the international prototype kilogram as the primary artifact.[2] Therefore, a nominal 100.0000 g mass would be associated with a small but finite uncertainty.

The acceptance criterion for instrument or system performance should be generated from a combination of the instrumental specifications from the manufacturer (S), the expanded uncertainty of the standard (U), and the metrological uncertainty of the measurement (12–13).

The basis for this may be found in a NIST publication: "An acceptable level of agreement between the user's measurements and the certified value and its expanded uncertainty overlaps any part of the user's tolerance band defined by the measured mean and the user-defined level of acceptability" (*14*).

This has been interpreted as "Add the CRM expanded uncertainty to the manufacturer's tolerance and make those the acceptance limits for satisfactory calibration performance".

For example, in ⟨857⟩, the absorbance accuracy for a UV spectrometer for values above 1.00 *A* is specified as $0.010*A_{\lambda}$, where A_{λ} is the certified value of the CRM at the specified wavelength, λ nm.

Assuming that A_{λ} is 1.452 *A*, for example, the absorbance accuracy required would be ±0.01452 *A*, which on rounding, in accordance with *General Notices, 7.20 Rounding Rules*, becomes ±0.015 *A*. The acceptance limits for "fitness for purpose" of the measured value of the CRM on the spectrometer, $A_{\lambda\ obs}$, should lie within the range of 1.437–1.467 *A*.

For a typical instrument, *S* might be ±0.004 *A* and *U* for the CRM might be ±0.007 *A*, yielding a combined value of ±0.011 *A*. This range lies comfortably within the acceptance limits of ±0.015 *A* and allows for the metrological uncertainty component.

The metrological uncertainty is generally smaller than *S* and *U*. For example, if *n* absorbance measurements of the CRM are made and *s* is the calculated standard deviation, then the metrological uncertainty at 95% confidence is calculated from the following equation:

$$\pm t_{(0.05,n-1)} \frac{s}{\sqrt{n}}$$

If *n* is 6, the value of the *t*-distribution is 2.571 for 95% confidence with 5 degrees of freedom. If *s* is 0.0022 *A*, the metrological uncertainty at 95% confidence is ±0.0023 *A*. Therefore, the calculated overall acceptance criterion becomes ±0.013 *A*. This range lies within the pharmacopeial acceptance limit of ±0.015 A.

MODULAR OR HOLISTIC CALIBRATION

For many analytical instruments and systems, it is both possible and desirable to carry out modular calibrations. For example, in an HPLC system, the pump flow rate may be checked independently using a certified digital flow meter over the specified operational range. In addition, holistic calibration reference standards may be developed to check the overall performance of the entire system including the application software. Generally speaking, for modular systems, whether chromatographic or spectroscopic, a combined approach is desirable wherever possible.

TRACEABILITY

From both a scientific and regulatory perspective, it is desirable to employ CRMs and reference materials (RMs) that are independent of the operating laboratory. For example, a primary or secondary standard with unambiguous calibration hierarchy traceable to NIST or other certification body is best practice. Taking mass as an example, the calibration hierarchy for an analytical balance is in accordance with *Balances* ⟨41⟩ and supported by its best-practice companion, *Weighing on an Analytical Balance* ⟨1251⟩.

As shown in *Figure 2*, the principal role of NIST and other NMIs is to provide the most-probable value of a primary CRM with the smallest possible uncertainty interval. The role of an accredited calibration laboratory is to provide traceable, secondary CRMs and reference materials for use in industry. The internationally agreed upon route for calibration laboratories to provide such traceability is by being accredited with ISO/IEC 17025 (*15*).

