ECA Foundation
Fostering harmonisation of GMP/GDP regulations

Guide for an Integrated Lifecycle Approach to Analytical Instrument Qualification and System Validation

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Guide for an Integrated Lifecycle Approach to Analytical Instrument Qualification and System Validation

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Version

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1 Rationale and Purpose of this Guide

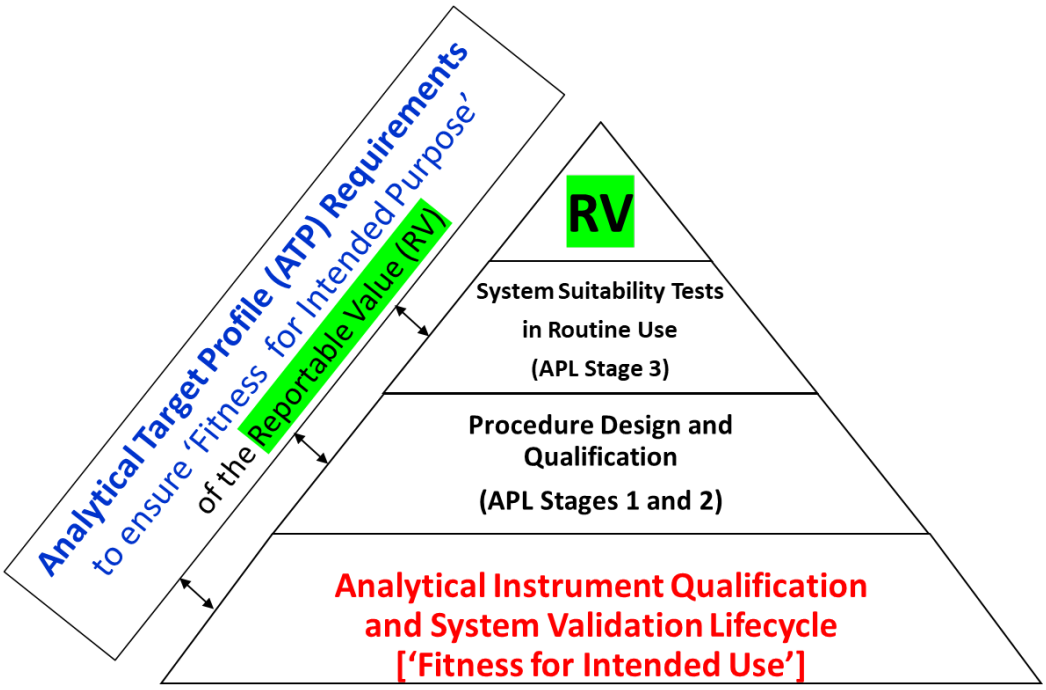
The purpose of a GMP analytical procedure is to provide a reportable value of the analytical characteristic / quality attribute being determined. The analytical procedure is applied to a test sample which may be an item or a test sample from a batch or lot. The reportable value found, using the analytical procedure, is compared with the specification for a quality attribute of the item, batch or lot in question.

The analytical procedure is developed and qualified in terms of its own User Requirements Specification known as the Analytical Target Profile (ATP). For more details of the ATP see the ECA AQCG Analytical Procedure Lifecycle Management (APLM) Guideline [1].

The relationship between the URS for 'Fitness for Use' of the Analytical Instrument or System (AIS) and the ATP for 'Fitness for Purpose' of the analytical procedure (AP) consistently delivering the quality of a reportable value is shown in Figure 1. The specific requirements for operating range of instrument and system must fall within the predefined limits required by an analytical procedure and ATP criteria. Ongoing verification is needed to manage potential changes over the lifecycle.

The analytical instrument or system used in an analytical procedure is a critical element in assuring a reportable value compliant with the ATP and forms the foundation for this assurance.

Figure 1: Relationship between Fitness for Use of Analytical Instruments and Fitness for Purpose of an Analytical Procedures



An earlier ECA AQCG guide used the term Analytical Procedure Lifecycle Management (APLM), however the final version of USP <1220> uses the term Analytical Procedure Lifecycle (APL) and the latter term is used throughout this Guide except where reference to the ECA Guideline is required.

This ECA Guide describes and discusses the lifecycle processes for specifying, purchasing, commissioning, calibrating or verifying correct operation against instrument specifications. Configuring application and control software and ensuring continued operation of analytical instruments and systems as well as decommissioning / retirement of an instrument or system. The primary focus of this guide is for analytical instruments and systems controlling them that are operated under the pharmaceutical GMP regulations. This summary outlines the general principles of the AIQSV Lifecycle that will be discussed in the main body of this guide in some detail and through the illustrative example appendices.

This Guide is intended to provide a synopsis and discussion of current regulatory guidelines and best practices in order that a laboratory user may decide on the scientifically sound and appropriate qualification approach to ensure that analytical instruments and systems are 'fit for intended use' consistent with their particular Quality Management System (QMS) and compliance requirements.

This Guide is not intended to be definitive nor to be seen as a form of regulatory diktat. The illustrative examples provided in the Appendices are intended to help illustrate the principles outlined in this guide but must be interpreted to fit each laboratory's requirements.

This Guide is intended to apply to analytical instruments and systems for both univariate methods such as single wavelength HPLC and UV spectrophotometric assays for example and multivariate methods for identification of materials using FTIR, FTNIR and Raman spectroscopies for example.

Univariate is a term commonly used in statistics to describe a type of data which consists of observations on only a single characteristic or attribute whereas multivariate encompasses the simultaneous observation and analysis of more than one outcome variable.

One of the current difficulties is that there is not an agreed framework with terminology and nomenclature across the breadth of the application of analytical chemistry. This is proving to be a barrier to finding compatible and acceptable approaches. For this reason, the development by Eurachem of an AIQ guideline [2] and the publication of The IUPAC Compendium of Terminology in Analytical Chemistry [3] in 2023 are particularly important in this context that will be discussed later in Section 2.

This barrier is typified by the continued use of the traditional (since the 1990s) modular 4Q's model in some sectors which causes difficulties in developing a cohesive lifecycle approach as discussed in Section 3.1.

Whilst the modular 4Q's model is not used directly in our lifecycle approach, many of its constituent activities are used and the model itself will be discussed.

The purpose of this ECA AQCG guide is to provide;

1. An overview and framework for a suggested lifecycle approach to establishing 'Fitness for Intended Use' for AIQSV including:
    a. the qualification and calibration of analytical instruments and systems as part of an Analytical Procedure Lifecycle (APL)
    b. approaches which are consistent with the principles of the FDA Process Validation guidelines 2011 [4], EU GMP Annex 15 [5] as well as USP General Chapter <1220> [6].

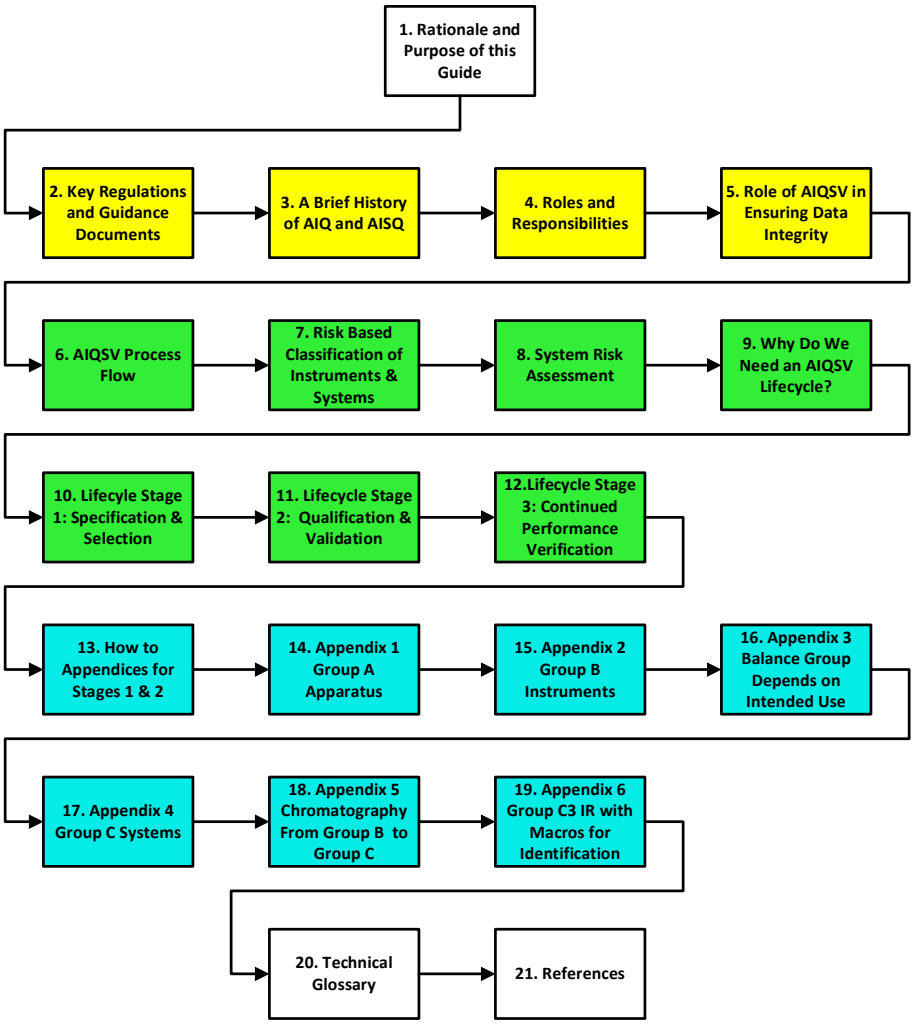
c. Descriptions and recommendations regarding the staged activities in the lifecycle.

2. Support for the on-going update of USP General Chapter <1058> on Analytical Instrument Qualification [7, 8]
3. Integrated instrument qualification and system validation with practical risk-based interpretation of regulations.
4. Guidance on the application of the lifecycle approach for existing instruments and systems.
5. A technical glossary covering terminology and usage, and wherever possible, identifying commonality to avoid confusion.

1.1 How to Use this Guide

The structure of this Guide is shown in Figure 2. After the Rational and Purpose of this are discussed, the Guide is divided into three sections.

Figure 2 Chapters and Appendices of this AIQSV Guide



The structure of this Guide is such that readers can move to a specific chapter depending on their needs at the time.

Yellow Section: Regulations, Guidance, Roles and Responsibilities plus Data Integrity

- This covers a discussion and interpretation of the regulations and guidance for Analytical Instrument Qualification combined with Validation of Laboratory Computerised Systems, a history of AIQ, the roles and responsibilities and how analytical instruments and systems can ensure data integrity in a regulated laboratory.

Green Section: Principles of AIQSV

- Presents a series of seven chapters discussing the process flow for instrument qualification and/or system validation, risk-based classification of analytical instruments and systems, a risk assessment to support the classification based on the intended use of the instrument or system, introduction to the three stages of the AIQSV lifecycle.

Blue Section: How to Appendices – Turning Principles into Practice

- The aim of this portion of the Guide is to turn Principles outlined the previous section into Practice. There are six specific Appendices:
- Group A Apparatus
- Group B instruments
- How the intended use of an analytical balance impacts the USP classification of the instrument
- Group C systems
- Chromatography from the chromatograph to a networked / SaaS chromatography data system
- NIR Spectrometer with macros used for identification of materials

White Section: Technical Glossary and References

The key to success with any instrument qualification with or without integrated system validation is to define the intended use (User Requirements Specification), preferably before selection of the item.

The key to understanding the life cycle is that a 'one size fits all' approach is inappropriate. A flexible approach is critical and that means the same analytical instrument or system could be treated differently depending how the intended use of the item is defined.

1.2 This Guide is not directly based on the 4Qs Model

The lifecycle model presented in this Guide is not solely or directly based on the 4Qs model(s) for several reasons as listed below.

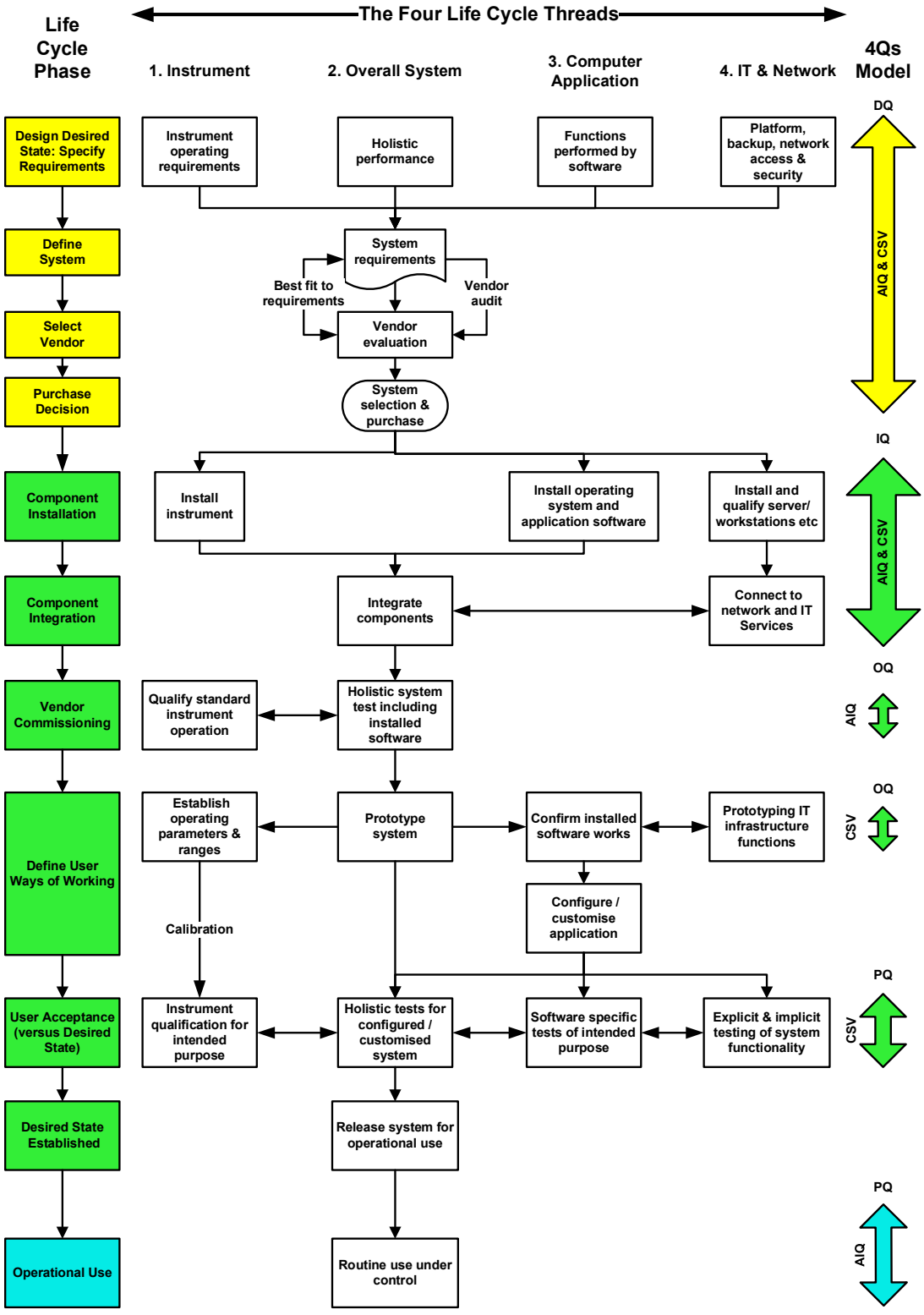
Some of these issues with the 4Qs model were identified 25 years ago.

- Usually, except for specialist analytical research, a laboratory does not design instruments or the controlling software but instead selects a commercial instrument or system. Therefore, a Design Qualification is inappropriate as there is no design to qualify but a selection based on intended use requirements.
- There is confusion between the different 4Qs model used for analytical instruments and the one used for software validation: Operational Qualification (including calibration) of an instrument is testing against user requirements but with software this is called Performance Qualification. If a laboratory has a software OQ performed by a supplier they may think the whole process is complete and the system validated but this leaves a compliance gap which can result in a citation.

- However, for laboratories who have previously aligned their analytical instrument qualification with the 4Q's model (see Figure 5, in Section 3). The lifecycle used in this Guide is seen in Figure 3 includes a high-level mapping of the traditional 4Q model against the proposals within this guide.
- The 4Qs model does not offer sufficient flexibility when it comes to computerised systems and therefore more granularity is required especially where both computer hardware and software need to be installed and commissioned, prototyped, configured and the entire system tested.
- The difference between the activities performed in Operational Qualification and Performance Qualification are often difficult to understand and in some laboratories, and often PQ is just seen as running system suitability test samples.

For these reasons, this Guide has not been based upon the 4Qs model(s) and recommends a flexible lifecycle approach Some activities such as installation and integration or supplier commissioning might be called IQ and OQ but the aim of this Guide is to provide a unified lifecycle model that is applicable to both analytical instruments and laboratory computerised systems. Chapter 4 examines these processes in more detail.

Figure 3: AIQSV Lifecycle Mapped Against the 4Qs Model



1.3 Scope: What's In and What's Out

This Guide covers the following topics:

- **Integrated Analytical Instrument Qualification and Computerised System Validation**: Commercial analytical instruments and computerised systems that control them as well as some software applications associated with analytical instruments e.g. bioassay collation and reporting software. These instruments and systems can be standalone, networked to informatics applications on a single site, a global system or in the Cloud via Software as a Service (SaaS). The configuration of the instrument or system operating in a regulated laboratory must be documented and placed under change control.
- **User Defined Programs and Macros.** Written to control instruments or process data.
  Note, the development and validation of analytical procedures is outside the scope of this Guide.
- **GMP Laboratories**: This Guide's primary audience are GMP regulated Analytical Development and Quality Control laboratories in the pharmaceutical and biotechnology industries as well as Contract Research Organisations (CROs) and Contract Manufacturing Organisations (CMOs)
- **Instrument and System Suppliers**: Organisations supplying commercial analytical instruments and systems to the organisations listed above will find this Guide helpful in understanding the overall approach for integrated qualification and validation in GMP regulated laboratories
- **Unregulated Research Laboratories**: Transfer of analytical procedures to Analytical Development and Quality Control laboratories in research will benefit from qualifying their instruments to help enable a better and more efficient technology transfer process
- **GLP and ISO/IEC 17025 Certified Laboratories**: The principles outlined here can also be applied to laboratories working to Good Laboratory Practice (GLP) and ISO/IEC 17025.

The following topics are excluded from the scope of this Guide:

- Non-commercial instruments and commercial instruments with custom hardware components
- Custom software applications
- Process control & Process Analytical Technology (PAT) instruments. The general principles outlined in this Guide apply for the instrument / sensor and controlling software but the multivariate software and statistical analysis are excluded from the scope.
- Laboratory Information Management Systems (LIMS), Electronic Laboratory Notebooks(ELN) and Laboratory Execution Systems (LES) without physical instrument connections
- Spreadsheets as the data integrity aspects are covered in the ECA Data Integrity and Data Governance Guide [9]

1.3.1 Computerised System Validation (CSV) or Computer Software Assurance (CSA)?

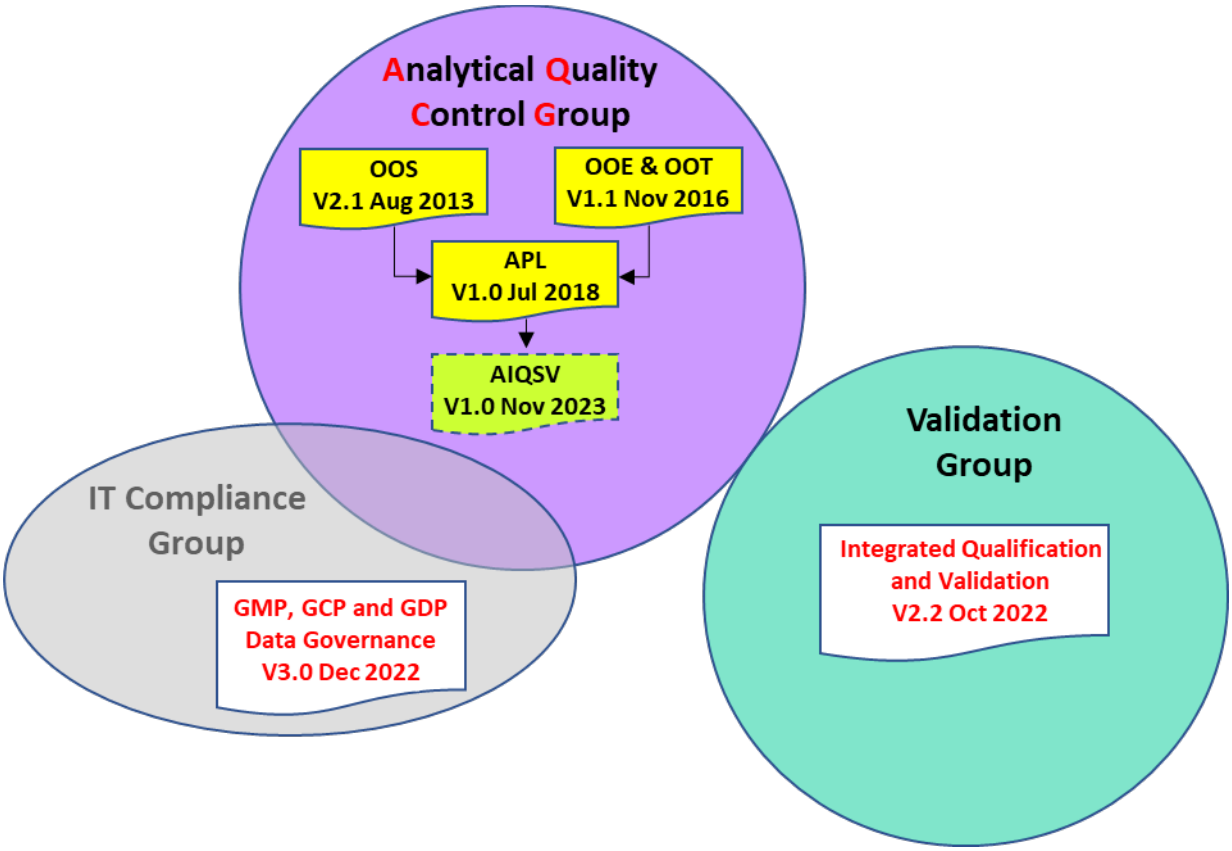
Although CSA has been touted as the replacement of CSV, the publication of the draft FDA guidance on the subject [10] in 2022 has shown that this is not the case as it will only replace one section of the FDA's General Principles of Software Validation [11]. Two articles critical of CSA are available [12, 13] as there is little in the draft guidance that replaced a risk-based and pragmatic interpretation of GMP regulations. Therefore, this guide will only refer to CSV.

1.4 Links to other ECA Guides

This guide forms part of a set of ECA Guide and are available on the member's area of the ECA website for download. As shown in Figure 3, the current ECA guidelines are:

- OOS Guideline, v2.1, August 2013 [14]
- OOE & OOT Guideline; v1.1 November 2016 [15]
- GMP, GCP & GDP Data Integrity and Data Governance Guideline; v3.0 2022 [9]
- Analytical Procedure Lifecycle Management (APLM), v1.0 July 2018 [16]
- Integrated Qualification and Validation Guideline V2.2 2022 [17]

Figure 4: Relationship with other ECA Guidelines



2 Key Regulations, Standards and Guidance Documents

This section includes an overview of current requirements associated with:

- Good Manufacturing Practice (GMP) Regulations and Guidance
- USP <1058> Analytical Instrument Qualification
- Good Laboratory Practice (GLP) Regulations and Guidance
- GAMP 5 Guide and Good Practice Guides
- Regulatory and Industry Data Integrity Guidances
- ISO/IEC 17025: 2017

It is critical to read, understand and interpret applicable GXP regulations, ISO standards and regulatory guidance documents and therefore this section is essential reading for members.

As ECA membership extends outside of the European Union, references to EU GMP implicitly reference PIC/S GMP which is identical except the reference to Qualified Person (EU) and Authorised Person (PIC/S).

It should be noted that most regulations and guidance documents lack consistent use of qualification and validation.

2.1 Good Manufacturing Practice (GMP) Regulations and Guidance

2.1.1 US GMP 21 CFR 211

US GMP was promulgated in 1978 before widespread computerisation in laboratories. There are two main sections applicable to qualification of analytical instruments and systems. Owing to the age of the cGMP regulations analytical instruments and systems are referred to as equipment.

> **Sec 211.63 Equipment design, size, and location**.
>
> *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 [18].*

The GMP regulations are simple as can be seen in bold text above and all are to be related to the definition of intended use.

> **Sec. 211.160 General requirements**.
>
> *(b) Laboratory controls shall include the* ***establishment of scientifically sound and appropriate*** *specifications, standards, sampling plans, and* ***test procedures*** *designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:…..*
>
> *(4) The* ***calibration of instruments****, apparatus, gauges, and recording devices at suitable intervals in accordance with an* ***established written program*** *containing specific directions, schedules,* ***limits for accuracy and precision****, and provisions for* ***remedial action*** *in the event accuracy and/or precision limits are*

> *not met.* ***Instruments****, apparatus, gauges, and recording devices* ***not meeting established specifications shall not be used*** [18].