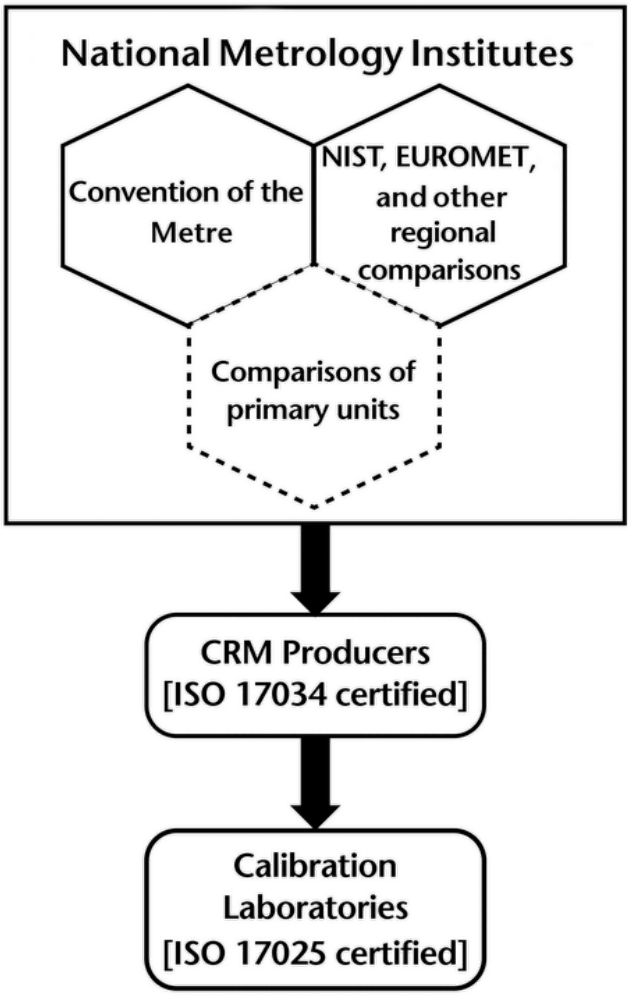

Figure 2. The traceability process.

TYPES OF CALIBRATION REFERENCE STANDARDS

For analytical instruments and systems, calibration reference standards fall into three distinct types:

1. Fundamental physical properties of matter (e.g., atomic emission line sources for spectroscopic wavelength calibration)
2. Artifact standards, which may be solid or physical devices (e.g., a digital resistance box for pH meter specific qualification)
3. Solutions, mixtures, and gases, which have traceability to primary standards (e.g., a liquid filter for the qualification of the ordinate scale of a spectrometer)

The choice of the type of reference standard will depend on the intent of the calibration and the requirements given in the below ⟨1000⟩ chapter.

For example, in ⟨857⟩, *Qualification of UV-Vis Spectrometers, Control of Wavelengths*, verification of the monochromator's wavelength accuracy is best accomplished using atomic emission line sources, where the reference emission line wavelengths are known much more accurately than the monochromator's resolution ability. However, these atomic emission line sources may also be used to qualify spectral bandwidth as discussed in ⟨1857⟩.

During the manufacture of UV-visible spectrometers, such sources are commonly employed. However, users also measure solutions and commonly use narrow-line, rare-earth solutions such as holmium oxide in perchloric acid, which is an intrinsic standard agreed upon between the national calibration laboratories (*16*).

CALIBRATION AND QUALIFICATION LIFE CYCLE

The perennial question of "who does what and when" is answered in the life cycle approach to calibration shown in *Figure 3*. The solid lines denote the primary process flows for establishing and confirming "fitness for purpose". Dotted or dashed lines indicate either feedback loops triggered by data generated during the ongoing performance phase or, in the case of the user requirements specification, support by the vendor.