All laboratory work must be scientifically sound including qualification of analytical instruments and validation of computerised systems; records of these activities must be retained as required by 21 CFR 211.194(d) [18]. As US GMP was issued in 1978, instruments must be calibrated rather than qualified which is a later concept. Therefore, most FDA 483 and warning letter citations refer to lack of instrument calibration rather than qualification deficiencies.

2.1.2 EU GMP Chapter 3: Premises and Equipment

The EU GMP regulation for equipment is even shorter than the US requirement but has the same intent and purpose.

> 3.34 *Manufacturing equipment should be* ***designed, located*** *and maintained to suit its* ***intended purpose*** [19].

2.1.3 EU GMP Chapter 6: Quality Control

The following clauses of Chapter 6 ae applicable for AIQSV:

- 6.5 … Laboratory equipment **should not be routinely moved between high risk areas** to avoid accidental cross-contamination.
- 6.6 The personnel, premises, and **equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations**
- 6.7 iii. **Procedures for and records of the calibration/qualification of instruments and maintenance of equipment**;

2.1.4 EU GMP Part II (ICH Q7)

EU GMP Part II or ICH Q7 has requirements for calibration and qualification of analytical instruments although *appropriate qualification* is vague:

- 5.30 **Control, weighing, measuring, monitoring and test equipment** that is critical for assuring the quality of intermediates or APIs should be **calibrated according to written procedures and an established schedule**.
- 12.82 **Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods**

2.1.5 EU GMP Annex 15: Qualification and Validation

The General clause of Annex 15 states:

> A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the **scope and extent of qualification and validation** should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes.

The Principle also states:

> Computerised systems used for the manufacture of medicinal products **should also be** validated according to the requirements of Annex 11.

Therefore, computerised systems need to have the hardware components qualified and the overall system validated as the integrated approach advocated in this Guide.

Three further clauses from Annex 15 are relevant to this Guide. The first is the ability to combine qualification documents in Clause 2.5:

> ***Qualification documents may be combined together**, where appropriate, e.g. installation qualification (IQ) and operational qualification (OQ) [5].*

This can be extended for some simpler Group C Type 1 systems where all phases of the life cycle can be combined into a single Integrated Validation Document (IVD) as discussed in Section 9.8. This document comprises a simple system description, user requirements, software configuration, traceability, test preparation, testing instructions with acceptance criteria, assumptions, exclusions and limitation of the testing, managing test deviations and a summary report [20].

The next two clauses show the order of work: defining the intended use of the instrument or system in a User Requirements Specification followed by the Design Qualification.

> **User requirements specification (URS)**
> 3.2. *The **specification for equipment**, facilities, utilities or systems should be **defined in a URS** and/or a functional specification. The essential elements of quality need to be built in at this stage and any GMP risks mitigated to an acceptable level. **The URS should be a point of reference throughout the validation life cycle**.*
> **Design qualification (DQ)**
> 3.3. *The next element in the qualification of equipment, facilities, utilities, or systems is DQ where the compliance of the design with GMP should be demonstrated and documented. The **requirements of the user requirements specification should be verified** during the design qualification [5].*

However, for analytical instruments and systems, a DQ phase is inappropriate because the laboratory usually does not design anything. What should happen in practice is that one or more instruments or systems are evaluated against the laboratory URS and the best one is selected and justified. A selection report replaces a DQ in this Guide.

2.1.6 EU GMP Annex 11 Computerised Systems

As stated in Annex 15, a computerised system must be validated under the requirements of EU GMP Annex 11 [21]. This applies to analytical systems with a separate workstation with installed software controlling the analytical instrument for acquiring, processing and storing data and reporting results (these are USP Group C systems as discussed in Section 2.2). The Principle of Annex 11 states that *IT infrastructure should be qualified*. This is assumed as the topic is out of scope in this Guide. The focus here are the main requirements of the Annex as applied to analytical systems:

- Risk management should be applied throughout the life cycle.
- Personnel must co-operate and have the qualifications and access permissions to perform their duties. This includes the supplier and IT. From a data integrity perspective, conflicts of interest should be avoided e.g. users with administrator privileges.
- Service providers, including IT, need an agreement covering the services offered and the roles and responsibilities offered. The need for an audit should be assessed and if carried out the report must be shown to inspectors on demand.
- The system must be validated. This includes defining intended use requirements that must be traceable throughout the system lifecycle. Requirements must include functional use, audit trail, electronic signature use (where implemented). In addition, the configuration settings must be documented as these define the intended use of the system. Testing must ensure that the intended use requirements are met.
- Once released for operational use the system must be under change control.
- IT support includes the following functions that will be part of the agreement mentioned earlier:
    - Backup and recovery
    - User account administration
    - Application administration and change control
    - Incident and problem management
    - Time synchronisation
    - Cybersecurity
    - Business continuity planning

Currently, Annex 11 is being revised and a new update is planned for late 2026 by EMA and PIC/S.

2.2 USP <1058> Analytical Instrument Qualification

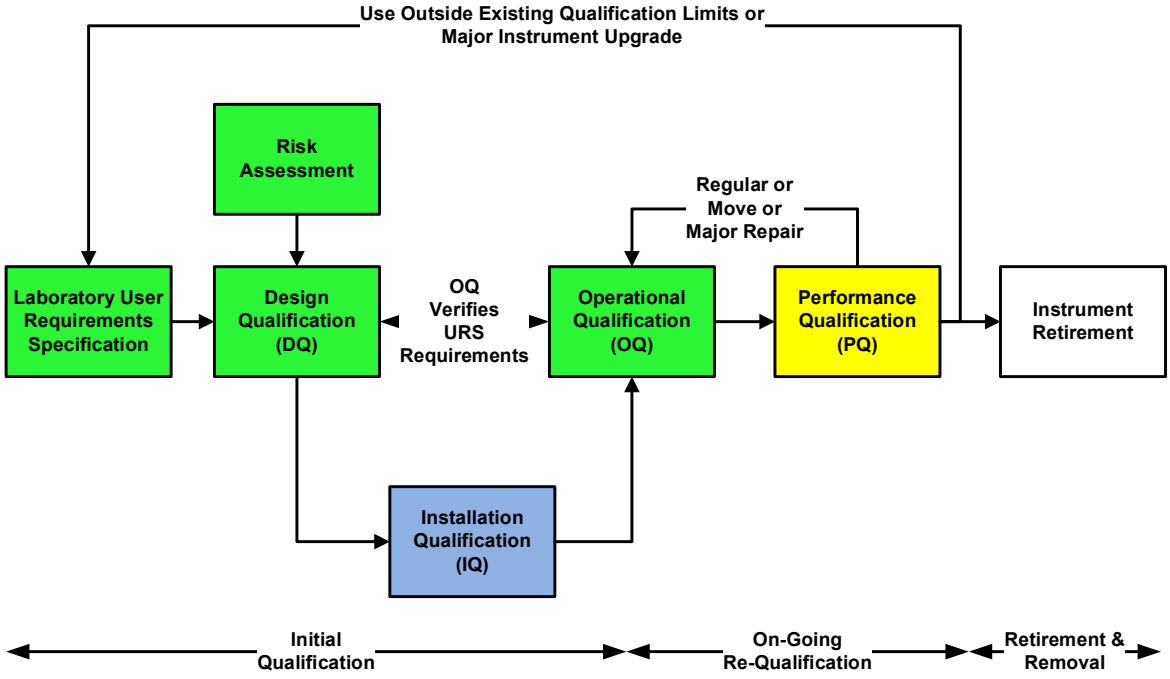
The United States Pharmacopoeia is the only pharmacopoeia to have a general chapter on analytical instrument qualification. USP <1058> is an informational (strong guidance) general chapter for the process for qualifying and validating instruments and systems but is implicitly lined to the mandatory general chapters that contain the instrument parameters and acceptance criteria that must be applied for each analytical technique. The history of USP <1058> is found in Section 4 of this Guide.

USP <1058> has a three-level risk-based classification (A to C) of apparatus, instruments and systems which are [22]:

- **Group A Apparatus**
  No measurement capability (e.g. nitrogen evaporator) or user calibration (e.g. volumetric flask). Qualification is by observation only.
- **Group B Instruments**
  Instruments that control a physical parameter (e.g. water bath) or have measurement capability (e.g. analytical balance)
- **Group C Systems**
  Instruments controlled by a separate computerised system (e.g. IR spectrometer)

More detail about these groups and the subtypes of each one is to be found in Section 7 and a risk assessment and classification system is described in Section 8.

Figure 5: Depiction of the AIQ 4Qs as a V Model [23]



Integrated instrument qualification and computer validation consists of four phases as shown in Figure 4 and the definitions of each are given below [22]:

- **Design Qualification**: DQ is the documented collection of activities that define the functional and operational specifications and intended use of the instrument.
    - The first stage is the writing of a laboratory user requirements specification for the instrument or system that states what the laboratory wants the instrument to do
    - The DQ (this can also be called design verification) shows that the selected instrument is suitable.
    - DQ may be performed by the instrument manufacturer or the user.
    - It is expected that user requirements will be minimal for commercial, off-the- shelf instruments.
    - Verification that the instrument specifications meet the desired functional requirements may suffice.
- **Installation Qualification**: 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.
    - For any instrument that exists on site but has not been previously qualified, or not qualified to current industry standards, existing documents should be collated and a risk assessment should be undertaken to determine the best course of action.
- **Operational Qualification**: 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.

- **Performance Qualification**: 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 intended use 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.

There are several issues with these definitions for AIQSV including:

- AIQ does not mention the requirements of the analytical procedure(s) to the run on the instrument or system as shown in Figure 1 – it is only implied.
- Writing the URS is a laboratory responsibility and not that of the supplier. The laboratory may use the supplier's specifications as a basis for their requirements but the URS needs to ensure regulatory compliance especially for ensuring data integrity.
- DQ mixes specification and selection.
- There is also a problem with PQ since many laboratories quality assurance functions still see the PQ as a defined limited validation activity after OQ and not as continuous monitoring of instrument performance throughout the life cycle of the instrument.

2.3 Good Laboratory Practice (GLP) Regulations and Guidance

2.3.1 US GLP 21 CFR 58

The US GLP requirements for equipment are similar to the US GMP regulations:

> 21 CFR 58.61: ***Equipment*** *used in the generation, measurement, or assessment of data and equipment used for facility environmental control shall be of* ***appropriate design and adequate capacity*** *to* ***function according to the protocol*** *and shall be* ***suitably located*** *for operation, inspection, cleaning, and maintenance [24].*

Whilst there is no explicit requirement for intended use, there is a requirement for the instrument to function according to the protocol which implies the same.

2.3.2 OECD GLP Principles of Good Laboratory Practice

Section 4 of OECD (Organisation of Economic Co-operation and Development) defines the requirements for Apparatus, Material, and Reagents, the first term refers to analytical instruments and computerised systems.

> 4.1. *Apparatus, including* ***validated computerised systems****, used for the generation, storage and retrieval of data, and for controlling environmental factors relevant to the study should be* ***suitably located*** *and of* ***appropriate design*** *and* ***adequate capacity*** [25].
> 4.2. *Apparatus used in a study should be periodically inspected, cleaned, maintained, and* ***calibrated according to Standard Operating Procedures****.* ***Records*** *of these activities should be* ***maintained****.* ***Calibration*** *should, where appropriate, be* ***traceable to national or international standards of measurement [25]****.*

For the first time in GXP regulations, we see that analytical instruments must be calibrated to national or international standards of measurement.

2.4 GAMP© 5 Guide and Good Practice Guides

2.4.1 GAMP© 5 Second Edition

All GAMP© guides have contained a classification of software in Appendix M4. Originally there were five categories but since the publication of GAMP© 5 first and second editions category 2 (firmware) has been discontinued [26, 27]. This is very disappointing as all USP <1058> Group B instruments contain firmware.

This Guide will ignore the fact that Category 2 software has been discontinued and reinstate it.

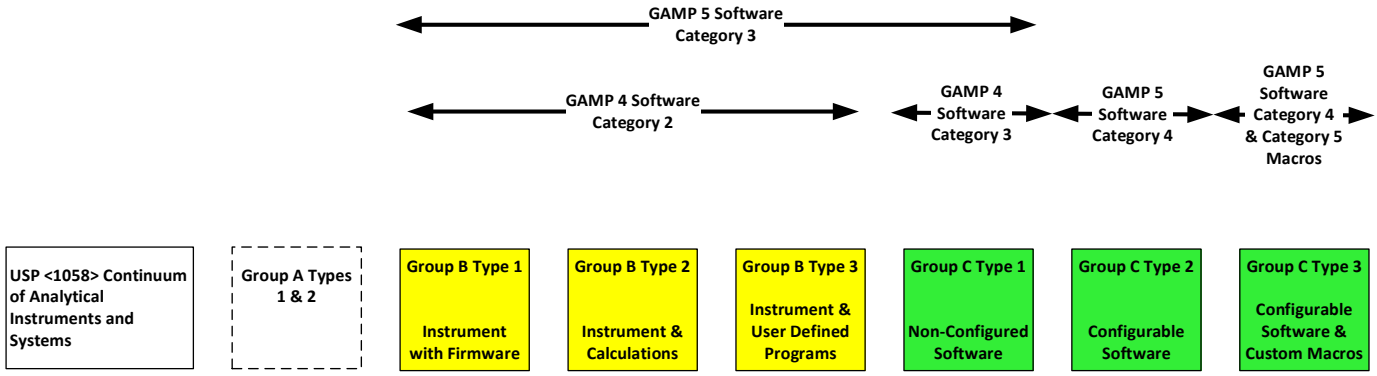
The categories of software used in this Guide are:

- **Category 1: Infrastructure Software**
  Operating systems, databases, languages and applications for cybersecurity, backup and restore, network management, help desk, hypervisor (for virtualisation)
- **Category 2: Firmware**
  Instruments controlled by software on a chip. This can be upgraded remotely or by the user both under change control and some instrument firmware can perform embedded calculations or allow the user to write application programs.
- **Category 3: Non-configured Commercial Product**
  The business process cannot be changed by the user. Run-time configuration can be performed e.g. definition of user roles and access privileges plus reports
- **Category 4: Configurable Commercial Product**
  The business process can be altered by the user. The mechanism varies from simple switches turning a function on or off to a language provided by the supplier (the latter is on the boarder of category 5 software).
- **Category 5: Custom Application and Modules**
  This category ranges from modules of custom code that are integrated with a commercial application or a complete application of custom code. This guide will only consider modules of custom code integrated with a commercial application, typically Category 4 software.

2.4.2 Mapping USP Groups to GAMP© Software Categories

Vuolo-Schuessler et al [28] discussed the USP <1058> instrument groups and mapped them versus the GAMP© 5 software categories. As this Guide has reinstated software Category 2, Figure 5 maps the software categories from GAMP© 4 [29] and GAMP© 5 [26, 27] against the USP <1058> groups [22].

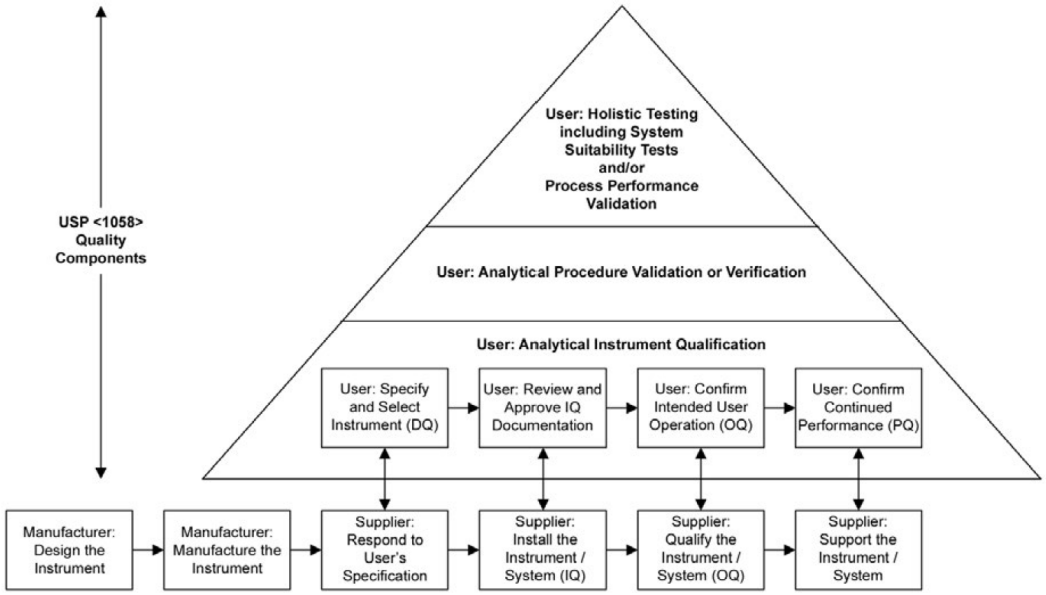
Figure 6: Mapping USP <1058> Groups to GAMP© Versions 4 and 5 Software Categories



As can be seen in the current GAMP© 5 Second Edition software Category 3 [27] encompasses a wide range of USP <1058> instruments: all Group B instruments and Group C type 1 systems. However for the purposes of this Guide and to align with the USP <1058> approach, the GAMP© 4 software Category 2 firmware has been reinstated to ensure a complete match with USP <1058> Groups and as it is a core requirement for all Group B instruments.

In an earlier article, a proposal was also made to modify and enhance the existing data quality triangle in USP<1058> [22] in **Figure 6** to show the extensive role of the supplier [30].

Figure 7: Proposed enhancement of the Quality Triangle in <1058> [30]



2.5 Regulatory and Industry Data Integrity Guidances

There are a wide variety of data integrity guidances available from regulatory authorities:

- GXP Data Integrity Guidance and Definitions, Medicines and Healthcare products Regulatory Agency MHRA [31-33]
- WHO Technical Report Series No.996 Annex 5 Guidance on Good Data and Records Management Practices, World Health Organisation [34] Note, this Guide ignores the 2021 guidance that replaced this document as it is a poor substitute.
- Guidance for Industry Data Integrity and Compliance With Drug CGMP Questions and Answers, Food and Drug Administration [35]
- PIC/S PI-041 Good Practices for Data Management and Integrity in Regulated GMP / GDP Environments Draft, Pharmaceutical Inspection Convention / Pharmaceutical Inspection Cooperation Scheme [36]
- OECD Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring, Number 22, Advisory Document of the Working Party on Good Laboratory Practice on GLP Data Integrity, Organisation of Economic Cooperation and Development [37]

As well as industry bodies:

- GAMP© Guide on Records and Data Integrity, International Society for Pharmaceutical Engineering [38]
- GAMP© Good Practice Guide on Data Integrity by Design, International Society for Pharmaceutical Engineering [39]
- Technical Report 80: Data Integrity Management System for Pharmaceutical Laboratories, Parenteral Drug Association (PDA) [40]
- Practical risk-based guide for managing data integrity, Active Pharmaceutical Ingredients Committee (APIC) [41]

The advice from these guidances will not be discussed further in this Guide as the ECA Data Integrity and Data Governance Guide [9] already has this information and readers are referred there.

However, where appropriate, specific data integrity considerations will be referenced in this Guide concerning qualification of instruments and validation of software.

2.6 ISO/IEC 17025: 2017 General Requirements for the Competence of Testing and Calibration Laboratories

Section 6.4 covers Equipment including measuring instruments and software and has similar requirements to GMP and GLP regulations but in much more detail than you can see in Sections 3.1 and 3.3: *In this version of the standard the term Equipment is used to refer to all types of laboratory resources, including measuring equipment, reference standards, reference materials, reagents, consumables, etc*. The relevant parts are listed here [42].

- *6.4.4 The laboratory shall verify that equipment conforms to specified requirements before being placed or returned into services*
- *6.4.5 The equipment used for measurement shall be capable of achieving the measurement accuracy and/or measurement uncertainty required to provide a valid result.*
- *6.4.6 Measuring equipment shall be calibrated when:*

- *the measurement accuracy or measurement uncertainty affects the validity of the reported results, and/or*
- *calibration of the equipment is required to establish the metrological traceability of the reported results.*

- *Types of equipment having an effect on the validity of the reported results can include*:
  - *those used for the direct measurement of the measurand, e.g. use of a balance to perform a mass measurement*
  - *those used to make corrections to the measured value, e.g. temperature measurements*
  - *those used to obtain a measurement result calculated from multiple quantities.*
- *6.4.7 The laboratory shall establish a calibration programme, which shall be reviewed and adjusted as necessary in order to maintain confidence in the status of calibration.*
- *6.4.8 All equipment requiring calibration or which has a defined period of validity shall be labelled, coded or otherwise identified to allow the user of the equipment to readily identify the status of calibration or period of validity* [42].

The issue with ISO/IEC 17025, from a pharmaceutical perspective, comes with the requirements for software.

> *Clause 7.11.2 The laboratory information management system(s) used for the collection, processing, recording, reporting, storage or retrieval of data shall be validated for functionality, including proper functioning of interfaces within the LIMS by the laboratory before introduction. Whenever there are any changes, including laboratory software configuration of modifications to commercial off-the-shelf software, they shall be authorised, documented and validated before implementation* [42].

There is no definition of the term validation in the context of software in the standard. However, the major problem comes in Note 2 of this clause.

> *Note 2: Commercial-off-the-shelf software in general use within its designed application range can be considered to be sufficiently validate*d [42].

This is marked contrast with the FDA comment 65 in the preamble to 21 CFR 11 regulations for electronic records and electronic signatures:

> *One comment suggested qualifying the proposed validation requirement in § 11.10(a) to state that validation be performed ''where necessary'' and argued that validation of commercially available software is not necessary because such software has already been thoroughly validated. The comment acknowledged that validation may be required for application programs written by manufacturers and others for special needs.*
>
> *The agency disagrees with the comment's claim that all commercial software has been validated. The agency believes that* ***commercial availability is no guarantee that software has undergone ''thorough validation''*** *and is* ***unaware of any regulatory entity that has jurisdiction over general purpose software producers****. The agency notes that, in general,* ***commercial software packages*** *are accompanied not by statements of suitability or compliance with established standards, but rather by* ***disclaimers as to their fitness for use****.*
>
> *The agency is aware of the complex and sometimes controversial issues in validating commercial software. However, the need to validate such software is not diminished by the fact that it was not written by those who will use the software* [43].

There are both GMP regulatory requirements and expectations for validation of software that will be outlined in this Guide. Qualification of an ISO/IEC 17015 laboratory must be undertaken if it is to be used for GMP analysis to ensure that work meets GMP regulations especially to ensure that technical controls are in place to ensure that data integrity, ALCOA++ criteria are met and complete data are generated; furthermore any OOS results are communicated to the sponsor organisation in a timely manner.
In addition, ISO/IEC 17025 is referenced also for the requirements of medical laboratories [44].

2.7 Official Medicines Control Laboratories Guidance Documents

Official Medicines Control Laboratories (OMCLs) have developed a very short core guideline (8 pages) on Qualification of Equipment which was updated in 2018 and has 10 specific analytical instrument annexes . These documents may be found on the OMCL website [45].

The core document states;

> *'The standard ISO/IEC 17025 requires that a laboratory shall have access to equipment that is required for the correct performance of laboratory activities. In particular, calibration programmes shall be established, reviewed and adjusted, including intermediate checks to maintain confidence in the calibration status. In order to guarantee harmonised interpretation and application of ISO/IEC 17025 requirements within the OMCL Network, the guideline "Qualification of Equipment" has been elaborated.'*

and

> *'From experience, the terms DQ (Design Qualification), IQ (Installation Qualification), OQ (Operational Qualification) and PQ (Performance Qualification) (not explicitly mentioned by ISO/IEC 17025) have been used in a non-harmonised way by the OMCLs. Therefore these terms have not been used in this document. This does not exclude their use in OMCL quality systems.'*

OMCL defines four levels of lifecycle activity ;

- Level I. Selection of instruments and suppliers
- Level II. Installation and release for use
- Level III. Periodic and motivated instrument checks
- Level IV. In-use instrument checks

The 10 annexes cover;

- Annex 1: Qualification of HPLC equipment (Levels III and IV)
- Annex 2: Qualification of GC equipment (Levels III and IV)
- Annex 3: Qualification of UV-Visible spectrophotometers (Levels I, III and IV)
- Annex 4: Qualification of IR spectrophotometers (Levels I, III and IV)
- Annex 5: Qualification of automatic titrators (Levels III and IV)
- Annex 6: Qualification of piston pipettes (Levels III and IV)
- Annex 7: Qualification of mass spectrometers (Levels III and IV)
- Annex 8 : Qualification of balances (Levels I to IV)
- Annex 9: Calibration/qualification of pH meters (Levels I to IV)
- Annex 10: Qualification of Atomic Absorption/Atomic Emission Spectrometers (Levels III and IV)

Strangely, all the 4 OMCL stages of the lifecycle are not covered in the annexes with the exception of balances.

In addition, the focus is on equipment not systems.

Validation of Computerised Systems is described in a separate core document, PA/PH/OMCL (08) 69 R7, and is not connected to the equipment guideline. It also states that

'This document should be considered as a guide to OMCLs for planning, performing and documenting the validation of their computerised systems. ***It is left to the professional judgement and background experience of each OMCL to decide on the most relevant procedures to be undertaken*** *in order to give evidence that their computerised systems are working properly and are appropriate for their intended use'*

Such an approach across laboratories is probably unacceptable under the GMPs for example, Annex 11 of EU GMP.

2.8 Traceable Standards for Calibration of Instruments and Systems & ISO 17034:2017

The use of traceable reference materials for the calibration and qualification of analytical instruments and systems is a requirement wherever practicable. The use of such reference standards is mandated by the major Pharmacopeias, European Pharmacopoeia (Ph. Eur.), the United States Pharmacopoeia (USP), the Japanese Pharmacopoeia (JP) , the British Pharmacopoeia (BP) as well as The International Pharmacopoeia (Ph. Int.) of the World Health Organisation (WHO). In addition, ISO 9001:2015 requires that;

> *an essential part of providing confidence in the validity of measurement results, measuring equipment shall be calibrated or verified, or both, at specified intervals, or prior to use, against measurement standards traceable to international or national measurement standards [46].*

ISO 17034 specifies general requirements for the competence and consistent operation of reference material producers [47]. It is intended to be used as part of the general quality assurance procedures of the reference material producer. The reference material producer shall also ensure that measuring equipment used in reference material production is used in compliance with the relevant requirements of ISO/IEC 17025 6.4.6 [See Section 3.6].

Details of specific traceable calibration materials will not be covered in this guide. The Pharmacopeias are the source for many requirements. Spectroscopic standards are widely used (e.g. caffeine and holmium for UV-VIS spectrometers) and further details may be found in the literature, for example for wavelength calibration in the NIR [48].

2.9 IUPAC Compendium of Terminology in Analytical Chemistry & Eurachem Equipment Qualification Draft Guide

There has long been a disconnection between the pharmaceutical requirements and the wider analytical chemistry community particularly in respect of nomenclature and terminology. The International Union for Pure and Applied Chemistry (IUPAC) produced the 1st edition of the Orange Book on Compendium of Analytical Nomenclature, Definitive Rules in 1977 and a 3rd edition in 1998. This book focused on technical aspects almost exclusively and did not reference validation or verification aspects explicitly. These omissions were remarkable as, in its intent, it stated that;

> *As analytical methods have become indispensable in nearly all fields of human activity, including research, development, production and service, straight forward, unambiguous nomenclature has become an absolute prerequisite.*

It did have a chapter on Quality Assurance of Analytical Processes but sadly the section 18.5, 'Calibration, standardization', was omitted as the source paper was not yet published and 18.6.1 on Quality Assurance in analytical laboratories was minimal.

Fortunately, after a gap of 25 years, a 4th Edition has been produced which now includes an entire chapter on Quality in Analytical Chemistry [3].

The key IUPAC 2023 definitions relating to quality are primarily based on ISO 9001:2015. These are summarised in Figure 8.

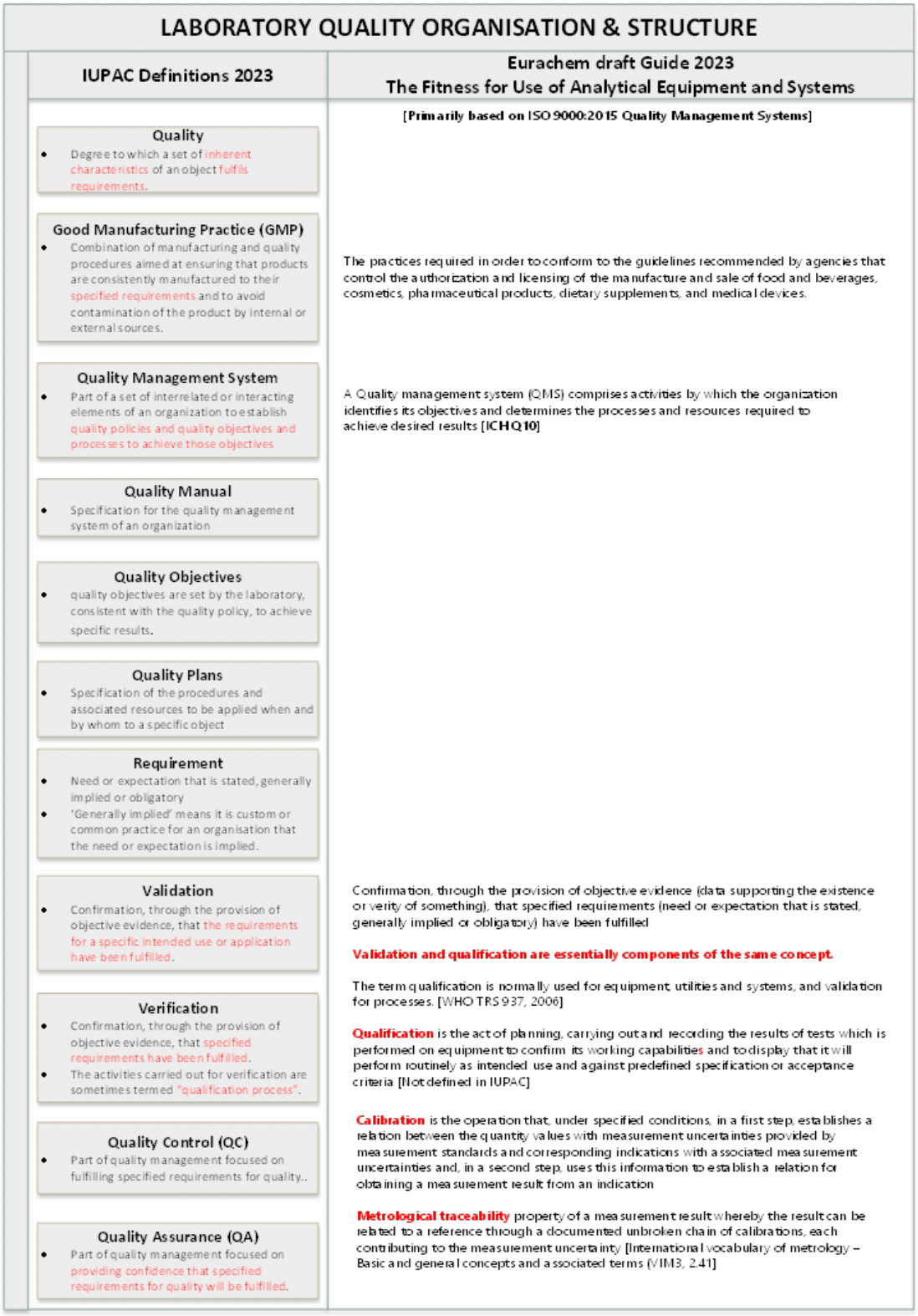
From a harmonisation viewpoint, the fact that ISO, IUPAC and the GMPs are all defining requirements as critical to validation and verification confirmation is a huge step forward.

In addition, also in 2023, Eurachem are in the process of drafting a guideline, for the first time, on 'The Fitness for Purpose of Analytical Equipment' A Laboratory Guide to the Life Cycle of Analytical Equipment, Equipment Qualification and Related Topics' [2]

Notwithstanding some issues with terminology, the draft provides a linkage between IUPAC and the ISO world which is compatible with the current and proposed processes within the pharmaceutical industry under the GMPs and pharmacopeial requirements.

These linkages are illustrated in Figure 8

Figure 8: IUPAC & Eurachem Quality & Organisation definitions



3 Brief History of AIQ and AIQSV

3.1 Equipment Qualification

The origin of a formalised process for the assurance of proper function of analytical instruments and systems occurred in the UK in the 1980's & 1990's. Two distinct organisations, the Analytical Methods Committee of the Analytical Division of the Royal Society of Chemistry (RSC) and a group from the Laboratory of the Government Chemist (LGC) as part of a government initiative the VAM (Valid Analytical Measurement) programme. There was an overlap and collaboration between these groups. The RSC initiative published by Instrumental Criteria Sub-Committee Reports in the Analyst, Analytical Proceedings of the Royal Society of Chemistry & AQUAL as well as Technical Briefs started in 1984.

The first formal paper on the 4Qs model was published in 1996 with the title ***The Development and Application of Guidance on Equipment Qualification of Analytical Instruments*** [49]**.**

From the outset issues with this model were identified:

> *The Working Group identified several aspects of EQ which caused particular problems.*
>
> *DQ is seen as primarily for manufacturers of instruments. Clearly this is true in relation to the design of the instrument itself, but an important aspect of the guidance has been to emphasise the role that users of instruments have in considering the intended use of the instrument and agreeing appropriate specifications with manufacturers and suppliers prior to its purchase.*
>
> *There is also confusion regarding the distinction between OQ and PQ* [49].

However, these were not considered to be insurmountable and the use of the model prevailed, confusion notwithstanding, which has continued for the next quarter of a century.

3.2 Analytical Instrument Qualification and USP <1058> 2008

USP <1058> [22] originated at a conference organized by the AAPS (American Association of Pharmaceutical Scientists) in 2003 entitled "Analytical Instrument Validation" where regulators, industry and suppliers were key participants. The first thing to change was "validation" because the attendees agreed that instruments are qualified and processes, methods, and computer systems are validated. Thus, analytical instrument qualification was born.

AAPS published a white paper of the conference in 2004 [50] and this was the basis of the draft of a proposed USP general chapter <1058> in 2005, and following review cycles it became effective in 2008. It is worth remembering at this point that USP general chapters between <1> and <999> are mandatory and those between <1000> and <1999> are informational in nature (strong guidance).

3.3 Analytical Instrument Qualification and USP <1058> 2017

AAPS held a session on the status of USP <1058> in November 2011 which included a critique by McDowall which was also published the same month [30]. An outcome from the meeting was the writing of a Stimulus to the Review Process article by Burgess and McDowall [51] in 2012. This proposed more granularity in Groups B and C and an integrated approach to analytical instrument qualification and computerised system validation (AIQ-CSV). For the first point there was more granularity for Group B instruments and Group C computerised systems to ensure that calculations and user defined programs were verified and an appropriate amount of validation was performed by the users for the second group. This includes the separation of configuration and customisation of software. Following public comments, a draft update to <1058> was issued in 2014 which after further review and became effective in 2018 [22].

3.4 Analytical Instrument Qualification and System Validation: Updating USP <1058>

Currently, a USP Expert Committee is reviewing and revising USP <1058> and the proposal is to change the title of the general chapter to Analytical Instrument Qualification and System Validation (AIQSV).

It has published three Stimulus to the Revision Process articles in Pharmacopoeial Forum for public comment on:

- A Life Cycle Approach to the Calibration and Qualification of Analytical Instruments and Systems to Establish "Fitness for Purpose" for Pharmacopeial Purposes, July 2020 [52]
- Analytical Instrument and System (AIS) Qualification, to support Analytical Procedure Validation over the Life Cycle, January 2022 [8]
- Measurement Uncertainty Evaluation Relevant to Analytical Instrument and System (AIS) Qualification—The Role of Measurement Uncertainty Concepts within the AIS, March 2022 [53]

The aim is to draft and issue a new draft of USP <1058> for public comment in 2024.

4 Roles and Responsibilities in AIQSV

There are multiple roles involved in AIQSV. Depending on the analytical instrument or system, its intended use and overall size the following roles and responsibilities may be involved in qualification and/or validation.

The minimum roles for a Group B instrument would be:

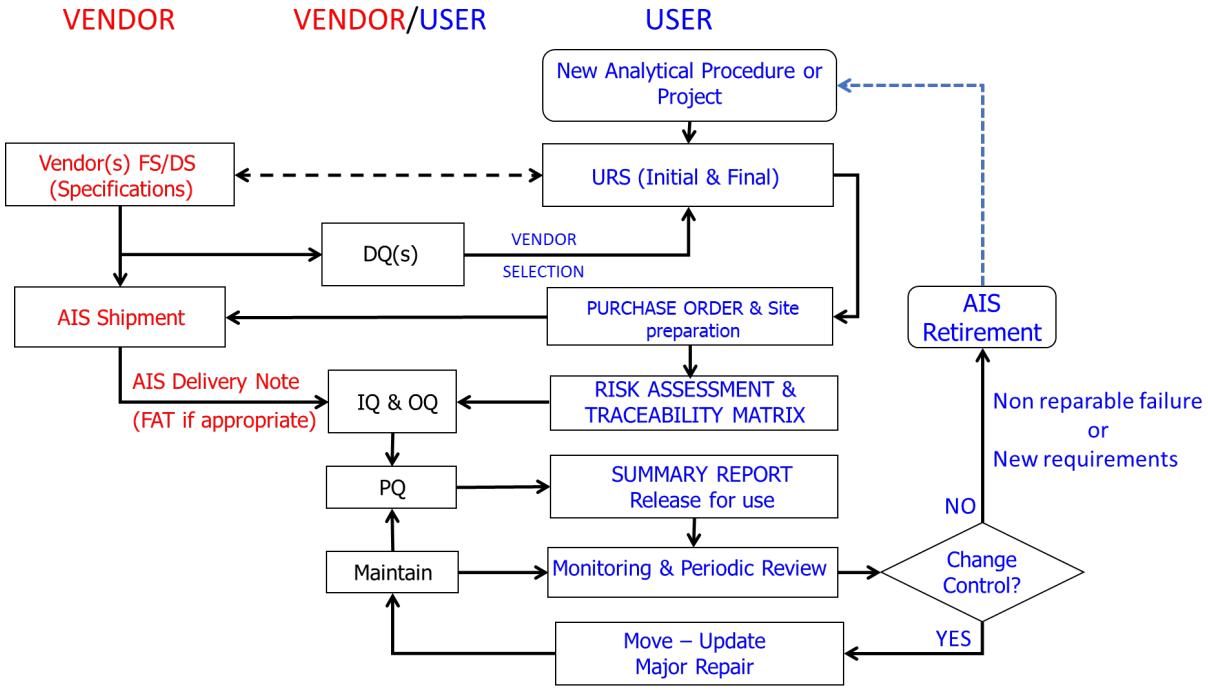
- Process Owner (who is also the data owner for data integrity and data governance),
- Users,
- Quality Assurance
- Supplier.

For a Group C system, additional roles required are:

- System Owner for IT platform support, records backup, cybersecurity, application administration etc.
- CSV group or consultant

In 2022, the USP JSC proposed an illustrative Life cycle model for AIS, to assign possible roles and responsibilities as part of the lifecycle process [8]. This proposal still retains the original 4Qs model nomenclature from USP <1058>.

Figure 9 USP illustrative AIQSV lifecycle [8]



- Maintain also includes repair and requalification
- Vendor's role in maintenance and repair is missing
- Vendor can also be in-house metrology group or support company during operational phase

4.1 Laboratory Roles

The most important role in the laboratory is the process owner, a role defined in EU GMP Annex 11 [21]

- **Process Owner**: *The person responsible for the business process* [21]
  Responsible and accountable for all qualification work and the data generated throughout the life cycle of the instrument or system.
  Granting, modifying or revoking user access to the instrument or system
  Responsible for that procedures and systems are in place to maintain and trending data from the instrument or system
  The process owner of a computerised system is also the data owner
  Authorising change control of an instrument or system
  Works with the System Owner to agree IT support of the analytical system formalised in an agreement.
  Note, that for a standalone Group C system the process owner is also the system owner

Other laboratory roles and responsibilities can be:

- **Users**: Must be trained by the supplier or suitably qualified personnel to use the instrument and application software as well as following applicable procedures. In addition, all users must ensure that ALCOA++ principles are complied with for data integrity and compliance with applicable regulations. Depending on the analytical instrument or system, user roles may be sub-divided e.g. analyst, trainee, supervisor etc.
- **Laboratory Administrators or Power Users**: Help specify the user and data integrity requirements for each item, help evaluate and select potential instruments and systems. They may help prototype operations and help in validate configured software. Networked systems e.g. CDS may require laboratory administrators to manage the business side of the application such as setting up of custom calculations, report templates, analytical methods etc.

4.2 Quality Unit or Quality Assurance

The extent of Quality oversight is dependent on individual company requirements. Organisation and nomenclature of Quality Control Unit, Quality Control and Assurance functions and assignment of responsibilities are also highly company specific. This Guide does not dictate or recommend specific steps that must be supervised by specific quality functions other than those required by regulation. Therefore, the term Quality Unit (QU) as used in the revised chapter 1 of EU GMP Guide [54], is used here.

- **Quality Unit / Quality Assurance**: Provide oversight of qualification and validation activities to ensure compliance with regulations and procedures.
  Key qualification and validation documents will normally require QA sign-off e.g. Validation plan, URS, validation summary report etc.
  During operational use of systems QA will provide quality oversight of analysis plus data integrity audits to ensure compliant operation of analytical instruments and systems.

4.3 Information Technology

The second role defined in EU GMP Annex 11 [21] is the system owner:

- **System Owner / IT Department**: *The person responsible for the availability, and maintenance of a computerised system and for the security of the data residing on that system [21].*
  Responsible for supporting the computer platform, backup, cybersecurity, change control and application support such as user account management, application configuration and backup etc.
  For networked systems an agreement must be in place with the process owner defining scope of support and the roles and responsibilities of both parties as well as metrics to monitor that the agreement conditions are met.
  As noted above, for standalone systems the process owner is also the system owner.

4.4 Purchasing

Although rarely mentioned in regulations or guidance documents, the Purchasing Department can make or break data integrity of analytical instruments and systems. If a laboratory spends time on evaluating which item to buy but Purchasing finds an "equivalent" item that is cheaper than proposed this can prolong data integrity problems. Buying on price may not be the best option in the long run.

A better option is to include Purchasing early in the evaluation process so that the criteria for selection are understood by them and the Department can negotiate the price, terms and conditions with the selected supplier before placing the order. If there are two possible suppliers, then this may allow Purchasing to obtain a better price and terms.

4.5 Supplier

The major player in AIQSV is the Supplier of the instrument and associated software, either directly via their sales force or via country agents.

- PIC/S PI-041 section 9.1.3: *Regulated users should ensure that vendors of systems have an adequate understanding of GMP/GDP and data integrity requirements, and that new systems include appropriate controls to ensure effective data management* [36]. This is important as analysis of IR Spectrometer FDA 483 Observations by Smith and McDowall found that a large number of citations were due to deficiencies such as lack of adequate security and no audit trail functionality [55]. Purchasing the wrong instrument could be the first step to a lifetime of non-compliance before the system is even delivered.
- *Suppliers must produce meaningful specifications* [22]. Furthermore, a supplier specification might be meaningless without information on how it was derived or tested. For example, a bench top centrifuge had a rotor speed of 3000 ±1 rpm except it was measured without a rotor [56].
- Provide service and maintenance for the lifetime of the instrument including timely information about instrument and software problems.
- Provide qualification documentation for installation and commissioning activities.
  PIC/S Guide PI-041 section 9.3: *Companies should ensure that computerised systems are qualified for their intended use. Companies should therefore not place sole reliance on vendor qualification packages; validation exercises should include specific tests to ensure data integrity is maintained during operations that reflect normal and intended use* [36]

- User manuals, quick help guides, on-line support coupled with training and support services for ensuring the users can use the instrument or system. In addition, professional services can be offered for configuration of software and validation of the system

4.6 In-House Metrology and / or CSV Groups

Larger pharmaceutical companies may have in-house metrology and / or Computer System Validation groups to help laboratories calibrate, qualify and / or validated analytical instruments and systems. These groups may replace some of the services provided by either the supplier or external contractors. There should be procedures for their work and acceptance criteria for any tests performed as well as the requirement for traceable materials and calibrated test equipment as appropriate.

4.7 Contractors / Consultants

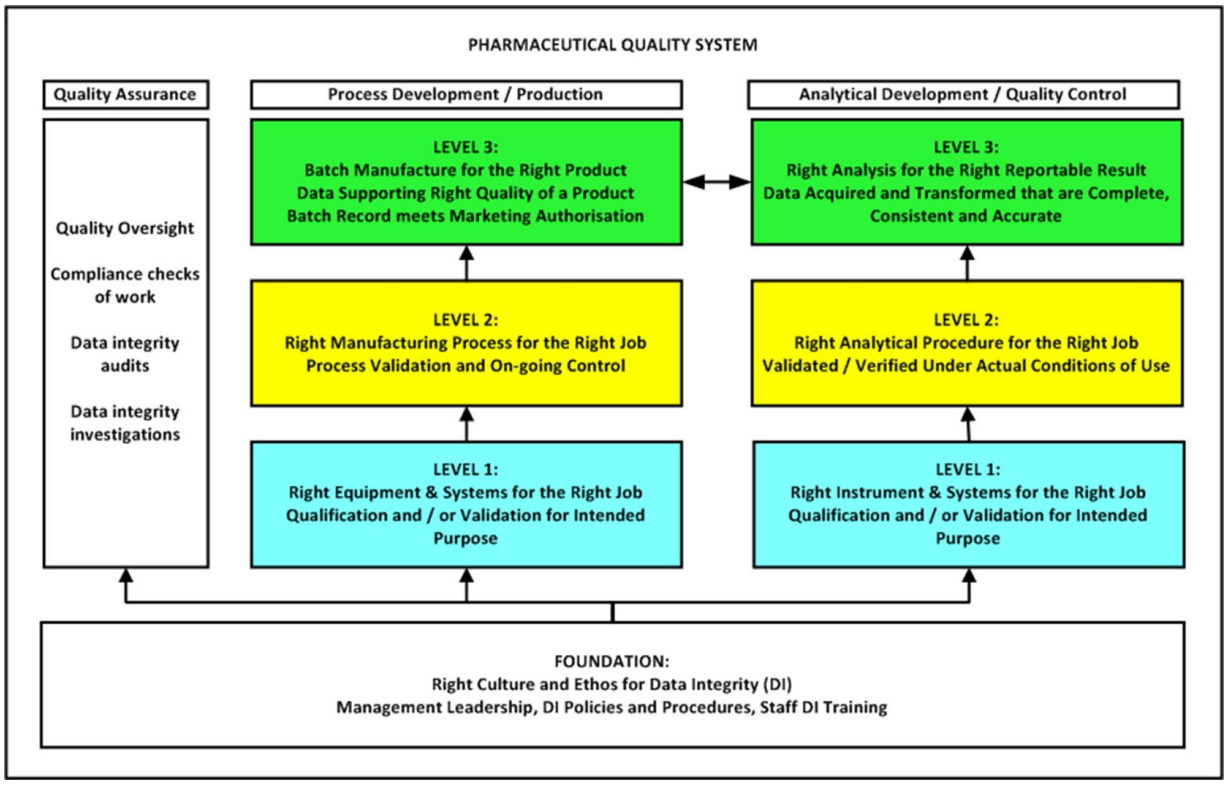
Service Providers / Consultants / Contractors: may be used for the calibration, maintenance or qualification of analytical instruments and validation of computer software. It is important that they follow company procedures for consistency of approach. Alternatively, evaluate any new approaches suggested by them for compliance with regulations, data integrity requirements and efficiency improvements.

5 Role of AIQSV in Ensuring Data Integrity

5.1 Data Integrity Model

The role of AIQSV for ensuring data integrity within the context of an overall Pharmaceutical Quality System (PQS) is shown in a Data Integrity Model [57-59] in **Figure 10**. This consists of a Foundation and three levels plus Quality Oversight. The portion of the model pertinent to Analytical Development and Quality Control portion is shown on the right of the model.

Figure 10 A Data Integrity Model [59]



The levels of the model are:

- **Foundation: Data Governance or Right Corporate Culture for Data Integrity**. The Foundation goes across all elements in an organisation and is the Data Governance layer which must contain management leadership, data integrity policies including data ownership, staff training in these procedures, management review including quality metrics and an open culture including the ability to Speak Up plus confidential whistleblowing. Analogous to building a house, there is a Foundation layer which is the right culture and ethos for data integrity and this must be led by senior management.
- **Level 1: Right Instrument or System for the Job:** Qualification of analytical instruments and validation of application software. Included here are calibration, point of use checks or system suitability test samples to confirm that the analytical instrument of laboratory computerised system is within user specifications before use.

- **Level 2: Right Analytical Procedure for the Job**: This is validation of analytical procedures or verifying pharmacopoeial procedures under actual conditions of use.
- **Level 3: Right Analysis for the Right Reportable Result**. Here production provides the laboratory samples for analysis taken to demonstrate adequate product quality and conformance with the product specification in the Marketing Authorisation (MA)

In addition, there is the role of QA for oversight of activities:

- **Quality Assurance**: shown on the left in **Figure 9** with the function to provide quality oversight throughout the Data Integrity Model e.g. ensure compliance with regulations, policies and procedures as well as performing data integrity audits and data integrity investigations.

More information about the Data Integrity Model can be found in the ECA Data Integrity and Data Governance Guide [9].

5.2 Important of AIQSV for Ensuring Data Integrity

AIQSV sits at Level 1 in the Data Integrity Model and therefore all work in the levels above are dependent on the right instrument and computerised system for the right job. If instruments and systems are not fit for intended use or are used outside of qualified or validated limits, then data and reportable results generated are suspect.

Therefore, it is important to of adopt an Analytical Instrument and System lifecycle (AIQSV) as an integral part of an Analytical Procedure Lifecycle (APL) approach as shown in Figure 1. If an analytical procedure requires measurement outside of a qualified parameter range, then there must be feedback to Level 1 to increase the qualification of that parameter to ensure that the measurement is carried out with a qualified analytical instrument or a verified macro.