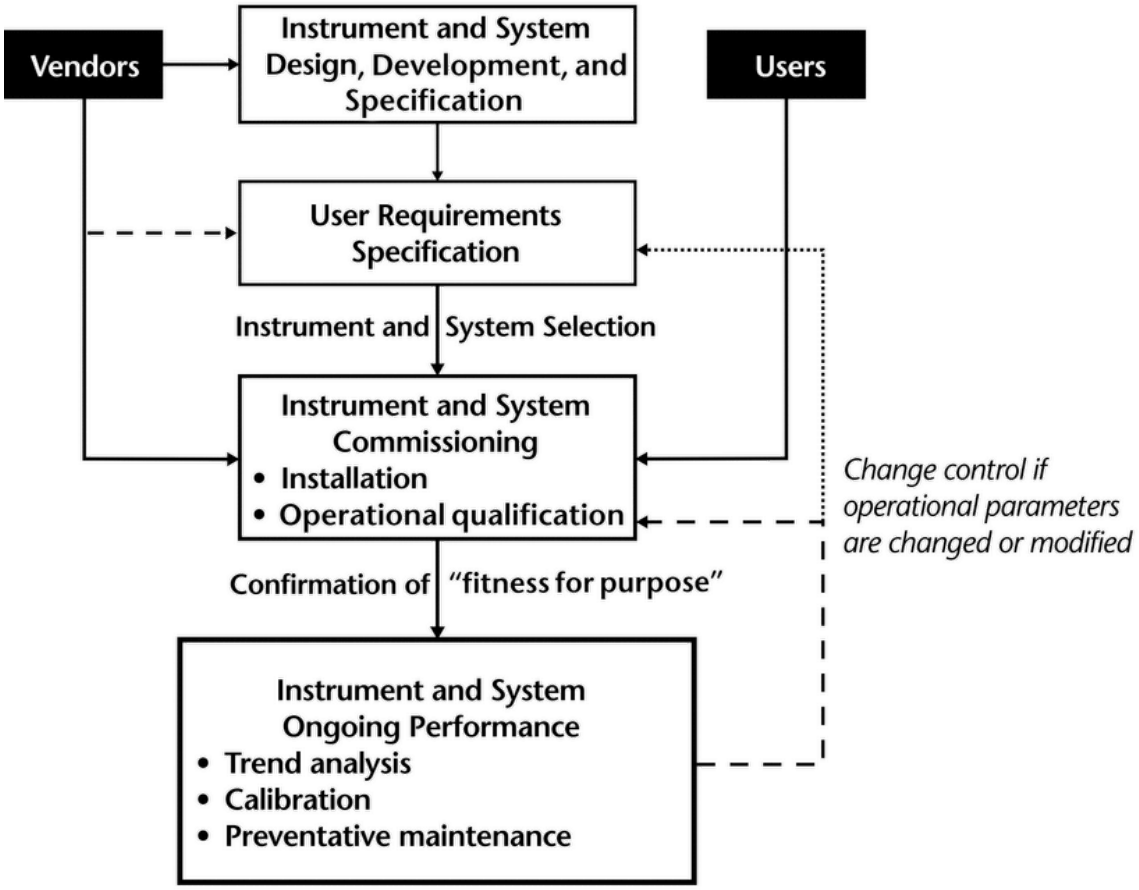

Figure 3. Generic flow for the calibration and qualification life cycle.

The generic process of calibration and qualification should be designed to allow confirmation of "fitness for purpose" at all stages in the life cycle including assurance of preventative maintenance and change control.

Users need to define their own control strategy to specify ongoing "fitness for purpose" by establishing the frequency of calibration, standards, and acceptance criteria that will be employed and trend analysis of the ongoing performance data from the instrument.

One important aspect of the calibration and qualification life cycle is the presence of change control feedback loops. For example, if the qualified operational wavelength range for a UV spectrometer was originally 240–600 nm, and the requirement is to extend this to 210–600 nm, then a new qualification standard is required to confirm "fitness for purpose". However, the user requirements specification needs to be reviewed to ensure that the instrument was correctly specified originally to allow the revision of operational range.

INSTRUMENT CALIBRATION STANDARDS

There is a lack of consistency among below ⟨1000⟩ chapters concerning calibration standards. Some allow, or even require, user-prepared calibration standards. Sometimes there is not a clear differentiation between standards required for assurance of proper instrument function and those for "fitness for purpose" in operational use. See *pH* ⟨791⟩, for example, where proper instrument function relies on voltage, temperature, and Nernstian conversion firmware, and operational use relies on the holistic measurement of standard buffer solutions.