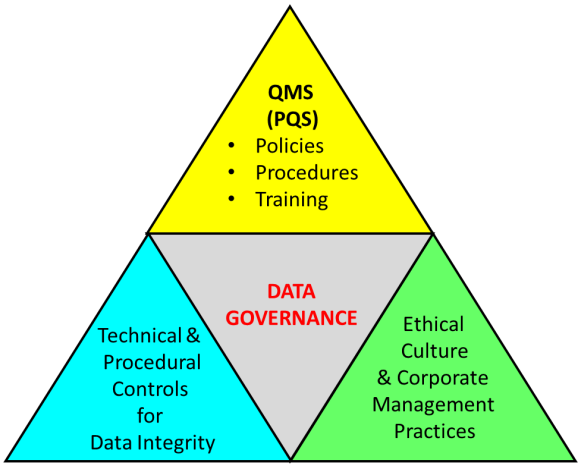
The same principle applies to the use of unvalidated or uncontrolled software functions for regulated analytical work; these must be validated under a change control request.

5.3 Importance of Adopting AIQSV as Part of an Analytical Procedure Lifecycle (APL) Approach

The current regulatory climate has highlighted deficiencies and concerns regarding data integrity, data quality and security in laboratories in a global context. These observational findings cover both poor data management practices and fraudulent activities. The lifecycle management approach for analytical procedures is an essential part of ensuring that analytical data are ‘fit for intended purpose’. The AIQSV approach provides an efficient and effective process as part of this requirement.

Data integrity and security is concerned with more than just the generation and security of correct numbers. It is concerned with the totality of arrangements under a QMS to ensure that data, irrespective of the format in which they are generated, recorded, processed, retained and used to ensure a complete, consistent and accurate record throughout the data life cycle in accordance with the ALCOA++ model [9].

Figure 11 Data Governance elements for AIQSV

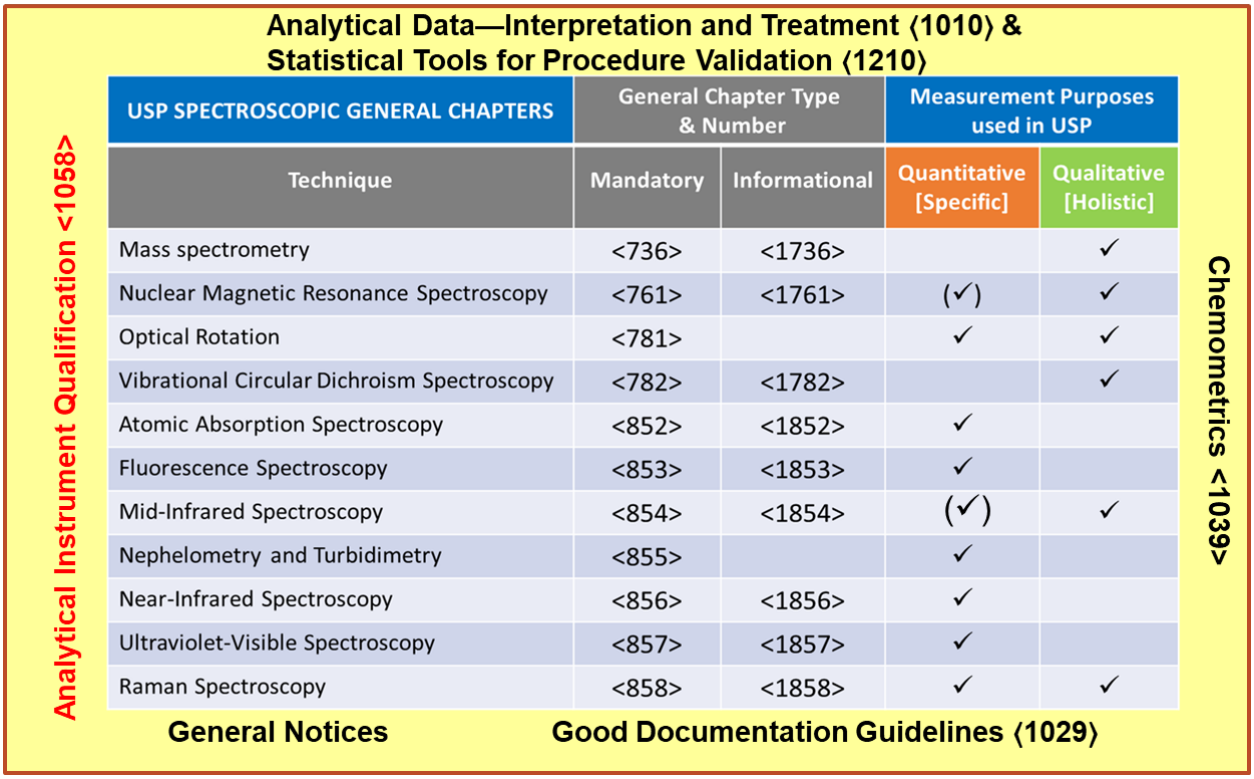


Data governance is the term used for the overall management strategy to ensure data integrity and security. Functional aspects within the laboratory and the quality function must be under control otherwise data integrity could be compromised despite the best efforts of all staff. Detailed requirements for the APLM are given in another ECA Guideline [16].

6 Analytical Instrument Qualification and System Lifecycle Process Flow

In 2021, in anticipation of official publication of <1220>, a USP Joint Sub-Committee was formed to consider the implications for USP General Chapter <1058> Analytical Instrument Qualification with particularly with respect to the spectroscopic General Chapters and the interrelationships between it and other General Chapters as illustrated in Figure 12 [8].

Figure 12 Interrelationships between the USP General Chapters and <1058>



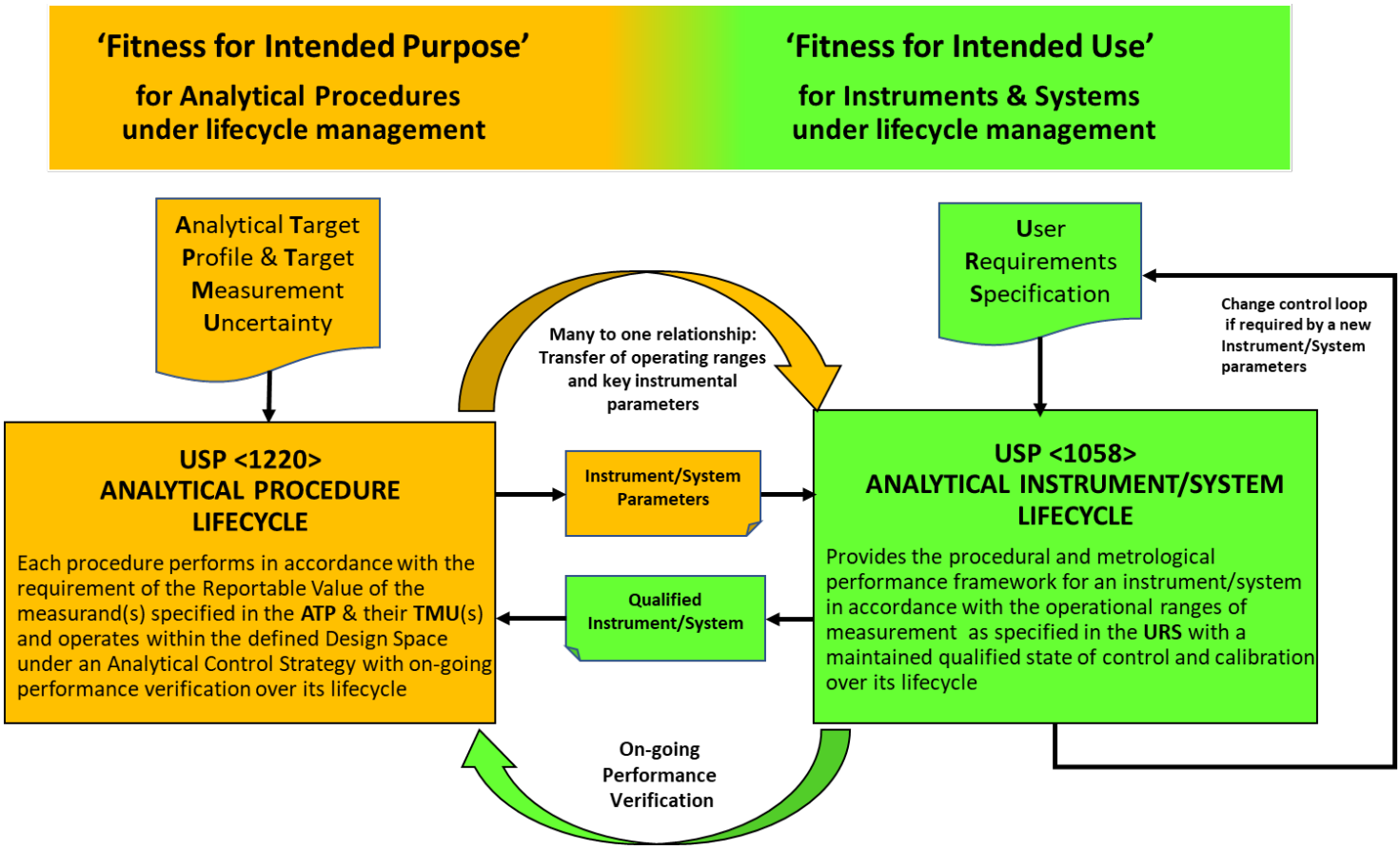
USP SPECTROSCOPIC GENERAL CHAPTERS	General Chapter Type & Number		Measurement Purposes used in USP	
Technique	Mandatory	Informational	Quantitative [Specific]	Qualitative [Holistic]
Mass spectrometry	<736>	<1736>		✓
Nuclear Magnetic Resonance Spectroscopy	<761>	<1761>	(✓)	✓
Optical Rotation	<781>		✓	✓
Vibrational Circular Dichroism Spectroscopy	<782>	<1782>		✓
Atomic Absorption Spectroscopy	<852>	<1852>	✓	
Fluorescence Spectroscopy	<853>	<1853>	✓	
Mid-Infrared Spectroscopy	<854>	<1854>	(✓)	✓
Nephelometry and Turbidimetry	<855>		✓	
Near-Infrared Spectroscopy	<856>	<1856>	✓	
Ultraviolet-Visible Spectroscopy	<857>	<1857>	✓	
Raman Spectroscopy	<858>	<1858>	✓	✓

6.1 Fitness for Intended Use versus Fitness for Intended Purpose

It is important to distinguish between 'Fitness for Intended Use' of an analytical instrument or system and its role within an analytical procedure which must be shown holistically to be 'Fit for Intended Purpose' as required by the Analytical Target Profile (ATP) and the Target Measurement Uncertainty (TMU).

A generic process flow of the interrelationship of an enhanced <1058> and <1220> is shown in Figure 13. The interactive lifecycles are dynamic processes. The success of the lifecycle approach depends upon Change Control and Deviation Management for both the Analytical Procedure and the Analytical Instrument/System used. Hence the QMS needs to be designed to support these activities with regular and proper Quality Oversight. Second person review is a critical activity.

Figure 13 Overview of USP <1220> and an enhanced USP<1058> lifecycles



'**Fitness for Intended Use**' for an analytical instrument and/or system, under lifecycle management, requires documented evidence that;

- It is metrologically capable of operating over the ranges specified in the analytical procedures in which it is to be used
- It's qualification and calibration baseline, as specified in the URS, is traceable to national or international standards
- It's overall metrological contribution to the uncertainty budget of the reportable value as small as practicable and should contribute not more than 1/3rd of the target measurement uncertainty of the analytical procedure specified in the ATP

and

- The instrument/system's critical parameters continue to be in a state of procedural and statistical control and within the established acceptance limits during ongoing performance verification using a metrologically sound process over the lifecycle.

This assumes that;

1. The ATP becomes a fixed document after the development process is completed and the metrological procedure is fully defined in APL Stage 1. (See **Figure** 1)
2. The Analytical Control Strategy may be subject to change over the lifecycle to ensure compliance with the ATP.
3. The URS is a controlled document using knowledge of the applications require at a fixed point in time.
4. Over the AIQSV and APL lifecycles, the instrument / system URS is subject to change control depending on changes needed for new or extended metrological requirements e.g. if requirements are linked to pharmacopoeial requirements.
5. Over the lifecycle, ongoing performance verification uses a metrologically sound process with traceability.

As part of the development of an enhanced version of <1058>, two additional Stimuli to the Revision Process articles were published in Pharmacopeial Forum in 2022.

1. Measurement Uncertainty Evaluation Relevant to Analytical Instrument and System (AIS) Qualification—The Role of Measurement Uncertainty Concepts within the AIS [53]

and

2. Analytical Instrument and System (AIS) Qualification: The Qualification Life Cycle Process [8]

The overall purpose of these integrated approach lifecycles, as illustrated below, is to provide a rationale framework within a Pharmaceutical Quality System as an integral part of data integrity and data governance [60]. This integrated approach is shown in more detail in Figure 14.

Figure 14 Analytical Process Flow within a Pharmaceutical Management System (PQS)

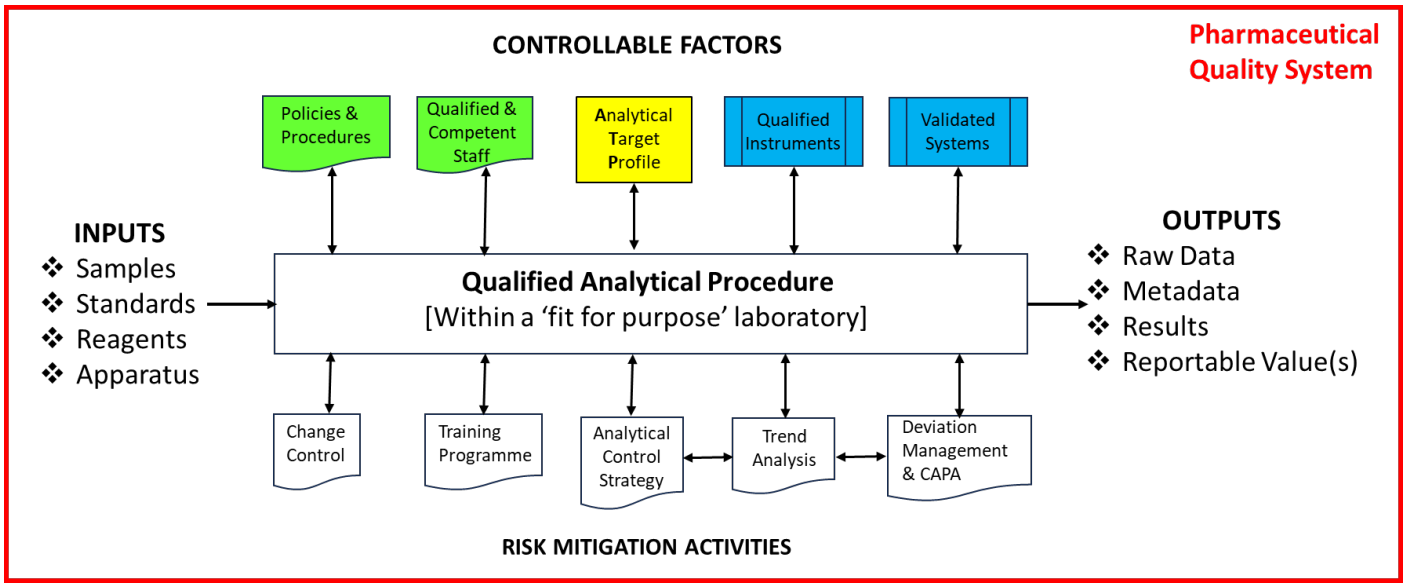
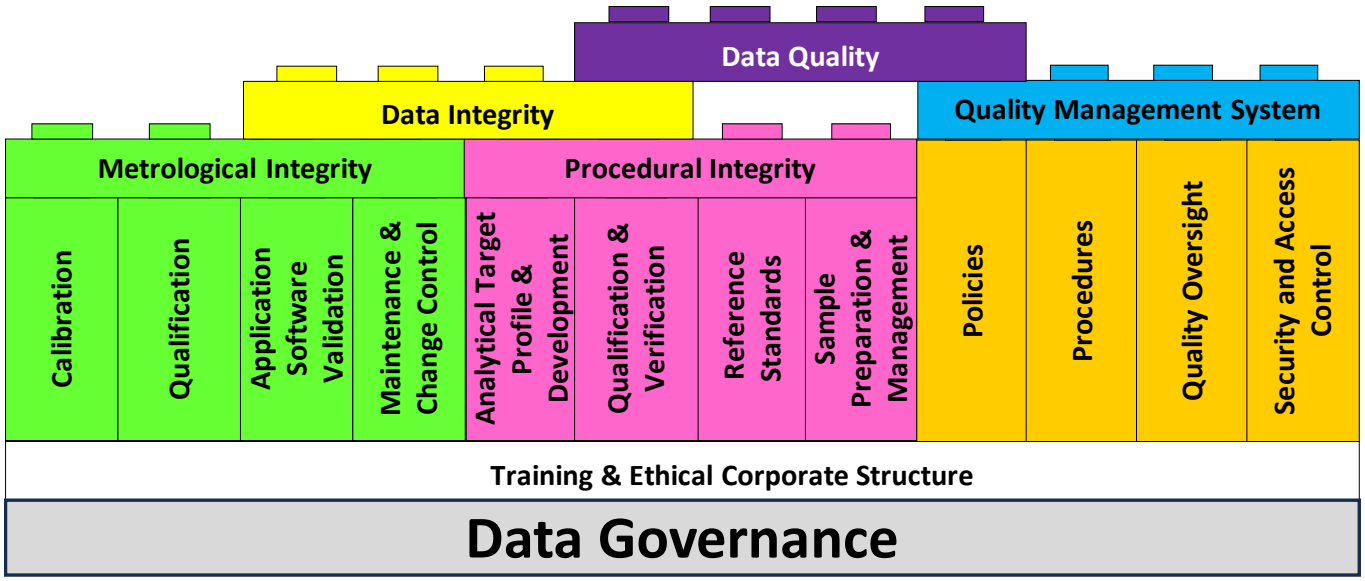


Figure 15 Lego© brick model for Data Quality within a Lifecycle approach



7 Risk-Based Classification of Analytical Instruments and Systems

USP <1058> has a risk-based classification of apparatus, analytical instruments and analytical systems, each item can be placed in one of three Groups A, B or C [22]. In the past, qualification and validation were two separate activities, instead USP <1058> integrates the two disciplines into a single approach to save time and effort.

For multiple instances of instruments and systems of the same make and model, there are economies of scale to be made as discussed in Section 10.2.4.

7.1 Definition of Intended Use is Critical

It will be reiterated throughout this Guide that the classification of any item of apparatus, analytical instrument or analytical system is based on the definition of intended use within a specific laboratory.

Even if an item is capable of a particular measurement or function, the deciding factor is does the laboratory use it for a regulated activity? This is discussed in more detail in Section 16 where the same make and model of an analytical balance can be classified into one of three Groups depending on its intended purpose.

This is the key to successful risk management and the resulting qualification and/or validation work required to demonstrate the defined intended use.

7.1.1 Same Instrument, Different Group Due to Different Intended Use

Furthermore, must be emphasized that the same instrument may be classified in a different Group depending on its intended use. Take, for example, a sonic bath where the classification will change based on the intended use:

- Group A: used to dissolve standards or samples with observation by an analyst to determine if the material has dissolved completely
- Group B: used to dissolve standards or samples but it requires a specific temperature or sonic energy which requires the instrument to be calibrated
- Group C: incorporation of the instrument into an automated system

Care must also be taken if the instrument is repurposed after purchase: the classification may change and if reassessment is not performed proactively it may result in a compliance gap.

All laboratory apparatus, analytical instruments and systems can be classified into one of three Groups as shown in Figure 15. The definitions for each of the three Groups will be given in Section 8.2 and the sub-divisions of each are discussed in Sections 8.3 and 8.4.

7.2 Definition of Groups A, B and C

7.2.1 Group A Definition of Apparatus

Group A includes the least complex and standard apparatus that are used without measurement capability or user requirement for calibration, such as a magnetic stirrer, or a vortex mixer or standard volumetric glassware. Proper function is ensured by observation, and no further qualification activities are needed for this group [22].

7.2.2 Group B Definition of Analytical Instrument

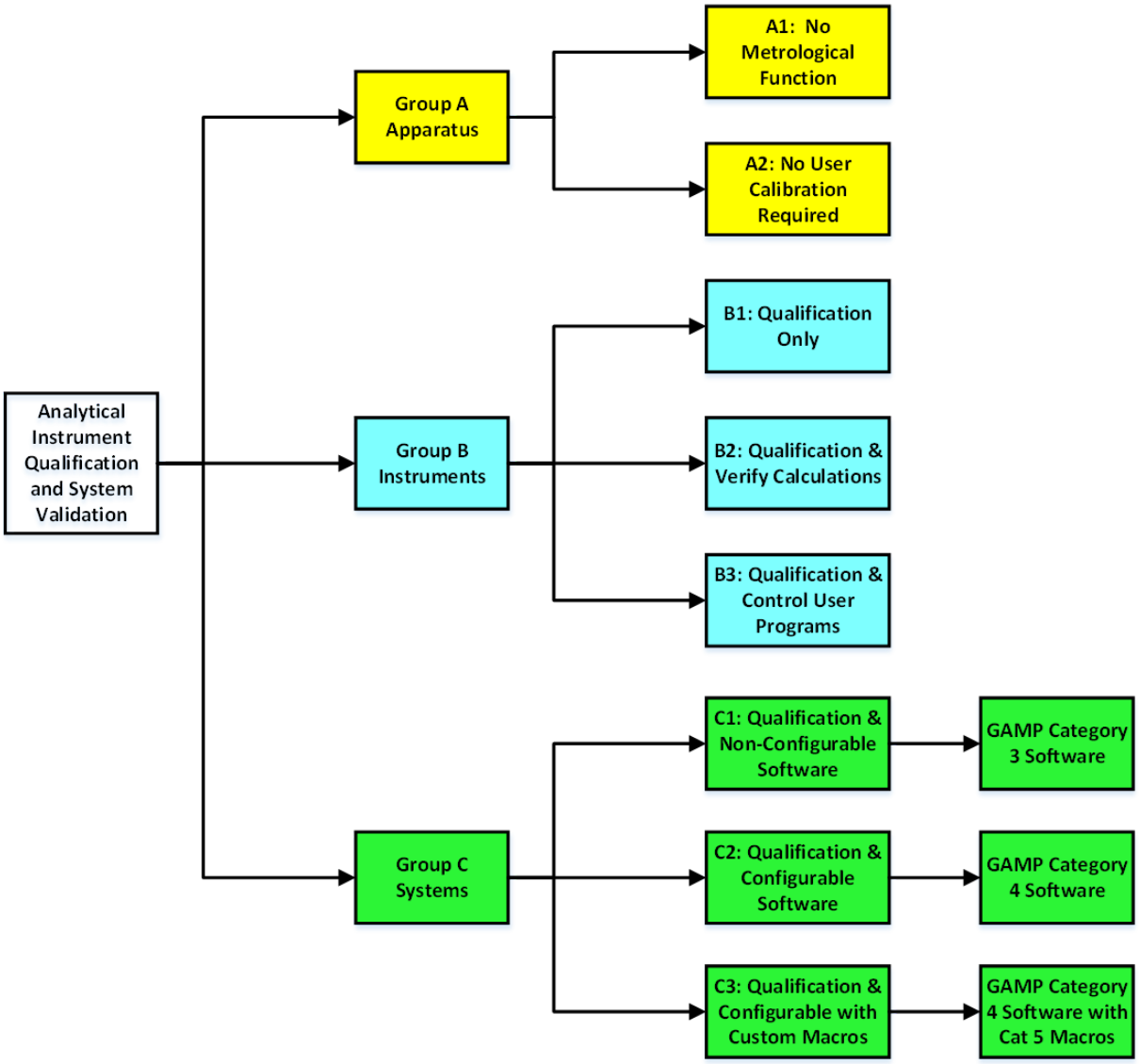
Group B includes analytical instruments that may provide a measurement or control an experimental condition that can affect a measurement. Examples include a pH meter or an oven. Proper function of instruments in this

group may require only routine calibration, maintenance, or performance checks. The extent of activities may depend on the criticality of the instrument in combination with the intended use [22].

Generally, these instruments have firmware that can be updated either by a supplier or by the user but only under change control.

In addition, modern instruments have functions that allow definition of define user identities, privileges per user role, basic administration of the instrument including changing the instrument clock that must be documented and controlled.

Figure 16: USP <1058> Classification of Apparatus, Analytical Instruments and Analytical Systems



7.2.3 Group C Definition of Analytical System

Group C comprises analytical instruments with a significant degree of computerization and complexity, such as high-pressure liquid chromatographs and mass spectrometers with a separate controlling computer with

application control e.g. Chromatography Data System. As such they meet the definition of computerised system and all elements of instrument qualification and software validation, must be considered to ensure proper functioning of systems in this group [22].

The GAMP software category determines the Group C sub-type of a system. Most laboratory software will fall into either Category 3 (Business process cannot be changed) or category 4 (Business process can be configured e.g. turn electronic signatures on or off). However, a major cause of confusion is parameterisation which can be performed on functions in both category 3 and 4 software. Parameterisation is setting the wavelength used to measure absorption of an analyte on a spectrometer or HPLC detector. If the wavelength is set at 220nm and then changed to 280nm, the business process has not changed. The instrument is still measuring the absorbance of an analyte regardless of wavelength. However, many people think this is configuration, but it is parameterisation, but it still needs to be controlled when people use the system e.g. method validation or analytical procedure. Further examples of parameterisation are:

- Changing the flow rate on an LC pump: process is the same just the flow rate differs.
- Wavelength scanning range with an IR or UV spectrometer.

7.3 Sub-Division of Group A Apparatus

Two sub-Groups have been proposed in a new SRP in Pharmacopoeial Forum which could be included in the new version of USP <1058>.

7.3.1 A1: No Metrological Function

Many of the items of apparatus that can be classified in this sub-Group are mixers, stirrers, shakers, nitrogen evaporators etc.

7.3.2 A2: No User Calibration Required

Apparatus falling into this sub-Group are Grade A volumetric glassware such as burettes, flasks and glass pipettes. Sieves that have been calibrated to a standard are also part of this sub-Group.

7.4 Sub-Division of Groups B and C

Software is pervasive throughout the instruments in Group B and systems in group C.

The subgroups in Groups B and C are shown in Table 1.

We stress that this is important only when these features are used i.e. intended purpose. Otherwise, if they are present but not used, then they are not relevant to the overall qualification or validation approach for the instrument or system. The issue then becomes one of system scope creep, therefore the intended use statement needs to be reviewed regularly to see that it is still current. This is best undertaken during a periodic review.

Table 1: Mapping USP <1058> Instrument Groups and GAMP© Software Categories

<1058> Group	GAMP© SW Category	Instrument Qualification Tasks	Software Validation Tasks
B Type 1 Firmware	2	• Define instrument operating ranges in URS • Install and qualify the instrument over predefined ranges	• Implicitly validate the software functions of the instrument during qualification • Define User Roles and access privileges, where appropriate • Ensure clock function, if present, is only changed by authorised users
B Type 2 Firmware & Calculation		• Define instrument operating ranges in URS • Install and qualify the instrument over predefined ranges	• Identify and document calculations used with input and output ranges • Implicitly validate the software functions of the instrument during instrument qualification • Check accuracy of the calculations during qualification • Define User Roles and access privileges, where appropriate • Ensure clock can only changed by authorised users
B Type 3 Firmware & User Programs		• Define instrument operating ranges in URS • Install and qualify the instrument over predefined ranges	• Implicitly validate the software functions of the instrument during instrument qualification • Define User Roles and access privileges, where appropriate • Ensure clock is only changed by authorised users • Control user defined routines by SOP including specification of the routine, review of program and testing against specification before release • Place under change control
C Type 1 Non-Config Software	3	• Define instrument operating ranges • Install and qualify the instrument over predefined ranges	• Define user functions • Install and qualify software • Test whole system versus URS • Release system • Place under change control

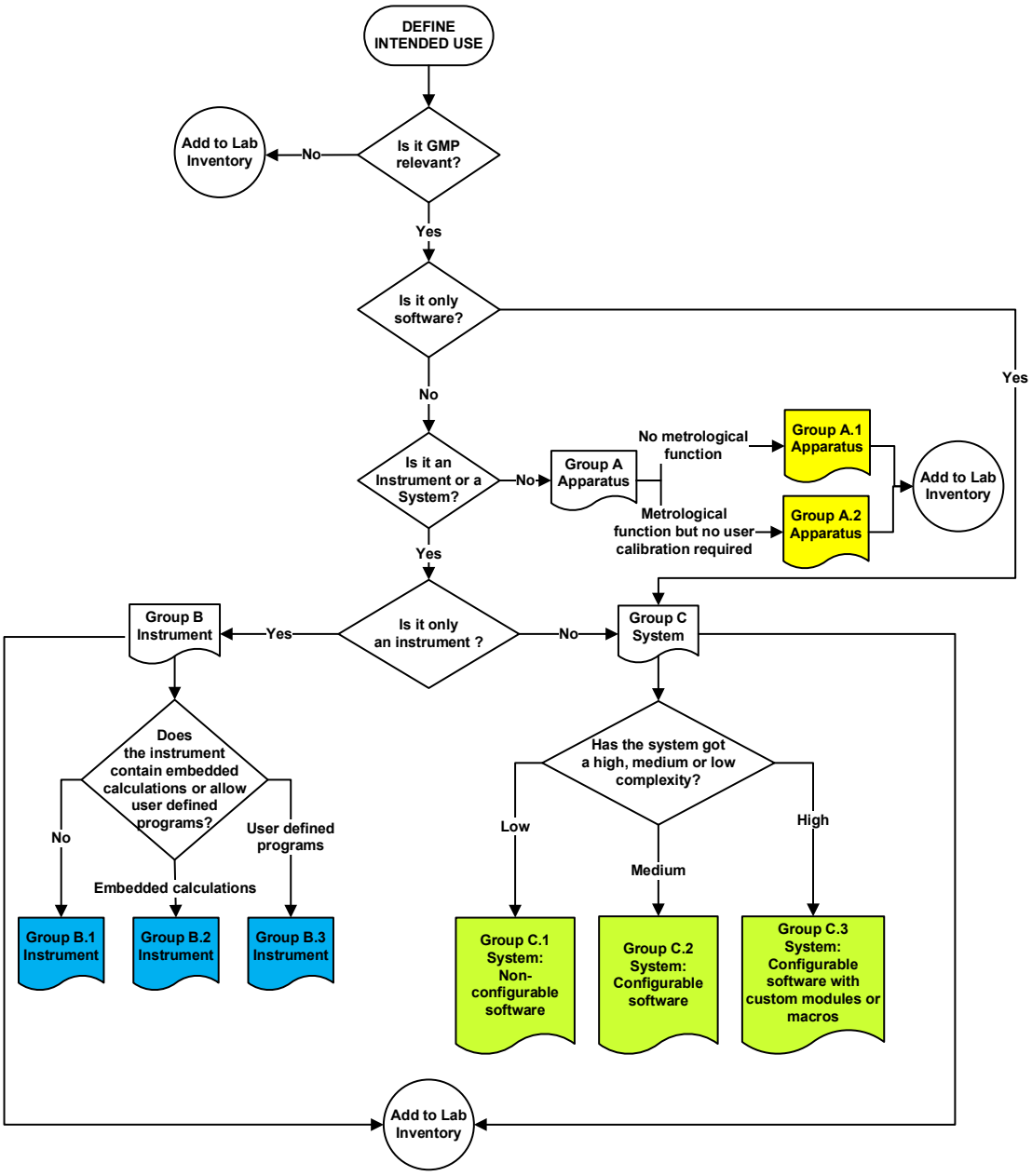
<1058> Group	GAMP© SW Category	Instrument Qualification Tasks	Software Validation Tasks
C Type 2 Configurable Software	4	• Define instrument operating ranges • Install and qualify the instrument over predefined ranges	• Define user functions and document software configuration • Install and qualify software • Leverage supplier software development to reduce lab testing • Configure software • Test configured system versus specifications • Release system • Place under change control
C Type 3 Configurable & Custom Software	4 + 5	• Define instrument operating ranges • Install and qualify the instrument over predefined ranges	• Define user functions and document software configuration • Install and qualify software • Leverage supplier software development to reduce lab testing • Configure software • Specify, code & test custom modules • Integrate with application software • Test configured system and macros versus specifications • Release system • Place under change control

8 System Risk Assessment

This risk assessment is used to classify which USP <1058> group and sub-division an item of apparatus, analytical instrument or analytical system belongs. This is to determine the extent of calibration, qualification and / or validation that is required to demonstrate fitness for intended use. The overall process flow of the risk assessment is shown in Figure 16. Although the focus of this guide is on the pharmaceutical GMPs, the relevance box is just as applicable to other QMS systems such as ISO/IEC 17025, ISO 17034 and the GLP regulations.

Figure 17: Risk Assessment to Determine the Extent of Calibration, Qualification and / or Validation [61]

Note this RA is not applicable to LIMS which are excluded from the scope of this guide.



If there are several of the same item e.g. variable volume pipettes, a single risk assessment only needs to be performed.

This risk assessment can be performed either before purchase (providing sufficient information about the features of the item and the way it will be used is available) or after purchase and training but before qualification and validation begins.

The risk assessment can be performed with a controlled and uniquely numbered template issued by QA or electronically within an Electronic Document Management System with electronic signatures.

8.1 Identification of the Item and a Statement of Intended Use

The first stage is gathering information about the item such as:

- Name, model and supplier of the item; identification of the software version if applicable
- Instrument or system owner, department and location
- If already purchased, the inventory or asset number should also be added

Then is essential to write a simple statement of the intended use of the item. This need only be a sentence or two and is NOT intended to be a substitute for the formal definition of intended use which is the URS or a copy of supplier literature. Examples are:

- Analytical Balance: Used for weighing reference standards and samples prior to analysis
- Chromatography Data System: Control of chromatographs and the acquisition, storage, interpretation and reporting of samples from in-process testing, finished product and stability testing.

8.2 Does the Item Carry Out any GMP Activities?

First a series of closed questions to identify if any GMP activities are carried out.

Does the item carry out any of the following GXP activities?	Check Box
1. Testing of drug product or API for formal release?	☐Y ☐N
2. Used for shipment of material e.g. data loggers?	☐Y ☐N
3. Non-clinical laboratory studies intended for submission in a regulatory dossier?	☐Y ☐N
4. Clinical investigations including clinical supplies or pharmacokinetics?	☐Y ☐N
5. Generation of, submissions to, or withdrawal of a regulatory dossier?	☐Y ☐N
6. Is the system used to store, backup or transfer electronic records supporting any of the above?	☐Y ☐N

Complete the appropriate box below.

All responses = NO, qualification and validation are not necessary as the item has no GXP function.

Go to 8.7 and complete the Qualification and Validation Statement

If any of the responses = YES, further risk assessment is required.

NO GXP Impact Validation / Qualification is NOT required – Go to 8.7 and complete the Qualification and Validation Statement.	☐	GXP Impact Validation / Qualification IS Required – go to Section 8.3 and question 7	☐

8.3 Is the Item Only Software?

Complete the following questions:

Is the Item classified as only Software?			Check Box
7. Is the item only software			☐Y ☐N
If Yes, go to question 8	☐	If No, Item needs to be assessed to see if it is Group A, Group B or Group C; Go to question 9	☐
8. Does it perform a GXP function or creates GXP records?			☐Y ☐N
If Yes, Item is Group C software – go to Section 8.6	☐	If No, then no further assessment of the software is required. Go to 8.7 and complete the Qualification and Validation Statement	☐

8.4 Is the Item USP <1058> Group A?

Complete the following questions:

Is the Item classified as USP <1058> Group A (Apparatus)?	Check Box
9. Is there any measurement capability of the item?	☐Y ☐N
10. Is the item user calibrated after purchase?	☐Y ☐N
11. Does the use of the item require more than confirmation by observation?	☐Y ☐N

If the answer to all three questions is No, then the item classified as is Group A.1.
If the answers to questions 9 &11 are Yes and 8 is No, then the item classified as is Group A.2
If the answers to all three questions are Yes, then the item is not Group A

.

Item is Group A.1 or A.2 and no further assessment is required. Go to 8.7 and complete the Qualification and Validation Statement.	☐	Item is not Group A further assessment is required – go to the next section and question 12.	☐

8.5 Is the Item Group B (Instrument) or Group C (System)

Is the Item classified as either USP <1058> Group B or Group C?	Check Box
12. Does the item measure values or control physical parameters?	☐Y ☐N
13. Does the item need user calibration?	☐Y ☐N
14. Is there a separate computer for control of an instrument and data acquisition?	☐Y ☐N

- If the answers to questions 12 and 13 are Yes and question 14 is No – the item is classified as Group B (instrument).
  Note: Some instruments in this category may have an operating system and even a database but the data are not accessible to a user or administrator and PIC/S Guide Section 8.9.1 notes: *Some very simple electronic systems, e.g. balances, pH meters or simple processing equipment which do not store data, generate directly-printed paper record*s [36]. Instruments with ring buffers ideally should be connected to an instrument data system to collect rather than print the record.
- If the answers to questions 12 – 14 are Yes, the item is Group C (system) that requires software validation with associated instrument qualification.
- Complete the table below.

Item is a Group B instrument and requires qualification. Go to questions 15-17. below	☐	Item is a Group C system that controls an instrument. It requires validation and qualification. Go to Section 8.6	☐

For Group B instruments with firmware (GAMP© software category 2) complete this further assessment:

Group B: Are there any Built-in Calculations or Can a User Write Programs?	Check Box
15. Is the instrument used without calculations or user defined programs? Group B1.	☐Y ☐N
16. Are there any built-in calculations used by the instrument but cannot be changed or configured? Group B2	☐Y ☐N
17. Can you write a user defined program with the instrument? Group B3	☐Y ☐N

Instruments in this Group may also have user access management functions that should be included in the overall instrument qualification.

Item is either Group B.1, B.2 or B.3 and no further assessment is required. Go to 8.7 and complete the Qualification and Validation Statement.

8.6 Group C Systems – How Much Validation Should I Do?

Determination of the extent of validation of Group C systems is by assessing the GAMP© Category of the application software used in the system and the impact of the records generated by it.

GAMP© Software	Application Software Used by the System Software Category Description	Check all appropriate
Category 5	Custom software application or custom extensions (e.g. macro, custom modules) to an existing commercial application	☐
Category 4	Commercially available configurable software that is configured to match the business process (Note that this is not configuring user roles or reports)	☐
Category 3	Commercially available standard non-configurable software package providing an off the shelf solution to a business or regulatory process	☐

Record Risk	Regulatory Impact of Data Generated by the System	Check Boxes
High Impact Records	Data are included in a registration dossier	☐Y ☐N
	Data supporting batch release of product, CTM or API	☐Y ☐N
	Stability data	☐Y ☐N
	Cleaning validation	☐Y ☐N
	Support to non-clinical laboratory studies	☐Y ☐N
	Clinical trial data from patient or supporting work	☐Y ☐N
	Calibration records for direct impact instruments and systems	☐Y ☐N
	Electronic signatures	☐Y ☐N
Medium Impact Records	In-process monitoring of drug product and APIs	☐Y ☐N
	Process validation	☐Y ☐N
	Analytical Method/Procedure validation	☐Y ☐N
	Qualification and computer validation records	☐Y ☐N
Low Impact Records	Management information	☐Y ☐N
	Planning documents	☐Y ☐N

Assessment: To determine the amount of validation required, identify the GAMP© software category versus the record impact by inserting a cross in the appropriate box of the matrix in the left-hand column of the table below. Then check the box required in the right-hand column.

Full validation requires a validation plan to be written that will define the lifecycle to be followed and the documented evidence to be generated. This enables further risk assessment to be conducted for lower risk systems in Software Category 4, such as leveraging supplier development and testing.

GAMP Software Category	5	Full	Full	Full	**Full Validation Required.** A validation plan will determine the life cycle and documented evidence needed for the system.	☐
	4	Reduced	Reduced Or Full	Full		
	3	Reduced	Reduced	Reduced	**Reduced validation Required.** The integrated validation document will be used to validate the system.	☐
		Low	Medium	High		
		Record Impact				

Note: Justification for a reduced validation of GAMP© Category 4 software generating medium impact records needs to be completed outside this system risk assessment.

Go to 8.7 and complete the appropriate section 4 item of Qualification and Validation Statement.

8.7 Qualification and Validation Statement

Depending on the assessment the appropriate box is checked in the table below and the assessor signs the risk assessment.

This risk assessment has determined that this item is/has:	
1. No GXP impact of the item	☐
2. Group A apparatus (A.1 or A.2) – no qualification impact	☐
3A. Group B1 instrument only – qualification required	☐
3B. Group B2 instrument – qualification required and calculation(s) verified	☐
3C. Group B3 instrument – qualification required plus control of user defined programs	☐
4A. Group C1 system –reduced validation required and instrument qualification	☐
4B. Group C2 system – full validation required and instrument qualification	☐
4C. Group C3 system – full validation of app & custom software & instrument qualification	☐
4D Software only – full validation required	☐
4E Software only – reduced validation required	☐

8.8 Instrument and System Inventory

When the risk assessment Is completed, the result must be entered into an inventory of analytical instruments and systems. It is important that both items that have a GMP impact as well as those that have no GMP impact are in the inventory together with the risk assessment numbers. If an item is updated in the future, this must be reflected in the inventory. If desired, the requalification and / or recalibration dates can be managed in the inventory.

8.9 Integrated Validation Document

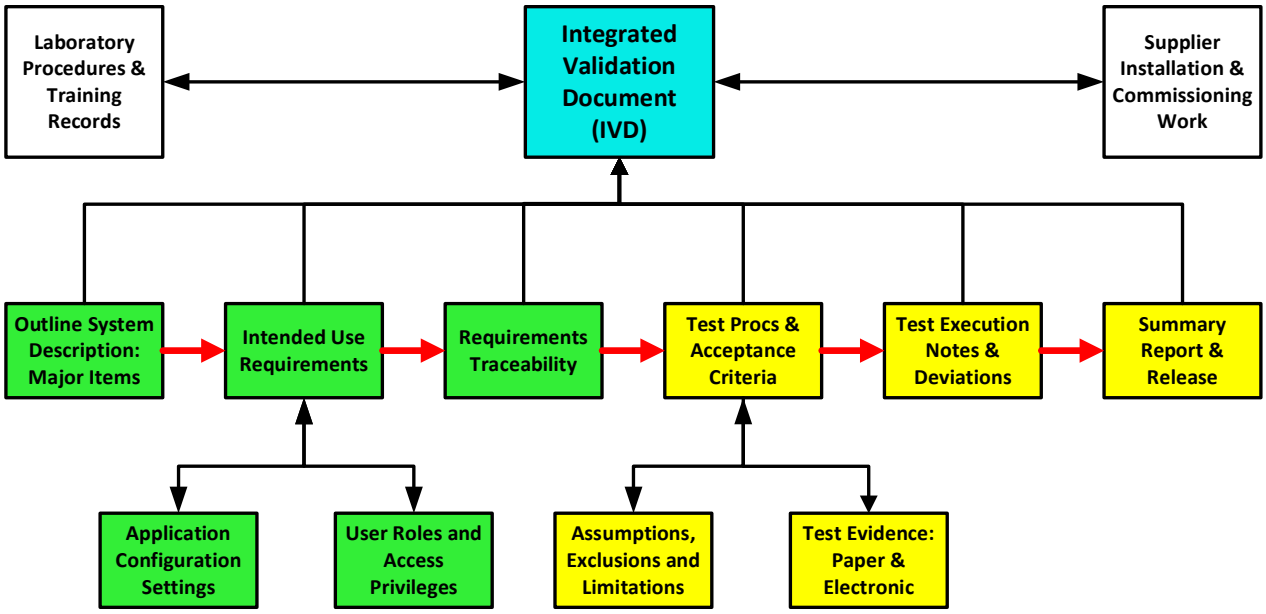
The risk assessment mentions the use of an Integrated Validation Document (IVD) for Group C1 systems that consist of an instrument controlled by GAMP© 3 software. To reiterate, GAMP© category 3 software is commercially available non-configured product (i.e. the business process automated cannot be changed but it is possible for configuration of user identities and user roles as this does not change the business process)

Laboratory software applications include:

- UV-Vis spectrometer used for scans and measuring absorbance at specific wavelengths.
- Total Organic Carbon (TOC) analyser.
- IR spectrometer used for identification of materials using the inbuilt functions of the software – not using in-house developed libraries (e.g. using appropriate reference standards to generate reference spectra).

This approach is not applicable when a system is interfaced to a laboratory informatics application.

Figure 18: Components of an Integrated Validation Document



8.9.1 Principle of the Integrated Validation Document

As noted in Section 3.1.3 EU GMP Annex 15 in clause 2.5 allows the merger of qualification documents and gives IQ and OQ as an example. The principle of the IVD takes this and condenses the whole suite of validation documents into one. From the risk assessment above, readers will note that this is only applicable to lower risk systems typically, but not exclusively, GAMP© Category 3 software. A description of the rational and justification can be found in the article by McDowall [20].

8.9.2 Description of an Integrated Validation Document

As the name suggests all key validation requirements for demonstrating intended use are contained in a single document as shown in Figure 18.

An IVD has two main sections: specifications and testing / reporting as discussed below.

Specifications shown in Green:

- **System Description**: A simple description of the main functions performed by the system along with a list of the main components.
- **Intended Use Requirements**: Consisting of a series of tables consisting of three columns: requirement number, the requirement and a trace to where the requirement is met e.g. test procedure, SOP, calibration, supplier documentation, etc. There are requirements sections for the function of the system, data integrity, IT support including backup electronic records, time synchronization, etc. Specification of the system is limited to requirements only essential to achieve the intended use and are statements of what the system MUST do rather than what it CAN do.
- **Definition of User Roles**: Typically, this is a table of the user roles against the access privileges allotted to each user role.

- **Configuration Settings**: A list of the application configuration settings is the last section for defining the intended use of the system.

Test and Reporting of the Configured System shown in yellow:

The configured system must be tested:

- **Test Procedures and acceptance criteria**
  - Documentation of any test preparation requirements.
  - Confirming the user roles and access privileges are correctly configured as specified as well as testing the security of the system.
  - Confirming the application has been correctly configured against the settings documented earlier in the IVD.
  - Requirements traced to test procedures cover intended use, record preservation, etc. including the acceptance criteria. If external calculations are being performed to verify those in the application are correct, don't forget to allow for differences in the number of significant figures and rounding between the two applications.
- **Assumptions Exclusions and Limitations of the test approach**
  As test procedures are developed by the team, it will become apparent why a test is being developed in a particular way. It is important to document any assumptions and limitations of the testing as well as why some requirements are excluded from testing e.g. why expiry of passwords is not tested or limited testing of access privileges per user role.
- **Test Evidence Collation**
  Both paper printouts and electronic records will be collected during the testing phase and the IVD contains sections that allow a tester to document the evidence and this makes the review of the testing quicker and simpler to perform. Screen shots will be kept to an absolute minimum and rely on the software to record evidence of testing whenever possible.
- **Test Execution Notes and Deviation Handling**
  If there are any problems or deviations executing the test procedures there is space in the IVD for documenting them and resolving problems e.g. the rationale for repeating part of a test
- **Test Summary Log and Release Statement**
  The end of the IVD there is a section for summarizing the testing. In addition, the tester must complete a release statement confirming/recommending if the system may be released for operational use or not. The whole document is reviewed by a second person who also confirms the release of the system. QA also review the completed IVD and documented evidence.

Referenced Documents

Not shown as a section in Figure 17, but the referenced documents section lists applicable documents associated with the IVD such as:

- Internal laboratory procedures and training records
- Supplier installation and commissioning documents (e.g. IQ and OQ).
- If a supplier does not provide these documents, instructions for the installation and commissioning can be written and included in the IVD.

8.9.3 Detail of Test Instructions and Test Evidence

Applicable to all instrument qualification and computerised system validation documentation is the level of test execution instructions and the documented evidence required. Too often companies and QA departments are ultra-conservative and over document testing with detailed instructions as shown in the left-hand column of Table 2 coupled with requests for copious screen shots.

Table 2: Comparison of Test Instructions for Risk Averse and Trained Users

Risk Averse Test Instructions	Test Instructions for Trained Testers
1. Access *file* on the top ribbon of the application 2. On the dropdown menu select *open file* 3. Select *browse* option 4. Open the *validation* folder 5. Select the file *validation.dat* 6. Open the file	1. Open the *validation.dat* file in the *validation* folder

Don't treat testers as if they are naïve people with mind numbing detailed instructions, testers are educated and trained; treat them as adults. In contrast, the instructions for a trained user to perform the same work is shown in the right-hand column of Table 2. The advantages are that these instructions are quicker to write, execute and review which permits the instrument or system to be put into service faster.

In the FDA's draft guidance on Computer Software Assurance on lines 579 – 582 it states:

> *As a least burdensome method,* ***FDA recommends the use of electronic records****, such as* ***system logs, audit trails, and other data generated by the software,*** *as opposed to paper documentation and screenshots, in establishing the record associated with the assurance activities* [10].

Therefore, write instructions for trained users and use the audit trail(s) in the system to self-document testing, as appropriate.

Only generate screen shots where it adds value and there is not an alternative method for documenting a key function in an audit trail.

9 Why Do We Need an AIQSV Lifecycle?

The 4Qs model (DQ, IQ, OQ and PQ) has been part of equipment qualification and analytical instrument qualification since the 1990s. As noted in Section 4.1, there were a few issues from the inception of this model. Therefore, to avoid confusion and misunderstanding, the 4Qs Model is not used as a basis for this Guide and it uses a AIQSV lifecycle phases based upon a 2022 USP Stimulus to the Revision Process article for the revision of USP <1058> [8]. It should be noted that this is a proposal but it is risk-based and good analytical science as well as investment protection.

Figure 19: Proposed USP <1058> Lifecycle Phases for Apparatus, Analytical Instruments and Systems [8]

	Examples of Risk-based Activities in the AISQ Life Cycle							
	Proposed <1058> AISQ Category of increasing risk							
	APPARATUS		INSTRUMENT			SYSTEM		
	A1	A2	B1	B2	B3	C1	C2	C3
LIFE CYCLE ACTIVITY	Apparatus: No metrological function	Apparatus: No User calibration required	Instrument: Firmware control	Instrument: In-built calculations	Instrument: User defined routines	System: Non configurable software	System: Configurable software	System: Configurable & customisable software
Risk Assessment	YES	YES	YES	YES	YES	YES	YES	YES
URS	NO	NO	YES	YES	YES	YES	YES	YES
Vendor FS/DS	NO	NO	NO	NO	NO	NO	CONSIDER	YES
DQ; Design Qualification	NO	NO	YES	YES	YES	YES	YES	YES
Vendor audit	NO	NO	NO	NO	NO	NO	CONSIDER	YES
Purchasing specification & PO	YES	YES	YES	YES	YES	YES	YES	YES
Site Preparation	NO	NO	YES	YES	YES	YES	YES	YES
IQ; Installation Qualification	NO	NO	YES	YES	YES	YES	YES	YES
OQ; Operational Qualification	NO	NO	YES	YES	YES	YES	YES	YES
PQ; Performance Qualification and/or User Acceptance Testing	NO	NO	CONSIDER	CONSIDER	CONSIDER	CONSIDER	YES	YES
Authorisation for use	NO	NO	YES	YES	YES	YES	YES	YES
Monitoring	NO	NO	YES	YES	YES	YES	YES	YES
Maintenance	NO	NO	YES	YES	YES	YES	YES	YES
Periodic review	NO	NO	YES	YES	YES	YES	YES	YES

This is a good start but there are problems such as Functional and Design Specifications for software don't really exist if the supplier is using an Agile development methodology. Therefore, the main sections of the life cycle used in this Guide are shown in Figure 19.