Recently, the FDA updated their *Questions and Answers on Current Good Manufacturing Practices—Laboratory Controls* to specifically answer the question "What material can be used as instrument calibration standards for chromatographic systems?":

"For chromatographic systems, instrument calibration standards should be chosen from highly purified materials that are well characterized and can be accurately weighed. Standards can be compendial (from USP) or non-compendial (e.g., from NIST, a chemical supplier, or produced in-house). Substances obtained from a chemical supplier or produced in-house should be purified and characterized using validated purification processes and validated characterization methods. Purification is necessary because impurities can add variation and interfere with analytical methods. Finished dosage forms generally should be avoided as standards because excipients in the finished dosage form may interfere with analysis." (*17*)

The FDA also cites the following four references:

- FDA guidance for industry (2015): *Analytical Procedures and Methods Validation for Drugs and Biologics*
- 21 CFR 211.160(b)(4): *Instrument calibration*
- 21 CFR 211.194(a)(2) and (c): *Method validation and reference standards*
- USP General Chapter *Chromatography* ⟨621⟩, *System Suitability*

The definition for "instrument calibration standards", somewhat confusingly, includes both instrument performance as well as method and procedure performance.

However, it is clear that the FDA requirement for standards, for chromatographic systems at least, is for traceability to USP, NIST, or by implication to an NMI.

A synopsis for those below ⟨1000⟩ chapters involving instrument calibration is given in the table below. The intent of this table is to differentiate between modular instrument functionality and holistic operational use and to indicate if user-prepared standards are currently acceptable.

***USP* General Chapter**	**Calibration Standard Specified**		
	Technique or	**RMs and CRMs specified**	**User-Prepared**

USP General Chapter	Property	Instrumental (Modular Functionality)	Operational (Holistic)	Standard?
	Technique or Property	RMs and CRMs specified		User-Prepared Standard?
		Instrumental (Modular Functionality)	Operational (Holistic)	
Elemental Impurities—Procedures ⟨233⟩ See also *Plasma Spectrochemistry* ⟨730⟩ and *Plasma Spectrochemistry—Theory and Practice* ⟨1730⟩	ICP–OES or ICP–MS	• Wavelength calibration in accordance with the manufacturer's applicable operating procedures • Detection mode and instrument parameters in accordance with the manufacturer's applicable operating procedures	Where appropriate reference materials are specified in chapter *Elemental Impurities—Limits* ⟨232⟩ or *Elemental Contaminants in Dietary Supplements* ⟨2232⟩, CRMs from a national metrology institute (NMI) or reference materials (RMs) that are traceable to the CRM of the NMI should be used	Yes
Total Organic Carbon ⟨643⟩	Oxidation to carbon dioxide	USP Sucrose RS	USP 1,4-Benzoquinone RS	Yes
Water Conductivity ⟨645⟩	Conductivity or resistivity	NIST (NMI) traceable resistors accurate to ±0.1%	None	No
Plasma Spectrochemistry ⟨730⟩ and *Plasma Spectrochemistry—Theory and Practice* ⟨1730⟩	Emission or mass	—	Commercially available single- or multi-element standard solutions, traceable to NIST or an NMI can be used in the preparation of standard solutions	Yes/No
Osmolality and Osmolarity ⟨785⟩	Depression of freezing point or vapor pressure	In accordance with the manufacturer's applicable operating procedures	Gravimetrically diluted sodium chloride in water	Yes
pH ⟨791⟩	Voltage, temperature, and Nernstian conversion	Temperature ±1°; no standards specified	• Buffer salts from NIST or an NMI • Instructions for the preparation of 9 standard buffers given in ⟨791⟩, *Table 2* • In addition, the use of commercially available buffer solutions for pH measurement calibration, traceable to NIST or an NMI, are referenced for use	Yes
Atomic Absorption Spectroscopy ⟨852⟩ and *Atomic Absorption Spectroscopy—Theory and Practice* ⟨1852⟩	Absorbance	Atomic line sources, see ⟨1852⟩	• Operational qualification (OQ) tests for flame AAS (zinc standard) and graphite furnace (copper standard) • Commercially available single- or multi-element standard solutions, traceable to NIST or to an NMI, can be used in the preparation of standard solutions	Yes
Fluorescence Spectroscopy ⟨853⟩ and *Fluorescence Spectroscopy—Theory and Practice* ⟨1853⟩	Intensity	Wherever possible analysts should use CRMs for calibration • Atomic line spectra • Rare earth oxide solutions • Polymethyl methacrylate doped references	• NIST traceable SRMs 2940, 2941, and 2944 • NIST SRM 936a Quinine either as a commercial solution or user solution, 1 mg/mL	Yes
Mid-Infrared Spectroscopy ⟨854⟩ and *Mid-Infrared Spectroscopy—Theory and Practice* ⟨1854⟩	Wavenumber and transmittance	Traceable 35-µm matte polystyrene film	None	No
Nephelometry and Turbidimetry ⟨855⟩	Absorbance	None	User-prepared formazin haze standards	Yes