The proposed qualification and documentation lifecycle is divided into three stages and the high-level process within each stage are shown in Figure 20.

Whilst suggested activities for all Groups and sub-types are shown, it is essential that each laboratory apply their own risk assessment and determine which activities are relevant to a specific item of apparatus, instrument or system.

Figure 20: Lifecycle Phases for Apparatus, Analytical Instruments and Systems Used in this Guide

	Examples of Risk-based Activities in the AIQSV Life Cycle							
	Proposed <1058> AIQSV Category of increasing risk							
	APPARATUS		INSTRUMENT			SYSTEM		
	A1	A2	B1	B2	B3	C1	C2	C3
LIFE CYCLE ACTIVITY	Apparatus: No metrological function	Apparatus: No User calibration required	Instrument: Firmware control	Instrument: In-built calculations	Instrument: User defined routines	System: Non configurable software	System: Configurable software	System: Configurable & customisable software
Stage 1: Specification and Selection								
Risk Assessment (RA)	YES	YES	YES	YES	YES	YES	YES	YES
URS (define intended use)	NO	NO	YES	YES	YES	YES	YES	YES
Evaluation and selection	NO	NO	YES	YES	YES	YES	YES	YES
Supplier Assessment	NO	NO	YES	YES	YES	YES	YES	YES
ID Critical Inst & DI controls	NO	NO	YES	YES	YES	YES	YES	YES
Selection Report	NO	NO	YES	YES	YES	YES	YES	YES
Supplier SW asessment	NO	NO	NO	NO	NO	NO	CONSIDER	YES
Purchasing specification & PO	YES	YES	YES	YES	YES	YES	YES	YES
Stage 2: Qualification and Validation								
Plan work Required from RA	NO	NO	YES	YES	YES	YES	YES	YES
Site Preparation	NO	NO	YES	YES	YES	YES	YES	YES
Supplier install and integration	NO	NO	YES	YES	YES	YES	YES	YES
Supplier commissioning	NO	NO	YES	YES	YES	YES	YES	YES
Prototying and Configuration	NO	NO	CONSIDER	CONSIDER	CONSIDER	CONSIDER	YES	YES
Update URS	NO	NO	CONSIDER	CONSIDER	CONSIDER	YES	YES	YES
Requirements traceability	NO	NO	CONSIDER	CONSIDER	CONSIDER	YES	YES	YES
User Acceptance Testing	NO	NO	CONSIDER	CONSIDER	CONSIDER	CONSIDER	YES	YES
Write SOPs and training	YES	YES	YES	YES	YES	YES	YES	YES
Instrumentation Log book	NO	NO	YES	YES	YES	YES	YES	YES
Authorisation for use	NO	NO	YES	YES	YES	YES	YES	YES
Stage 3: Continued Performance Verification								
Operational SOPs and Training	NO	NO	YES	YES	YES	YES	YES	YES
Use of Instrument Logbook	NO	NO	YES	YES	YES	YES	YES	YES
Trend Analysis and Monitoring	NO	NO	YES	YES	YES	YES	YES	YES
Preventative Maintenance Calibration & Requalification	NO	NO	YES	YES	YES	YES	YES	YES
Repair	NO	NO	YES	YES	YES	YES	YES	YES
Change Control and Configuration Management	NO	NO	YES	YES	YES	YES	YES	YES
Monitoring IT support	NO	NO	YES	YES	YES	YES	YES	YES
Periodic Review	NO	NO	YES	YES	YES	YES	YES	YES
Revalidation	NO	NO	YES	YES	YES	YES	YES	YES
Record Management/Archiving	NO	NO	YES	YES	YES	YES	YES	YES
Instrument/system retirement	NO	NO	YES	YES	YES	YES	YES	YES

9.1 Lifecycle Approaches for Analytical Procedures and Analytical Instruments & Systems

The lifecycle approach for analytical procedures, USP General Chapter <1220>, was developed over 12 years before becoming an official in May 2022 [6]. It considers the holistic validation activities that take place across the lifecycle of an analytical procedure and provides a framework for the implementation of a lifecycle approach. More details regarding this life cycle approach are given in a previous AQCG guideline [16].

9.1.1 Stages of the AIQSV Lifecycle

In the same way as the ECA APLM guide [16] is structured, there are three stages for the management of analytical instruments and systems as shown in Figure 21. Within each of these stages, the associated lifecycle elements will be discussed in more detail together with requirements for outcomes and documentation or records.

- Stage 1: Specification and Selection of Instruments and Systems
- Stage 2: Qualification/Validation of Instruments and Systems

- Stage 3: Continued Performance Verification of Instruments and Systems

9.1.2 Threads for all Lifecycle Stages and Phases

The next three Sections of this Guide will be a journey through the AIQSV lifecycle. For each of the stages and the phases within each of the stages there must be consideration of up to four threads:

- **Instrument**
  This thread is focused on the item of apparatus or instrument, the latter can be from either Group B or Group C. As Group B instruments are controlled by firmware and the functions must be included in this thread rather than under the Application thread.
- **System**
  Integration of all the threads together for Group C systems
- **Software Application**
  Group C instruments have a separate workstation or equivalent with application software that must be specified in more detail along with the configuration settings and user roles with the corresponding access privileges
- **IT & Network**
  Here the IT platform support and services need to be considered such as time synchronisation, cybersecurity, backup restore, configuration of the application, user account management etc.

In the Appendices, there will be tables identifying which tasks are required throughout the lifecycle for specific items of apparatus, instruments and systems:

Lifecycle Phase	Life Cycle Threads			
	Instrument	System	Application	IT & Network
System Risk Assessment				
Specify User Requirements				

The lifecycle presented in this Guide will be based upon the phases presented in Figure 21.

9.2 Control of Lifecycle Processes

9.2.1 Essential Policies and Procedures

Some considerations for an AIQSV lifecycle:

- Procedures should be risk based and flexible within defined limits to fit the qualification and validation to the intended use of the instrument or system.
- Procedures should be compatible with regulatory requirements and guidelines from competent authorities and pharmacopoeias.
- Lifecycle operations should be codified within a Quality Management System's policies and procedures and include risk assessment and risk management methodologies.

- Laboratory management should ensure that adequate time is allowed for staff to define requirements and evaluate instruments and systems. Rushing this phase of the lifecycle may cause the selection of the wrong item resulting in an operational lifetime of additional work as a key function is missing.
- Purchasing should be brought into the lifecycle early to ensure that they understand the rationale for purchase and do not subvert the laboratory selection process.

9.2.2 Ensuring Data Integrity

Data integrity is a critical requirement for both selection, qualification / validation and operational use of any instrument or system.

- Analytical instruments or systems must ensure that any data generated meet applicable ALCOA++ criteria for data integrity [62, 63].
- Hybrid systems are the worst possible option to implement in a GMP laboratory. Hybrid systems or standalone instruments that fail to meet data integrity requirements should not be purchased unless no other systems are available and proper ALCOA++ procedural/technical controls can be established.
- Both the WHO and PIC/S data integrity guidance documents do not recommend use of hybrid systems and advocate their speedy replacement [34, 36]. Moreover, the proposed update of EU GMP Annex 11 discusses the incorporation of additional technical controls to ensure data integrity [64] implying hybrid systems are obsolescent from a regulatory perspective.

The approach for implementing any computerised system should be:

- Streamline the process to be automated wherever possible to eliminate paper records and use electronic signatures wherever possible [9, 59, 65-67]
- Data vulnerabilities of any analytical instrument or system should be known and mitigated by technical rather than procedural controls
- Documentary evidence should be electronic, not paper, and should be generated for the entire lifecycle and be based on structured risk assessment(s).

Please refer to the ECA Data Governance and Data Integrity Guide for further information [9].

9.2.3 Flexibility is Key for Effective AIQSV

Never use a one size fits all approach for AIQSV or you will end up doing too much for most items and too little for others.

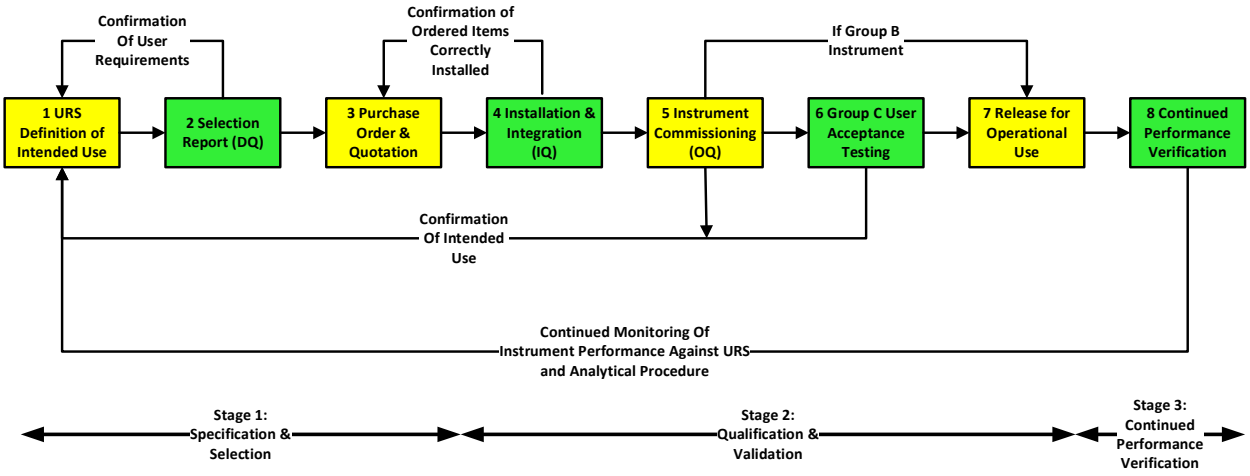
The key is flexibility: define the intended use for each item and develop a risk-based approach from there.

Always remember the regulatory and pharmacopoeial requirements that are applicable to the analytical technique for which the item is used must be incorporated in the URS.

9.2.4 Documented Evidence of Actions

A process flow of activities for Stage 1 and Stage 2 has been proposed in Figure 20 which would allow documentation and protocols to be identified enabling full traceability.

Figure 21: Expected High-Level Qualification and Validation Documentation for Stages 1 - 3

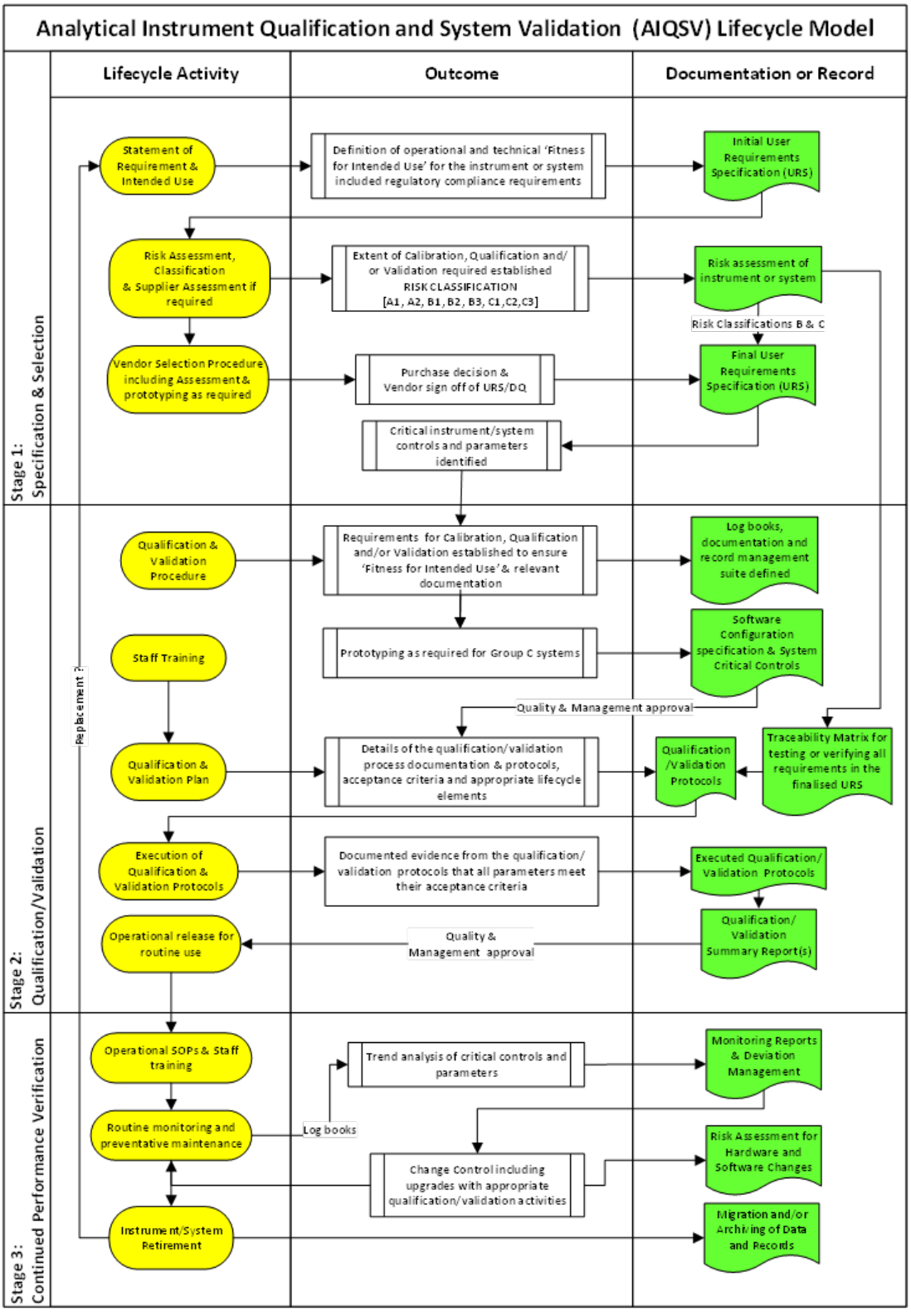


Key Document Steps

1. **User Requirement Specification**:
   Defines the laboratory's technical and operational requirements necessary to meet the performance requirements of analytical procedures and pharmacopoeial requirements. Security, user account management, IT support and cybersecurity as appropriate.
2. **Selection Report**:
   Documents the fit between the selected instrument or system and the user requirements. It may also encompass a review of supplier qualification documents and professional services.
   Note: For critical instrument selection and/or where a substantial investment is required, selection should include demonstration and evaluation "on-site" as this is indicative of the supplier's ability to provide support
   There should be reduced supplier assessment with C1 systems as they are GAMP© software category 3. With Group C2 and C3 systems there will be a supplier assessment or audit which may form part of the overall selection report.
3. **Purchase Order and Quotation**:
   This provides the baseline for the components to be installed in the next phase of the process. It is important to involve purchasing in this process as the selected system and item should not be substituted simply to save money.
4. **Installation and Integration**:
   In many cases this will be performed by the supplier or their agent and demonstrates what was ordered has been delivered and installed correctly. Qualification documents are usually provided by the supplier but must be reviewed pre and post execution by the laboratory.
5. **Instrument Commissioning**:
   Tests the instrument parameters against the requirements in the URS. This can be performed by the supplier, a third party, in-house metrology group or the laboratory.
   If there is no software, then the instrument can be released for operational use.

6. **System Testing**:
   Group C systems will require testing of the configured system including correct functioning against user requirements as well as data integrity and IT support such as backup.
7. **System Release for Operational Use**:
   This can vary from company to company. Release could require a statement in a qualification / validation report, a formal release statement or a change control form.
8. **Continued Performance Verification**:
   Continued performance verification can be composed of several steps with different frequencies such as system suitability checks using reference standards or calibrated materials or requalification. The aim is to demonstrate, directly or indirectly that the instrument or system continues to meet the requirements in the URS. The relationship between what work is performed after maintenance or repairs must be documented along with acceptance criteria. The principle here is that provided an instrument passes a well-designed verification test, continued use of the system is supported.

Figure 22: Overview of the AIQSV Lifecycle

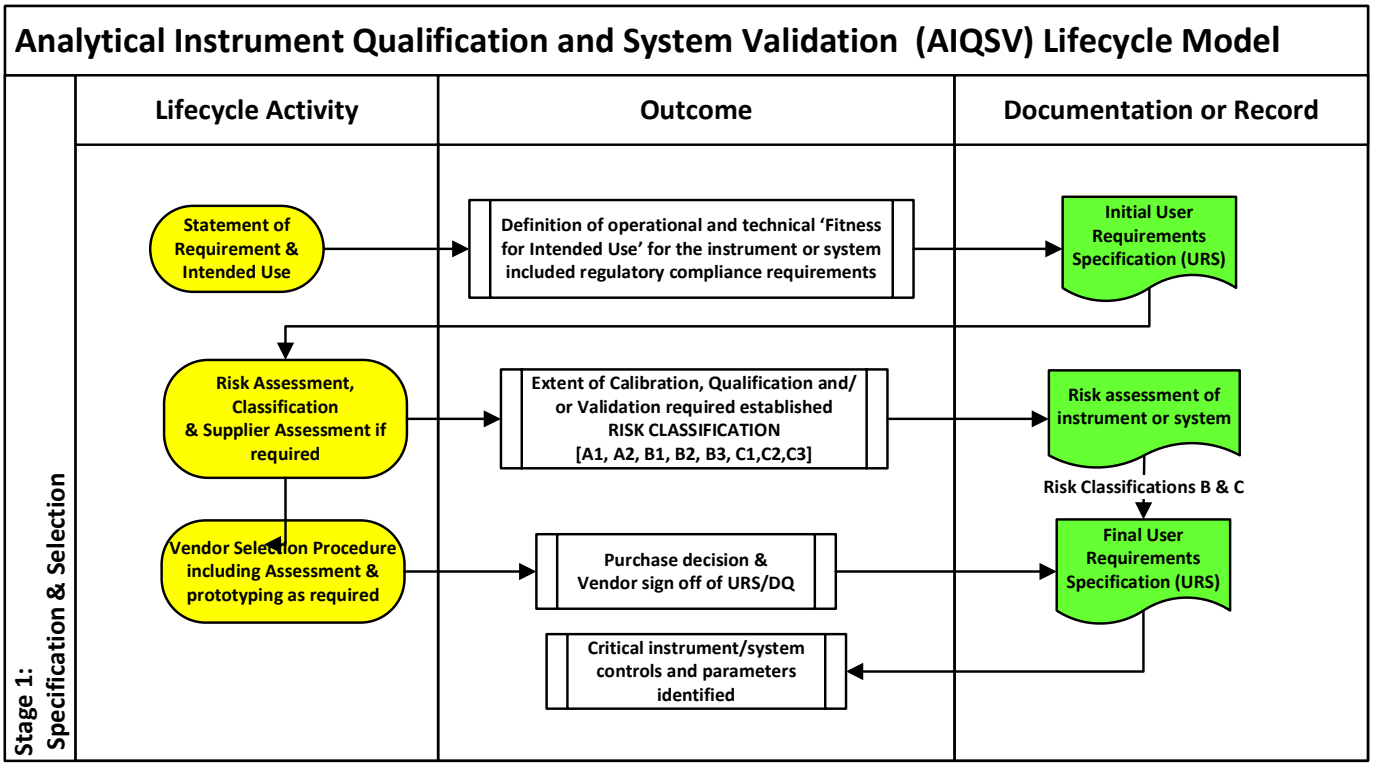


10 Lifecycle Stage 1: Specification and Selection

10.1 Introduction

This part of the lifecycle is the most important but audit evidence suggests that is either not performed at all or performed poorly. This is especially the case when there is a rush towards the end of a fiscal year to spend budget or lose it. The key to the whole of the life cycle process is the documentation of user requirements which reflect the intended way of working. It is important that a laboratory does not copy the supplier's specification as the parameters may be measured under conditions that a laboratory cannot match or, more frequently, the operating conditions or test methodology employed are inappropriate for the actual intended use.

Figure 23: The Detail of Stage 1 of the AIQSV Lifecycle



10.2 A Documented User Requirements Specification is a Statement of Intended Use

A URS is the first stage to instrument or system selection and most probably will change throughout the lifecycle of an instrument or system as the item use changes. Although there is a regulatory requirement a specification is important to obtaining the right instrument or system for the right job as shown in **Figure 9**.

10.2.1 Advice for Writing User Requirements

- A defined user requirements specification (URS) is a mandatory regulatory requirement to define intended use of any analytical instrument or system. Without a URS, it is not possible to demonstrate that an instrument/system is fit for intended use.
- A URS for a commercially available analytical instrument is expected to be concise and comprehensive but should not slavishly copy a supplier's specification. USP <1058> states that for commercial instruments the requirements are expected to be minimal [22].

- However, this implies formal specifications – not informal or virtual ones. Further, the requirements in the URS should be established using risk management principles.
- How minimal is minimal for an analytical instrument?
    - A pH meter will require only a few lines compared with a mass spectrometer and instrument control software.
    - Instrument operating parameters must be defined along with acceptance limits.
      The latter can be based on the requirements in pharmacopoeial general chapters, where applicable.
- Considerations for specifying software:
    - Firmware for Group B1 and B2 can be included in the specification for the instrument with the addition of calculations for Group B2.
    - Where user defined programs are used with Group B3 instrument, these are best handled by a separate SOP for the specification, build and test process
    - Software specifications for group C instruments require a more encompassing and detailed requirements covering both functional requirements (to perform the analysis) as well non-functional requirements such as security, user access privileges, configuration of the application audit trail, time synchronisation, calculations etc.
- Larger networked systems may require process mapping and redesign for an electronic process using electronic signatures. The redesigned process maps can be used as a basis for writing user requirements.
- We will see examples of how to do this in the Appendices (Sections 14 - 19) of this Guide.

10.2.2 A URS is a Living Document

The process owner / data owner is responsible for ensuring that requirements for both Group B instruments and Group C systems are documented.

- At the start of the process a laboratory will write a generic document for system selection, this is the responsibility of the process owner to manage. As such the make and model of the instrument and the name and version number of the software application are unknown
- The URS **may** be updated when different supplier's instruments and systems are evaluated to include new uses that were not considered when the first version of the URS was written
- When the system has been selected, the URS **must** be reviewed and updated to reflect the instrument or system to be purchased.
  Alternatively, if there is a controlling software wait until the system is installed and the key users are trained and the ways of working are fixed and then update the URS.
- Larger systems may require a configuration specification to document application settings, user roles and the corresponding access privileges.
- From experience, the URS for software **may** be updated when test scripts are written to prototype and refine the requirements as well as add or delete existing ones

10.2.3 Optional Tasks: Selection Tests and Request for Proposal

If the instrument acceptance criteria are based on pharmacopoeial requirements then no further work is required but for software you'll need to define evaluation tests and selection criteria based on the requirements in the URS. These can aided by using situations that have occurred in the laboratory in the past with some analytical procedures.

Larger systems may require a document called an (Invitation to Tender ITT) or a Request for Proposal (RFP) which are sent to potential suppliers who will respond with a tender or proposal. The URS should be converted into the RFP but omit any prioritisation that may have been done as this will bias the responses from suppliers.

10.2.4 Second Time Around?

When purchasing the same instrument or system reference the existing URS. However, ensure that the requirements are still the same and that the software and firmware versions are the same.

Many of the phases in Stage 1 can be omitted as the supplier, make, model of the instrument or version of the system are already known. The only work that would be performed would be to verify the instrument / system's applicability, the correct installation and commissioning. For Group C systems, configuration of the same version of software and verification that it is correct should be sufficient with cross reference to the original validation.

10.3 Supplier Selection and Qualification Process

10.3.1 Instrument, System and Supplier Selection

- Instrument and system selection should be based on objective evaluation against the laboratory user requirements specification using any evaluation tests that have been devised including how the instrument or system handles problems.
- Purchasing solely on price is not advised.
- A holistic evaluation of the supplier's QMS, instrument / system, overall service / support package /user training for different roles and supplier reputation is advised. Supplier should be on approved supplier list or at least undergo supplier management.
- Does the Supplier understand GMP and data integrity requirements?
  PIC/S PI-041 Section 9.1.4 states: *Regulated users should ensure that vendors of systems have an adequate understanding of GMP/GDP and data integrity requirements, and that new systems include appropriate controls to ensure effective data management* [36].
- Generate a list of potential suppliers if appropriate and send the RFP and evaluate the responses
- Visit or talk with existing users to understand how the instrument or system works operationally. If going through a supplier these will be the good customers.
- Integration of the instrument into an overall laboratory data and information management strategy is critical.
- A selection report is recommended that justifies why a supplier and instrument / system was chosen.

10.3.2 Supplier Software Assessment or Audit

- A software assessment or audit is required for Group C2 and C3 systems to determine the quality of software development, testing and support. This should be performed before confirming supplier selection and should only be performed on the short-listed supplier to save resources.

- This can be performed remotely or on site depending on time / travel and cost. The recommended minimum is a remote assessment via video conference and cannot be performed adequately using a questionnaire.
- The aim of this assessment is to confirm that there is an adequate QMS in place but most importantly the outcome is necessary for justifying reduced User Acceptance Testing
- Adequacy of the QMS can be demonstrated off-line using supplier provided material. If not, spend a small amount of time gathering information about the QMS especially if it is certified to a recognised quality standard e.g. ISO 9001.
- The reason for video conference or on-site assessment is that you will want to see how software is developed and tested using Agile tools (e.g. Jira or DevOps) how risks are managed and changes controlled. Suppliers rarely write software functional or design specifications now, the development process is managed with software tools that contain the records such as epics, user stories, requirements derived from each story, acceptance criteria, code management, code reviews, software testing and error management. GAMP© 5 Second edition Appendices D8 and D9 outlined the justification for acceptance of this approach [27]. The outcome of this portion of the assessment will either be a second report or a sub-section in the selection report.
- Leveraging the supplier's development work: a configurable application is GAMP© category 4 which is commercially available configurable software which allows the business process to be modified. However, many Category 4 applications have Category 3 (non-configurable) functions that are only parameterised. How to differentiate of GAMP software categories 3 and 4 is critical to the use of the IVD. Category 3 software cannot change the business process it automates: it does exactly what is says in the brochure. Nothing more, nothing less. Although run time configuration is possible e.g. definition of user roles and access privileges, report formats but the business process cannot be changed.
- A major cause of confusion is parameterisation which can be performed on functions in both category 3 and 4 software. Parameterisation is setting the wavelength used to measure absorption of an analyte on a spectrometer or HPLC detector. If the wavelength is set at 220nm and then changed to 280nm, the business process has not changed. The instrument is still measuring the absorbance of an analyte regardless of wavelength i.e. the business process is unchanged. However, many people think this is configuration, it is parameterisation, but still needs to be controlled when people use the system e.g. method validation or analytical procedure. Further examples of parameterisation are:
    - Changing the flow rate on an LC pump: process is the same just the flow rate differs.
    - Wavelength scanning range on an IR or UV spectrometer.
- If the software assessment is adequate and a supplier has tested Category 3 software functions why should the laboratory repeat this work? However, it requires an assessment report to justify this.
- Although this is a way to reduce the UAT, it does not mean that no software testing should occur: the laboratory still must demonstrate fitness for intended use against the URS.

10.3.3 Supplier Assessment and Agreement for Software as a Service (SaaS)

The requirements for any SaaS application should be included in a section in the URS which may point to a supplier specification for the virtual infrastructure used in the application deployment.

As more laboratory applications e.g. Chromatography Data Systems and Laboratory Execution Systems have options to be operated as SaaS as well as on-premises, an effective agreement is not just a regulatory requirement

e.g. Annex 11 clause 3.1 [21] but business critical. Proposed changes to Annex 11 may require a supplier to support an inspection if the supplier claims that the system is validated [64].

Considerations for a SaaS deployment include:

- If SaaS is an option for the software, then the supplier assessment needs to include how virtual infrastructure is specified, generated, qualified and controlled as the supplier is now your IT Department for the application.
- Has the supplier qualified their cloud service provider?
- Are the supplier's IT staff suitably qualified and trained including GXP awareness?
- If Software as a Service (SaaS) is the way to deliver an application, then a technical agreement is required before issuing the purchase order as required by Annex 11 clause 3.1.
- The agreement must include:
    - Key personnel and deputies from the organisation and SaaS provider
    - Defined roles and responsibilities of both parties
    - Escalation procedure for both parties
    - Service levels and metrics
    - Reporting intervals
- The SaaS agreement will be discussed in detail in Section 18.3 . This is also similar to the agreement required for internal IT Support and one is required under Annex 11 clause 3.1 [21].

10.4 System Risk Assessment

A system risk assessment should be conducted at the start of the selection process but also reviewed at the end of it to see if there are any changes to the outcome. Once complete, the tasks for the Lifecycle Stage 2 (qualification and validation) can be planned and, where appropriate, ordered. The risk assessment is described in detail in Section 8.

10.5 Identification of Critical Instrument Controls and Parameters Including Data Integrity Functions

This section is important as it provides the link between the actual functions within an analytical instrument and how these influence the generation of the reportable value. Many users are simply told that this is the way to perform an analytical procedure but fail to understand the way an analytical instrument works.

10.5.1 Critical Instrument/System Controls and Parameters

In order to assure 'Fitness for Use' for an analytical instrument or system, two questions need to be addressed by the User.

1. How does the analytical instrument or system function in generating data/results/reportable values?
2. What are the specific requirements for operation of the analytical instrument or system within their particular laboratory?

The second question is usually answered in the URS as described in section 11.2 of this guide.

The first question is more difficult to answer in that it requires technical knowledge of the analytical instrument or system's metrological processes within the laboratory.

Many sophisticated instruments and systems, for example Fourier Transform spectroscopic systems, have built in diagnostic routines provided by the vendor which allow the monitoring of functionality not accessible to the routine user for monitoring and metrological control purposes. Ideally reference standards should be traceable but if internal reference materials are used there needs to be a documented justification for their use.

However, the identification of critical instrument/system controls and parameters is both necessary and sufficient for lifecycle performance. An example identification process is illustrated using the most common laboratory instrument; an analytical balance used for weighing samples and reference standards in accordance with USP requirements. A knowledge of the operating principles and constraints is needed. For more information see for example [68-70].

10.5.2 Mandatory Requirements according to USP <41> Balances

There are three AIQSV mandatory requirements for an analytical balance namely accuracy, repeatability and establishment of a minimum weight [71].

1. The accuracy of a balance is satisfactory if its weighing value, when tested with a suitable weight(s), is within 0.10% of the test weight value.
2. Repeatability is assessed by weighing one test weight not less than 10 times. Repeatability is satisfactory if twice the standard deviation of the weighed value, s, divided by the desired smallest net weight (i.e., smallest net weight that the users plan to use on that balance), does not exceed 0.10%.
3. The minimum weight, M_{min}, is established by the repeatability measurement and is the smallest net amount of material that may be weighed on the balance in conformance with the 0.10% limit. The minimum weight, M_{min}, is described by the inequality $M_{min} \geq 2000s$. If the repeatability standard deviation, s, obtained is less than 0.41d, where d is the scale interval of the balance, then the inequality becomes $M_{min} \geq 820d$.
   Note that the minimum weight applies to the sample weight, **not** to the tare or gross weight.

Requirements 1 & 2 are usually recognised but not always the third.

However, we also need to consider 'in use' performance aspects over the AIQSV lifecycle and take note of the best practice guidance document USP <1251> Weighing on an analytical balance [72] which gives examples of factors that can influence balance performance whilst the balance is in use and include:

- The performance of the balance and thus the minimum weight can vary over time because of changing environmental conditions.
- Different operators may weigh differently on the balance—i.e., the minimum weight determined by different operators may be different.
- The standard deviation of a finite number of replicate weighings is only an estimation of the true standard deviation, which is unknown.
- The determination of the minimum weight with a test weight may not be completely representative for the weighing application.
- The tare vessel also may influence minimum weight because of the interaction of the environment with the surface of the tare vessel.

Table 3: USP <1251> Additional Analytical Balance Parameters

Property	Definition	Examples	Acceptance Criteria
Sensitivity[1]	Change in the displayed value divided by the load on the balance, which causes this change.	The test load at or sufficiently close to the capacity of the balance.	NMT 0.05% deviation from 1 (the sensitivity of a correctly adjusted balance
Linearity[1]	Ability of a balance to follow the linear relationship between a load and the indicated weighing value. Nonlinearity usually is expressed as the largest magnitude of any linearity deviation within the test interval.	From 3 to 6 points over the range of the balance.	NMT 0.05% deviation
Eccentricity	Deviation in the measurement value caused by eccentric loading—in other words, the asymmetrical placement of the centre of gravity of the load relative to the load receiver. Eccentricity usually is expressed as the largest magnitude of any of the deviations between an off-centre reading and the centre reading for a given test load.	Performed in the centre of gravity and the four quadrants (for rectangular platter shapes) or at analogous locations for other platter shapes. Test load usually should be 30% of the capacity of the balance or higher (refer to the manufacturer's manual for any possible upper limit).	NMT 0.05% deviation

The identification of these critical controls is essential particularly for Continued Performance Verification (Lifecycle Stage 3) discussed in Section 13 of this guide.

Hence, three additional instrument controls need to be in place and monitored over the Stage 3 of the AIQSV lifecycle, namely sensitivity, linearity, and eccentricity. These three properties contribute to systematic deviations; i.e., they limit the accuracy of the balance and are summarised in Table 3 based on USP <1251> [72]. The periodicity of review and trending of these parameters [73] should be decided on a risk assessment but keep in mind that an analytical balance is one of the most critical instruments in any laboratory.

10.5.3 Data Integrity functions

Technical controls for ensuring data integrity requirements that should be available in some analytical instruments and system software are:

- Security: accounts for each named user
- User roles and access privileges. No laboratory user should have deletion or administrator privileges
- Controls for ensuring that the right instrument is used, it is qualified and is fit for use on the day of analysis

[1] Use certified weights with an appropriate weight class (e.g., according to International Organization of Legal Metrology R111 or American Society for Testing and Materials E617)

- Controls for enforcing workflows
- Attribution of actions of an individual performing the work
- Date and time of the work (no laboratory user has access to the instrument clock and check for accuracy are recorded in the instrument log book with any corrections to be made)
- Use of electronic signatures, if applicable
- Audit trails that cannot be turned off containing readable and understandable entries

In some cases, if the application software does not provide say security functions, log on via the operating system should be implemented so that a laboratory user can only access the instrument software and have no access to the data in directories.

10.6 Purchase and Receipt of the Instrument or System

The crossover to Stage 2 starts with the quotation from the supplier and the resulting purchase order which may be supplemented with the supplier selection report. As mentioned earlier in Section 5.4, ensure that the Purchasing Department is involved to negotiate the price and contractual terms and conditions before placing the purchase order.

The quotation is the beginning of configuration management of the instrument or system as it will list all components and documents that will be purchased by the laboratory.

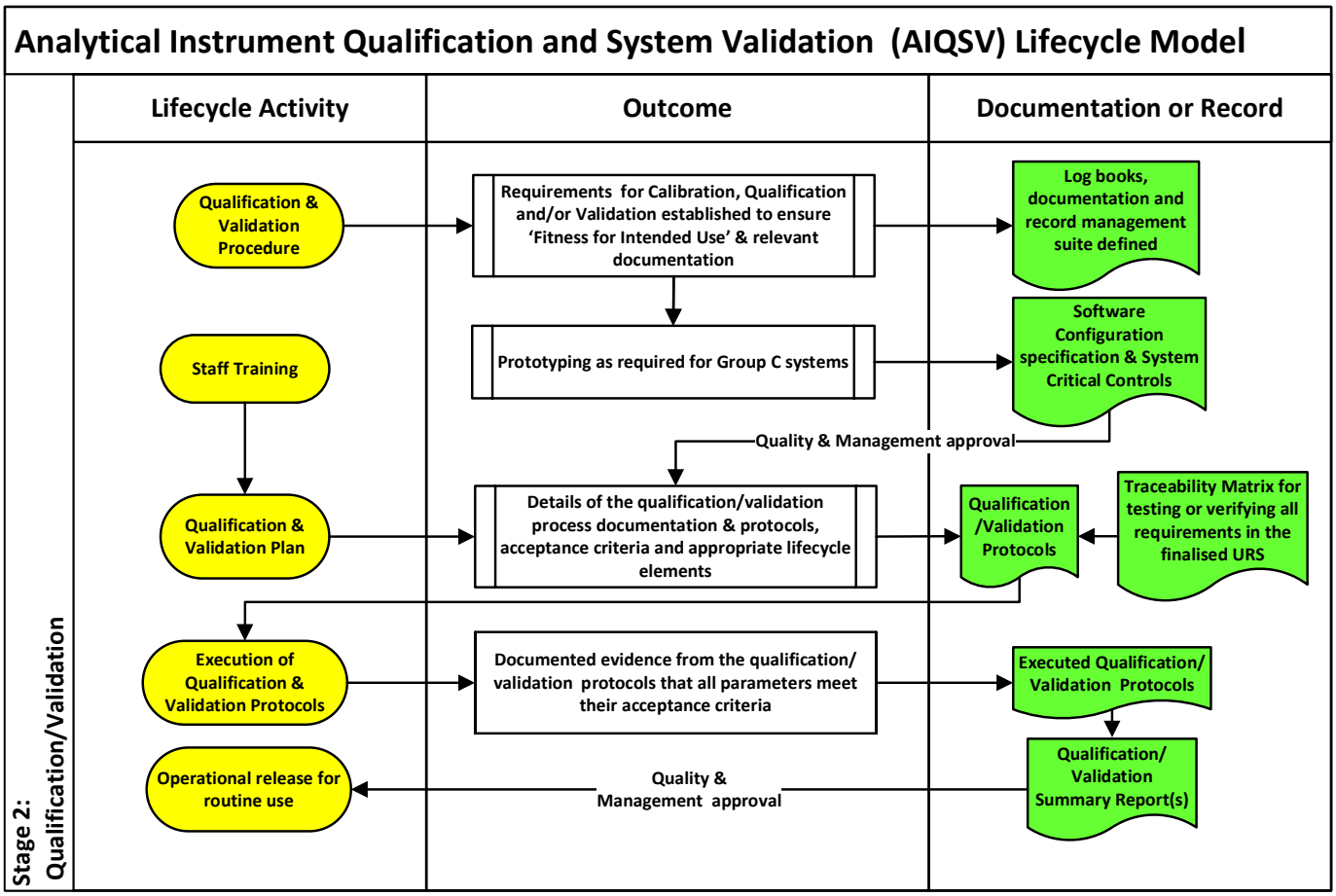
When delivered, the items should be checked against the purchase order to ensure that all components have been delivered.

11 Lifecycle Stage 2: Qualification/Validation of Instruments and Systems

11.1 Introduction

Qualification and validation work in this stage of the life cycle can vary from relatively straightforward check to show that an instrument has been installed correctly and is calibrated within the URS acceptance limits of key parameters to qualification of the instrument and validation of the controlling software especially for a system such as a chromatography data system.

Figure 24 The Detail of Stage 2 of the AIQSV Lifecycle



11.2 Calibration and Qualification of Instruments Using Traceable Standards & CRMs

Many analytical instruments in Groups B and C will undergo calibration as part of an overall qualification. This is typically performed using traceable reference standards or calibrated instruments followed by adjustment of the parameter within acceptance criteria. This should be differentiated with a system suitability test or point of use where an instrument generated value is compared with a reference standard on the day.

The former is discussed in this section and the SST/point of use check in Section 11.3.

11.2.1 Introduction

Calibration of critical instrument metrological parameters is normally accomplished using traceable reference materials. The term calibration in the laboratory is generally used in the sense of verifying that a particular property of a reference standard is within an acceptance range of values. This term may be defined as:

> *The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard* [74].

This is not an engineering definition of calibration which normally implies adjustment to bring an instrument into a state of control. For example, one definition supporting this engineering definition is;

> *Calibration is the process of configuring an instrument to provide a result for a sample within an acceptable range. Eliminating or minimizing factors that cause inaccurate measurements is a fundamental aspect of instrumentation design* [75].

On the other hand, qualification is defined in EU GMP glossary as;

> *Action of proving that any equipment works correctly and actually leads to the expected results [74].*

In this Guide we will use the EU GMP Glossary definitions of calibration and qualification. Note that the term verification is not defined in the EU GMP glossary.

11.2.2 Mean Value Acceptance Criteria for Calibration/Qualification.

There are a number of options, much used in the Pharmacopeias, which have acceptance criteria based upon either standard deviation or absolute ranges. However, they are not consistent. For more information see [76] for a discussion of decision rules

11.2.3 The Concept of Measurement Uncertainty

All metrological measurements are subject to error. The way in which we quantify these errors depends upon the approach. Traditionally, in analytical chemistry, we partition these errors into two types namely accuracy and precision [77]. Alternatively, these two error types are combined to give a measurement uncertainty of a value at a stated confidence level usually 95% [78].

The USP General Chapter <1010>. goes on to state that 'In ISO, accuracy combines the concepts of unbiasedness (termed trueness) and precision. The details of how this is done using the concept of error budgets is not required for this guide but those seeking more detailed information should see [79] and [80].

11.2.4 CRMs (Certified Reference Materials) and Measurement Uncertainty

Traceable reference materials used for the calibration of instruments are usually CRMs. These materials were briefly discussed in Section 3.7 of this Guide. CRMs certified values must come with a stated measurement uncertainty.

The issue becomes one of how a laboratory can demonstrate proper calibration/qualification compliance using measurements of CRMs on particular instruments.

11.2.5 Measurement Uncertainty Usage in Calibration for Absorbance Accuracy of UV Spectrometer

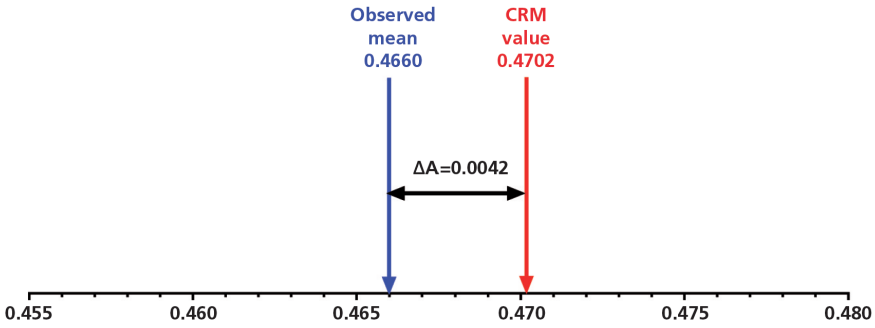
A Certified Reference Material (CRM) for absorbance is used that has traceability to a National Measurement Institute (e.g. NIST). It is known that the spectrometer's wavelength scale error is small enough not to cause any significant absorbance error at the wavelength of interest.

Using the recommended operational procedures, six independent measurements of the CRM are performed at the wavelength of interest and the following absorbance data are obtained: 0.464, 0.468, 0.463, 0.465, 0.467, and 0.469.

The CRM has a certified absorbance value of 0.4702 at the wavelength of operation.

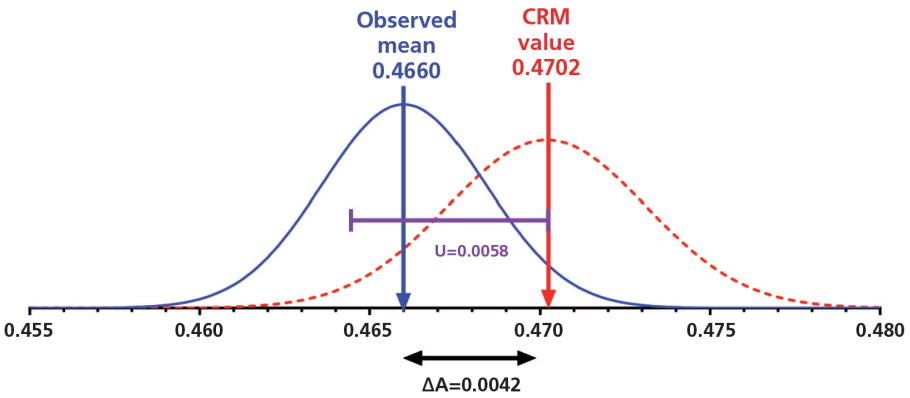
We calculate the mean of our observed absorbance and get a value of 0.4660 which is a difference, ΔA, of 0.0042.

Figure 25 Comparison of mean absorbance and the certified value of the CRM



Therefore, can we conclude that our spectrometer is inaccurate? The answer is no because we have not taken into account the uncertainties in the CRM and our measurement of the CRM on our spectrometer. Therefore, because all measurements are subject to error, we can draw the distributions around these values and calculate a combined 95% confidence value (U) for the measured CRM. The value of U includes a contribution from the observed precision value found on our spectrometer and this confidence interval includes the mean of the observed values. Therefore, we can conclude that our spectrometer is accurate. For details of the calculation see ***Fehler! Textmarke nicht definiert.***

Figure 26 Comparison of the uncertainties of mean absorbance and the certified value of the CRM



An alternative approach is to use simple acceptance limits based upon a statement contained in the NIST SRM 1930 Glass filters certificate.

> *'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'[i]

This has been interpreted as 'Add the CRM's expanded uncertainty to the manufacturer's tolerance and make those the acceptance limits (AL) for satisfactory calibration performance'. It is very easy to calculate and apply.

Hence *AL*=±(U+A)

Suppose that an CRM absorbance value which has an expanded uncertainty ±0.0049 (*U*) absorbance units and the instrument manufacturer's specification, (*A*), at that absorbance value, is ±0.005 absorbance units. Hence simple addition gives Acceptance Limits of ±0.0099 absorbance units from the certified value.

However strictly speaking we should also take into account the contribution of the CRM measurement ie the standard error of the measured mean corrected for the number of determinations.

$$AL = \pm t_{(0.05,n-1)} \frac{s}{\sqrt{n}} + \left(U + A\right)\right)$$

These correct limits will be a little larger than the acceptance limits based on just (*U+A*) which are more conservative. From a compliance perspective the acceptance limits based on just ±(*U+A*) are 'fail safe' so would be acceptable. For more information see [81] and [82].

11.3 System Suitability Test / Point of Use Checks

Point of use and SST checks on the day are an integral part of ensuring data quality and data integrity by ensuring the instrument can perform an analysis. This is discussed in Phase 3 of the lifecycle in Section 12, however it is important to mention here that the checks performed on the day should be related, either directly or indirectly, to specified requirements and acceptance criteria in the URS.

In addition, results should be plotted and trended against the respective acceptance criteria as required by EU GMP Chapter 6 clause 9 [73], see section 12.4.

11.4 Plan the Work to Be Performed

There is a great disparity of work required to qualify instruments and systems in Groups B and C respectively and this needs to be planned accordingly following the outcome of the system risk assessment.

11.4.1 Group B Instruments

The range of qualification work required will consist of:

- **Group B1**: Correct installation of the instrument and qualification / calibration of the instrument's operating ranges
- **Group B2**: Correct installation of the instrument and qualification / calibration of the instrument's operating ranges and verification of the embedded calculation(s) as part of the qualification of the instrument

- **Group B3**: Correct installation of the instrument and qualification / calibration of the instrument's operating ranges.
  An SOP should be used to specify, build, verify and manage all user defined programs

11.4.2 Group C Instruments

The range of qualification and validation work will consist of :

- **Group C1**: Correct installation and qualification of the instrument and software, typically by the supplier. Validation of the system using an Integrated Validation Document described in Sections 9.8 and 17.1.
- **Group C2:** Correct installation and qualification of the instrument and software, typically by the supplier. Validation of the system as defined in a validation plan that will outline the phases of the project.
- **Group C3**: Correct installation and qualification of the instrument and software, typically by the supplier. Validation of the system as defined in a validation plan that will outline the phases of the project plus the macros developed for operational use in this stage of work. Once the system is operational, an SOP will be required to specify, build, test and manage all macros developed by the laboratory.

The validation plan required for Group C2 and C3 systems can be considered further risk management dependent on the outcome of the supplier assessment in the Lifecycle Stage 1.

11.4.3 Key User Training

Depending on the instrument or system being qualified or validated, key user training should be considered as early as possible in this Lifecycle Stage. This will allow the laboratory to understand the functioning of the item as well as speed the overall qualification and / or validation.

11.4.4 Site Preparation

Information from the supplier should be used to ensure that the site when the system or instrument will be installed is ready for the engineer to do their work such as:

- Adequate space for the item to be taken from Good Inwards to the intended location (either bench or free standing)
- All required services are available (e.g. power, gases, extraction, water, network access, etc.)
- Health and Safety requirements are put in place using the supplier's recommendations

11.5 Supplier Installation and Commissioning

The work in this phase consists of the following elements and is applicable to all Group B instruments and Group C systems. Where supplier documentation is used it must be integrated into the suite of qualification or validation documentation supporting the intended purpose of the item. This can be achieved through procedures controlling these two processes.

11.5.1 Pre-Execution Review of Qualification Documents

- Evaluation and review of supplier installation commissioning / qualification documents against the requirements and associated acceptance criteria in the URS for the instrument before execution. The data integrity of the results reported must be verified. If application software is to be installed the corresponding documentation also needs to be reviewed and may involve the company's IT staff and/or a laboratory administrator.