USP General Chapter	Calibration Standard Specified			
	Technique or Property	RMs and CRMs specified		User-Prepared Standard?
		Instrumental (Modular Functionality)	Operational (Holistic)	
Near-Infrared Spectroscopy ⟨856⟩ and *Near-Infrared Spectroscopy—Theory and Practice* ⟨1856⟩	Transmittance, transflectance, and reflectance	• USP Near IR System Suitability RS • Methylene chloride (with talc for transflectance) • TS5 liquid • Water vapor • Traceable polytetrafluoroethylene (PTFE) carbon-doped references	—	No
Ultraviolet-Visible Spectroscopy ⟨857⟩ and *Ultraviolet-Visible Spectroscopy—Theory and Practice* ⟨1857⟩	Transmittance (absorbance)	• Atomic lines • Rare earth solutions and glasses traceable to NIST or an NMI • Certified liquid and solid filters traceable to NIST or an NMI	Certified liquid and solid filters traceable to NIST or an NMI	Yes
Raman Spectroscopy ⟨858⟩ and *Raman Spectroscopy—Theory and Practice* ⟨1858⟩	Intensity Raman shift	Laser line	Raman ASTM shift standards	No

It is apparent that there are a number of diverse approaches that are not harmonized across the analytical instrument chapters. The reasons for this include:

- Historical custom and practice within specific techniques
- Lack of availability of appropriate traceable standards
- Lack of a common approach for calibration across instrument Expert Committees and Expert Panels within USP
- Lack of a general chapter on analytical instrument qualification (⟨1058⟩) until relatively recently
- Evolving regulatory interest on "fitness for purpose" for instruments and systems in the laboratory

USER-PREPARED CALIBRATION STANDARDS

If calibration standards are prepared by the user, the assigned value and its associated measurement uncertainty is no longer independent of the laboratory. In addition, the risk associated with user-prepared calibration standards is highly dependent on the integrity of the preparation methods employed and the importance of the procedure. The risk is generally lower for holistic standards than for functional standards if a proper calibration hierarchy is in place.

The difficulty of preparing in-house standards particularly for the ordinate scale of an instrument cannot be underestimated. The standards of and the practices in a laboratory compliant with ISO 17034 (*18*) or ISO/IEC 17025 (*15*) are very different from a routine quality control (QC) laboratory. The preparation of in-house standards should not be undertaken unless staff have the appropriate training and skills and the environment in which to prepare them, with the necessary dedicated glassware, water quality, etc. For example, the NIST procedure for making acidic solutions of potassium dichromate (SRM 935) are particularly challenging (*19*).

However, this independence is not always achievable owing to the lack of traceable standards.

Traceability to primary standards should be assured wherever possible and the assigned value should be generated using a statistically designed protocol (*20*).

The most common usage for such standards is for holistic ongoing operational assurance of control rather than instrument functionality.

For example, consider *Optical Rotation* ⟨781⟩. The manufacturer will usually rely on a physical artifact standard such as a quartz halfwave plate for calibration of optical rotation during manufacture and commissioning of the instrument. They may also demonstrate "fitness for purpose" holistically using a solution of NIST Sucrose (SRM 17f) as this will, in part, mimic normal analytical use. However, the NIST SRM will have its own expanded uncertainty budget. As soon as the user prepares a solution, they will need to define their own uncertainty budget including that of the NIST SRM and the effect of temperature, etc. This is not a trivial process (*21*). Another disadvantage of the use of laboratory-prepared solutions is that, if an out of control value is found, it can be more difficult to establish the root cause.

Just as ISO/IEC 17025 (*15*) is used to establish traceability for a calibration laboratory, ISO 17034 (*18*) is the internationally agreed upon route for RM producers to provide such traceability for manufacturing in characterization, most-probable value assignment, etc., and, if the most-probable value is associated with the appropriate expanded uncertainty budget, then this how a defined CRM is produced under ISO/IEC 17025.

BEST PRACTICES FOR INSTRUMENT CALIBRATION

Best practice is to use the most stable artifact with the smallest uncertainty budget. For example, for routine monitoring of UV–Vis and near-infrared spectrometers, solid or liquid filters traceable to an NMI, for both wavelength and absorbance accuracy qualification, provide the most reliable option for the user.

However, this is not always an option if the appropriate traceable standards are either non-existent or not readily available. For example, in *Nephelometry and Turbidimetry* ⟨855⟩, functional or holistic standards are not currently available as traceable standards and the user is reliant on the manual preparation method, which is both difficult and potentially hazardous in inexperienced hands.

For some techniques, e.g. ⟨791⟩, which has had a long history, the latest custom and practice has not always been applied:

- There are no functional standards specified for the measurement, e.g. voltage and temperature. The calibration relies upon holistic measurement of traceable buffers. This means that the integrity of measurement of an unknown relies primarily on the preparation accuracy of the bracketing calibration buffers selected.
- There is no differentiation between primary and secondary buffers for calibration.
- There is an explicit requirement that buffer solutions for calibration are prepared using traceable salts.
- The instructions for volumetric preparation of buffer solutions are sparse and based upon molarity.
- Best practice (*22*) indicates the use of gravimetric preparation (molality) with explicit preparation instructions (*23–24*).
- Certified pH values of the primary buffers are given to three decimal places in ISO Guide 80 (*20*) and are given to two decimal places in ⟨791⟩, *Table 2*.

- There has been an discrepancy in ⟨791⟩, *Table 2* for many years concerning the assigned value of 6.86 at 25° for the Equimolar phosphate 0.05 m buffer versus the value of 6.87 given in the *European Pharmacopoeia* (25). This is resolvable with the internationally recognized IUPAC data value of 6.865, which, when rounded, yields 6.87. The origin of the current USP value appears to be from an older 1988 National Bureau of Standards (NBS) reference value of 6.863 (26).
- While the two general chapters are not currently harmonized, at least the standard values from the primary buffers should be consistent for such an important parameter.

RECOMMENDATIONS FOR THE NEXT CYCLE 2020–2025

Given the importance of the analytical instrument general chapters in the *USP*, especially in the context of calibration and data integrity, it is recommended that, for the 2020–2025 cycle, consideration be given to:

1. Formulating a consistent approach for functional and holistic calibration of instruments and systems
2. Planning a prioritized revision timetable for analytical instrument general chapters
3. Revising ⟨1058⟩ to include life cycle concepts of ICH Q12 and ECs
4. Incorporating measurement uncertainty concepts into analytical instrument general chapters

REFERENCES

1. American National Standards Institute. ANSI IEEE 1012–16: Standard for System, Software, and Hardware Verification and Validation.
2. P Bedson and M Sargent. The Development and Application of Guidance on Equipment Qualification of Analytical Instruments. *Journal of Accreditation and Quality Assurance*. 1:265–274, 1996.
3. US Food and Drug Administration. FDA Guidance for Industry. *Process Validation: General Principles and Practices*. Rockville, MD. January 2011.
4. European Commission Directorate-General for Health and Food Safety. EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 15: Qualification and Validation, 30 March 2015.
5. International Council for Harmonisation. ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (Step 3)*, 3.2.3.2, November 2019.
6. Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification, *Pharm. Forum.* 39(5), Sept.–Oct. 2013.
7. Fitness for Use: Decision Rules and Target Measurement Uncertainty, *Pharm. Forum.* 42(2), Mar.–Apr. 2016.
8. Analytical Target Profile: Structure and Application throughout the Analytical Lifecycle, *Pharm. Forum.* 42(5), Sept.–Oct. 2016.
9. Analytical Control Strategy, *Pharm. Forum.* 42(5), Sept.–Oct. 2016.
10. Proposed New USP General Chapter: The Analytical Procedure Lifecycle ⟨1220⟩, *Pharm. Forum.*, 43(1), Jan.–Feb. 2017.
11. The NIST Reference on Constants, Units, and Uncertainty: Uncertainty of Measurement Results, Glossary. National Institute of Standards and Technology, Gaithersburg, MD. https://physics.nist.gov/cuu/Uncertainty/glossary.html.
12. C. Burgess. Calibration of instruments: is your UV spectrometer accurate enough?, *Pharm. Tech.* 38(1); 2014.
13. C Burgess, JP Hammond. Is your spectrometer in calibration?, *Spectroscopy Europe*. 28(2); 2016.
14. D Becker, et al. Use of NIST Standard Reference Materials for decisions on performance of analytical chemical methods and laboratories. NIST Special Publication 829. National Institute of Standards and Technology, Gaithersburg, MD, 1992. https://www-s.nist.gov/srmors/certificates/archives/1930.pdf.
15. International Organization for Standardization. ISO/IEC 17025: General requirements for the competence of testing and calibration laboratories. Geneva, Switzerland, 2017.
16. JC Travis, et al. Intrinsic Wavelength Standard Absorption Bands in Holmium Oxide Solution for UV/visible Molecular Absorption Spectrophotometry. *J. Phys. Chem. Ref. Data*, 34(1); 2005.
17. US Food and Drug Administration. https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practices-laboratory-controls.
18. International Organization for Standardization. ISO 17034: General requirements for the competence of reference material producers. Geneva, Switzerland, 2016.
19. National Bureau of Standards. *NBS Special Publication 260-54*. pp 41–44; 1977.
20. International Organization for Standardization. ISO Guide 80: Guidance for the in-house preparation of quality control materials (QCMs). Geneva, Switzerland, 2014.
21. NIST SRM 17f certificate of analysis. 2013 reference 3; ICUMSA–Methods Book, Method GS2/3-1; The Braunschweig Method for the Polarisation of White Sugar by Polarimetry; ICUMSA Publication Department, Norwich Research Park, NR4 7UB, UK; 1994.
22. IUPAC Measurement of pH: Definition, Standards, and Procedures. *Pure Appl. Chem.*; 74(11):2169–2200; 2002.
23. R G Bates. *Determination of pH*. Wiley, New York; 1973.
24. International Organization for Standardization. Table 1 in ISO Guide 80: Guidance for the in-house preparation of quality control materials (QCMs). Geneva, Switzerland, 2014.
25. *European Pharmacopoeia*, 2.2.3 Potentiometric determination of pH; 07/2016:20203.
26. National Bureau of Standards. *NBS Special Publication 260-53*, Table 1. p 8; February 1988.

[a] Burgess Analytical Consultancy Limited.

[b] The Lendings, Startforth Barnard Castle, Co Durham, DL12 9AB, United Kingdom.

[1] JP Hammond private communication.

[2] As of May 20, 2019, this artifact has been replaced by traceability to fundamental constants of nature. See https://www.nist.gov/si-redefinition for more information on redefinition of the kilogram.

Auxiliary Information- Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
ELASTOMERIC COMPONENTS FOR INHALATION PACKAGING/DELIVERY SYSTEMS	Desmond G. Hunt Principal Scientific Liaison	GCPD2020 General Chapters - Packaging and Distribution

Page Information:

Not Applicable

DocID: GUID-C08C1081-FE7B-498D-A608-7E3B68F7F18E_10101_en-US