- There is wide variation in how labs "deal" with failed qualification tests. The principles of OOS apply, but not as dogmatically as sample testing. Ideally the actions take in the event of a qualification test failure needs to be agreed in a quality agreement.
- Qualification documents can be combined if required to streamline supplier installation and commissioning phases
- Instrument commissioning parameters and acceptance criteria should match those defined in the laboratory URS

11.5.2 Executing and Reviewing the Completed Work

- Some of this work will involve calibration of the instrument using certified reference materials (CRMs) and test instruments calibrated to national or international standards e.g. temperature probes. Alternatively, a calibration certificate of the instrument from the supplier may be used.
- If software is being qualified or used to execute qualification tests it must **NOT** be executed using the default account, rather a named account should be created so that work is attributed to a named individual even if that is a supplier's service engineer.
- The completed qualification documents must be reviewed along with any electronic records generated. Ideally the completed records are electronic rather than paper. However, manual execution of active PDF or Word documents is unacceptable as there is no verifiable attribution of action.
- If the work is carried out on the service engineer's computer, copies of the e-records must be left with the laboratory. Converting dynamic instrument records to static PDF documents is not acceptable [33, 35].
- When reviewing a completed protocol, particular attention should be paid to any repeat work or deviations from the plan to ensure that the work has been completed correctly and there are no missing or orphan data [83].
- Any installation and commissioning of an application including a database should be conducted on unconfigured software. It is the responsibility of the process owner in the laboratory to determine and configure the application settings, security and user roles not the supplier.
- Any user roles created as part of the qualification or validation work should be deactivated prior to release for operational use
- Some Group B instruments have basic user roles and access privileges that will need to be configured after the qualification is complete and this needs to be documented either in the URS, SOP or configuration specification.
- For Group B instruments, providing that the URS requirements have been met, the instrument can be release for operational use.
- Ensure that there is an instrument maintenance and use logbook available as described in Section 12.11.

11.5.3 Interfacing Group B Instruments to Informatics Applications

- Group B instruments that are interfaced to informatics applications such as a LIMS, ELN or LES, additional qualification and validation work is required.
    - Demonstrate the ability to transfer data automatically from the instrument to the application. Manual triggering of data transfer is not recommended as this can be an opportunity for data integrity violations of only transferring acceptable data. However, if manual triggering is the only option, then enhanced checks are required to ensure the integrity of the transfer.
    - If applicable, methods and any sample information downloaded to the instrument.
    - Some instruments have the ability to act as a terminal for the informatics application with a workflow determining when data will be transferred to the database.

11.6 Prototyping and Configuring the System

Applicable to all Group C systems, this is an optional phase of work that is to understand how the system would operate in use. It consists of evaluating how the application works with different application settings.

- After key user training the various configuration settings can be prototyped to find the best operational fit. The process can be undocumented, provided this is stated in the validation plan.
- Can paper and any spreadsheet calculations be eliminated and electronic signatures implemented
- Where possible, electronic workflows should ensure the steps in an analytical procedure are followed, the correct instrument is used, the instrument is fit for use on the day and ideally a single data storage location is dictated by the system to save time when work is reviewed by a second person.
- The outcome of the prototyping should be a formal configuration specification of the application settings.

11.7 Updating the URS

The URS used for selecting the system will be generic and, at a minimum, must be updated to reflect the name and version of the application being validated. This information must be on all validation documents.

- Ensure that all requirements are uniquely numbered to enable traceability throughout the lifecycle [21] to other stages of the life cycle e.g. installation, commissioning, testing or an SOP
- If applicable, the numbering should permit linkage between the user requirements and the application configuration settings (e.g. link URS and configuration specification)
- During prototyping and user acceptance testing, will be necessary to update the laboratory URS used for selection to one for the specific application and version purchased.
- Modification of the updated URS during writing the user acceptance test protocols is also a common occurrence. It also demonstrates that the validation team understand that the URS is a living document.

11.8 Requirements Traceability

- For Group C systems, Annex 11 clause 4.4 states that requirements must be traceable throughout the lifecycle of a computerised system [21]
- This can be built into a table as will be demonstrated with the IVD for a system as outlined in Section 8.8 or it can be a separate document: a Traceability Matrix
- Often the traceability matrix is generated towards the end of a validation project. This is a mistake as what happens if a critical requirement has been omitted from testing? It is better to check the traceability of requirements as early as possible in this stage of the lifecycle instead of leaving it to the end and find some requirements have been omitted from the verification of acceptance testing.

11.9 User Acceptance Testing (Performance Qualification)

The key to this part of the lifecycle is knowing how the instrument or system including the application software for Group C systems functions. The apply a scientifically sound and logical approach (critical thinking) coupled with common sense.

- This is testing the overall Group C system (consisting of the instrument and configured application software) against the updated user requirements and configuration specification.
- An overarching UAT plan can offer advantages in presenting how the separate test protocols are linked together. In addition, the test environment is defined and what will be tested and, just as important, functions and components of the system that will not be tested.

- The assumptions, exclusions and limitations of the test approach are a key was of managing and documenting risk as not everything can be tested in a system.
- The supplier's software development work can be leveraged into the UAT at this point if there was a successful supplier software development assessment. For example, software functions that are only parameterised can be assumed to work and implicitly tested. The focus should be on configurable functions, data integrity requirements and key IT support such as backup and restore.

11.10 Write Procedures and User Training

EU Annex 15 clause 3.12 "*The completion of a successful OQ should allow the finalisation of standard operating and cleaning procedures, operator training and preventative maintenance requirements*." [5]. To ensure that the system is ready for operational use SOPs and training in them must be undertaken:

- Procedures for various user roles should be written and approved
- Training must be provided to ensure that the instrument is used correctly and within established limits
- IT staff supporting the system must also be trained in procedures and the records required to demonstrate that they have been executed correctly

11.11 Establish the Instrument Logbook

- As required by 21 CFR 211.182 [18] and EU GMP Chapter 4.31 [84] an instrument maintenance and use log book must be established for the instrument or system.
- At a minimum this must be a bound and paginated book that allows all the analysis, repairs and maintenance work to be recorded. This is discussed in more detail in Section 13.3.

11.12 Operational Release for Routine Use

- This can occur for Group B analytical instruments at the end of the commissioning phase or after the user acceptance testing for a Group C system.
- A formal release is required which can be part of a commissioning document, a separate validation summary report outlining the work performed in the life cycle or a change control form.

11.13 Validation of Multiple Instances of the Same Group C System Software

If there are multiple instances of the same Group C system, the first instance must be full validated. As long as the software version is the same in the remaining instances, the first validation can be leveraged into succeeding validations to drastically reduce the amount of work performed. An example of such an approach is shown in Table 4. Here, three instances of the same software version have been purchased over time and the validation from the first instance is used to reduce the work required to validate the other two instances.

The table mentions a common document, this is a single document applicable to all instances e.g. URS provided all three instances perform the same functions, configuration specification and global procedures.

An alternative approach is to include instancing in the URS and validation plan.

Table 4 An Example of Leveraging Validation of One Instance of the Same Software to Other Instances (where user requirements are essentially the same)

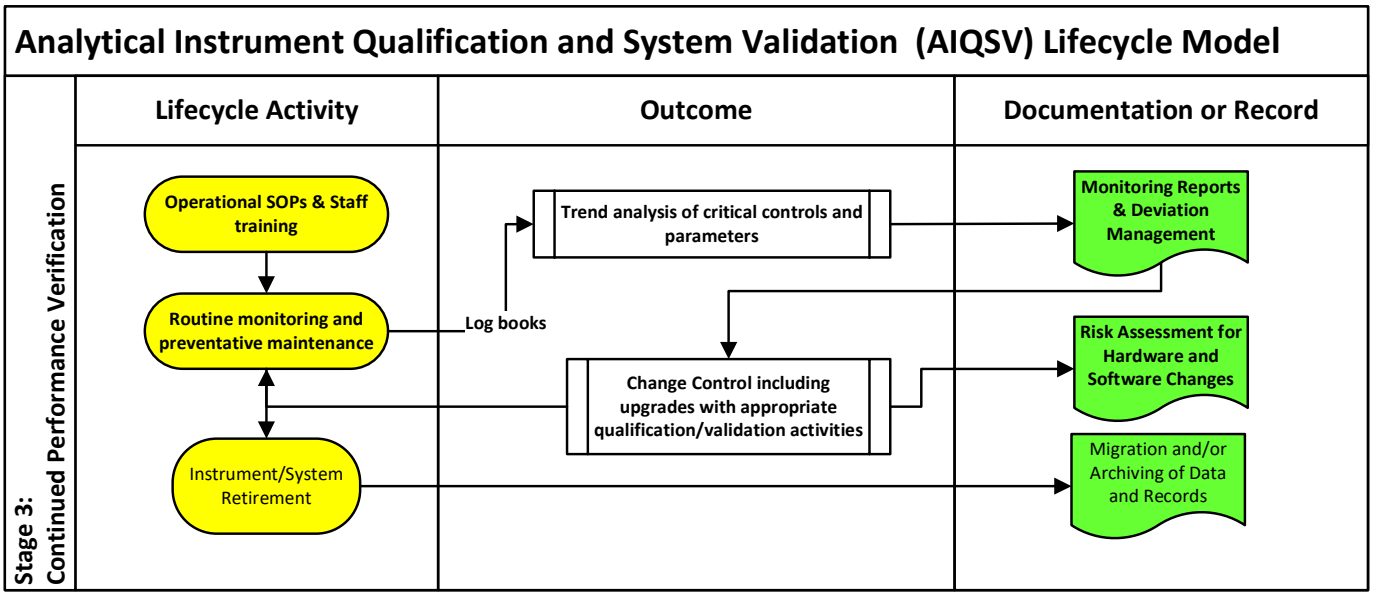
Validation Document	Instance 1	Instance 2	Instance 3
System Risk Assessment	Common document		
Validation Plan	Common document		
User Requirements Specification	Common document		
Supplier Software Assessment	Common document		
Supplier Qualification	Common document		
Purchase Order	✓	✓	✓
Supplier Installation and Integration	✓	✓	✓
Supplier Commissioning	✓	✓	✓
Configuration Specification	Common document		
Traceability Matrix	Common document		
User Acceptance Test Plan	Common document		
Configure System	✓	✓	✓
UAT TS Security and Access Control	✓	✓	✓
UAT TS Analysis and Calibration 1	✓		
UAT TS Analysis and Calibration 2	✓		
UAT TS Reporting including Electronic Signatures	✓		
UAT TS Compliance features e.g. Audit Trail	✓		
UAT TS Backup and restore	✓	✓	✓
UAT TS Data Reprocessing	✓	✓	✓
SOPs for all User Roles	Common documents		
Validation Summary Report (for each instance)	✓	✓	✓

12 Lifecycle Stage 3: Continued Performance Verification

12.1 Introduction

This stage of the lifecycle is the longest that can last from a state of the art instrument or system being installed to a museum artifact being retired, depending on the strategy for instrument or system replacement by the laboratory / organisation.

Figure 27 The Detail of Stage 3 of the AIQSV Lifecycle.



12.2 Operational SOPs and Training

- If not performed in Stage 2 as described in Section 12.10, then the SOPs must be written and training provided for all users before the system is used.
- It is preferable to have the SOPs written in Stage 2 rather that Stage 3 as the procedures will be available as the instrument or system becomes operational

12.3 Operational Use of Instrument Logbooks

Instrument logbooks are critical for monitoring correct use of the instrument or system but often suffer from common errors. Logbooks can be either bound paper of electronic but must comply with the following regulations:

- EU GMP Chapter 4.31 states …. *They should be used to record in **chronological order**, as appropriate, any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out [84].*
- 21 CFR 211.182 states: *A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. …*
  *The persons performing and double-checking …… shall date and sign or initial the log indicating that the work was performed. **Entries in the log shall be in chronological order [18]**.*

- A common mistake with logbooks is that there are separate sections for operational use, maintenance and repair, requalification etc. The regulations above are explicit, there must be a single section where everything is logged in chronological order - regardless of what class the entry falls under.
- There should be space for an analyst to enter their initials for each entry plus space for the instrument or system owner to review entries on a periodic basis to see that the item is functioning correctly.
- Some routine calibration data will be trended as described in Section 12.4

12.4 Routine Monitoring Through Trend Analysis

Continued Performance Verification of instruments and systems is an essential part of assuring on going 'fitness for use'. Simple methods of visualising time related data and establishing trending of critical control parameters should be carried out. This visualisation of data will reveal any potential problems and issues with the state of instrument/system control.

The compliance driven diktat of 'if it's in specification on the day everything is ok' should be supported by historical trend data. However, it is required to trend only critical control parameters, as established during the Risk Assessment, and not adopt an 'everything must be trended' approach.

Product Quality Reviews may require more rigorous statistical evaluation of data over the lifecycle, for example capability indices, to monitor the state of control against the requirements in the URS and the ATP. This can be coupled with a comprehensive check of the documentation status or it can be a part of an Annex 11 periodic review for Group C systems [21].

Detailed guidance on the methods used for trend analysis and statistical evaluation of data is provided in an earlier ECA AQCG Guideline [85].

This guideline applies primarily to physicochemical -based laboratory testing resulting in continuous data (variables, for example assay, impurity values, hardness etc., which may be assumed to be normally distributed) or discrete data (attributes for example, particle counts, identity tests or cosmetic quality defects derived from AQLs which are not normally distributed). However, for discrete data, it may also be applicable to the microbiological laboratory.

In addition, the USP Measurement Quality and Data Quality Expert Committee have recently published a short position paper specifically on Stage 3 of the APL [86]. A much longer and more detailed paper is to be published in Analytical Chemistry.

12.4.1 Trend analysis example of the absorbance accuracy of a UV spectrometer

By way of example, let us assume that a laboratory has decided to check the accuracy of a UV spectrometer on a weekly basis using a single measurement of a certified reference material, CRM, traceable to NIST at a wavelength of 261nm. The CRM certificate, contains the information that absorbance standard has a value of 0.9762 with an expanded uncertainty, U, of ± 0.0034.

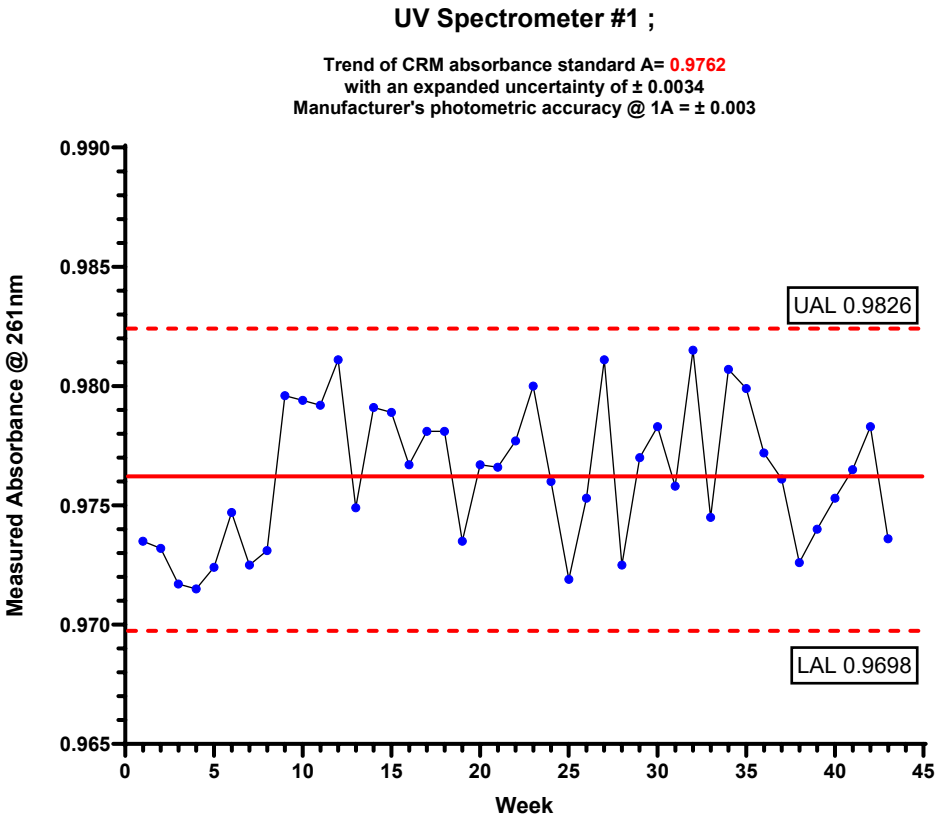
The performance as measured over an operational year yielded 43 data points.

As described in section 12.2.5, the absorbance acceptance criteria for compliance can be calculated by adding the CRM expanded uncertainty to the spectrometer's uncertainty, in this example 0.003A, to give a value of 0.0064 and hence limits of 0.9698 to 0.9826.

This is displayed in Figure 27. Comfortingly, the mean value of the measured absorbances is essentially the same as the certified value. Clearly all data are in compliance but the question is 'Is the instrument in a state of control?'.

Just looking at the data pattern raises questions especially over the first 10 weeks as was discovered during Product Quality Review.

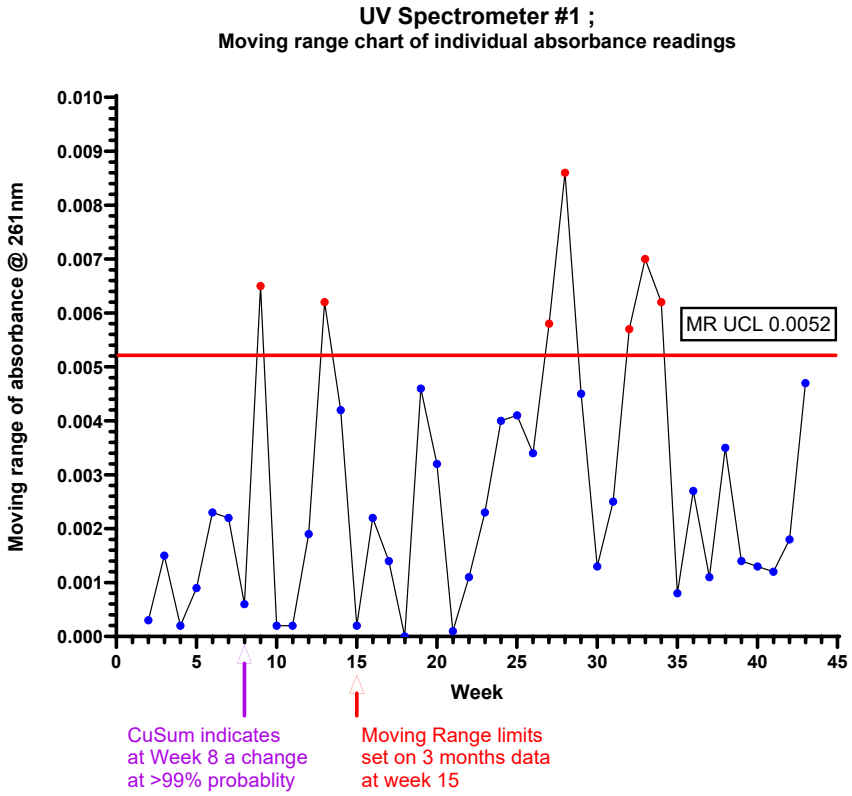
Figure 28 UV Spectrometer #1; Trend of CRM absorbance data over 43 weeks



As we only have an individual data point at each time point, we can use a moving range plot. This moving range is simply the absolute difference between successive weekly absorbance values. Details of the method are to be found in ECA _AQCWG_ SOP 02_OOE OOT_v1.2_July 2023 or standard text books on statistical process control.

As we are interested in range differences, we are only interested in calculating an upper control limit. Usually it is recommended to establish this limit on at least 30 data points. However, in this example, the first 15 data points over approximately 3 months were used . The upper control limit is found by multiplying the ratio of the mean range divided by 1.128 by three. In this instance this yielded a value of 0.0052.
The plot of moving range is shown in Figure 29.

Figure 29 UV Spectrometer #1 ; Moving range chart of individual absorbance readings



This moving range plot clearly indicates that 7 week's values were out of control in spite of being in compliance.

In addition, a CuSum analysis (not shown here) of these data indicated that at about week 8 there was a change, with statistical probability of >99%, resulting in changes of mean and standard deviation!

For the first 8 weeks, the mean value was 0.9728 with a standard deviation of 0.0010 and for the remaining 35 weeks the mean value was 0.9771 with a standard deviation of 0.0026. An investigation into the first 8 weeks of data is certainly required as both the mean and the standard deviation are atypical.

12.5 Preventative Maintenance, Repair, Calibration and Requalification

Critical analytical instruments and systems should have preventative maintenance contracts in place for regular service visits. Typically, these visits are linked with requalification or recalibration afterwards. All work must be recorded in the instrument logbook.

All Instruments/ systems may fail or components may wear out and have to be replaced. Action needs to be taken as indicated below. In addition, some instruments and systems require updates or patches of the software and any revalidation work also needs to be under change control and this is discussed in Section 13.7. There needs to be documented procedures in place to return the instrument to operational use after repair etc.

- Where practicable, the laboratory can undertake simple instrument repairs e.g. replacement of HPLC pump seals or replacement UV lamp coupled with requalification of the flow rates at the top and bottom of the operating range or wavelength accuracy specified in the URS. Results of this should be within the acceptance limits specified. This work must be recorded in the instrument logbook along with any requalification activities necessary.
- Major repairs may require the supplier, agent or a qualified third party to carry out the work and document that the instrument still functions correctly against the requirements in the URS. Again, the instrument logbook must record these activities and cross reference any paperwork left by the service engineer.

12.6 Change Control and Configuration Management

12.6.1 Group B Instruments: Updating Firmware

Instrument firmware updates must be carried out under change control:

- If performed by a supplier's service engineer, there needs to be advance warning of this so that the process owner can read and understand the release notes to see what is changing and what new features are being added. Any post update testing is required must be documented.
- Firmware updates can also be carried out by laboratory users if the instrument is connected to the internet but this must be carefully controlled
- A better approach is to update the firmware as part of a preventative maintenance and recalibration / requalification visit activity, then the latter should demonstrate fitness for intended use of the new firmware.
- The instrument log book or configuration records should document the new version of the firmware and the date it was installed.

12.6.2 Group C Systems: Updating Application Software

This section focuses on updating the instrument control software rather than maintenance of the system e.g. operating system patches and antivirus signature definitions. The maintenance changes could be applied automatically using a pre-approved change control process, however the application software updates may trigger revalidation of part or all of the system depending on the scope of the changes.

Application software updates must be carried out under change control:

- Software updates can encompass database patching as well as application patches and updates.
- Operating system patches or updates, database patching come under the responsibility of the IT department independent of the laboratory for networked systems and the impact of each change should be managed by reading and understanding the release notes for each update and, if possible, evaluate each in a test environment. If not, at least the change request must have a roll-back plan available. The impact of the change will determine the amount of requalification / revalidation work required. However, leaving the system unchanged until the application is out of support is not advised as several minor upgrades is simpler to manage rather than a single major change involving multiple software versions.
- Before beginning a change, ensure that the whole system: application, operating system and associated GMP records and metadata are properly backed up with at least two verified copies of the system. These

must be stored securely just in case of problems with the update and you need to restore the current system.

- For application updates, the usual Pharmaceutical Industry approach is not to change anything. However, this is a mistake as new updates bring bug fixes and new functionality that may be useful. The additional revalidation should involve relatively minor work compared with a big bang approach for infrequent updates and should follow the procedure outlined in the last bullet point.

12.6.3 SaaS Software: The Validation Treadmill

In contrast with the usual Pharmaceutical Industry approach of once validated make no changes, a SaaS application is updated on a 3 – 4 month basis. The process owner gets the upgrades regardless as this is part of the contract with the supplier. New versions come with relatively few new functions and bug fixes but the laboratory has limited time to evaluate the release notes and functionality – typically 2 – 3 weeks. Change control must be very efficient along with any revalidation work undertaken.

12.7 Monitoring IT Support

The IT agreement should have key performance indicators established along with metrics to monitor them. Reports should be produced regularly by the IT service provider (internal and / or external) to the process owner to see how the support is performing. Typical examples could be:

- Backup performance on schedule and listing of problems
- Speed of user account management or configuration changes
- Help desk response times
- Incidents and problems with the system
- Monitoring of the hardware platform
- Change control times for those impacting the application rather than the IT infrastructure

12.8 Periodic Review & Revalidation

Annex 11 of EU GMP Clause 11 requires a periodic evaluation or review that applies to Group C computerised systems in the laboratory [21]:

> *Computerised systems should be periodically evaluated to confirm that they remain in a valid state and are compliant with GMP. Such evaluations should include, where appropriate, the current range of functionality, deviation records, incidents, problems, upgrade history, performance, reliability, security and validation status reports* [21].

- The frequency of the review should be risk based commensurate with the criticality of the system, the records generated and the use to which they are put. Shorter frequency is necessary for higher risk systems
- A schedule for laboratory systems to undergo periodic review must be in place and followed
- Reports need to be available for the review
- CAPA actions must be put in place to correct any problems found, which may include partial or complete revalidation in cases where changes have been made and insufficient thought has been given to the cumulative impact of such changes since the last full validation.

12.9 Migration or Archiving of Data and Records

12.9.1 Data Migration

Migration of data from one application version to another from the same supplier should be relatively simple if the supplier provides automated migration tools. One consideration is whether the new version is backwards compatible with the other version. A selection of data should be checked to show that the same content, value and /or meaning is maintained in both the old and new versions. It is less about identical numbers as there could be rounding differences between the two versions but is the same decision made? For more detail see [58].

12.9.2 Data and Record Archive

Potentially more problematic is the archive of data as dynamic data must remain dynamic throughout its lifecycle [33, 35, 36].

Many Group C system data and metadata are proprietary and cannot be migrated from one supplier's system to another. Therefore, there are a number of possible options to consider:

- **Museum**: maintain the system so that it can read the data. Providing that the instrument can be disconnected to save bench space this can be an option in the short term but longer term people can forget how to use the system, the hardware platform may deteriorate or malfunction.
- **Virtualisation**: If the hypervisor supports the operating system, the application could be virtualised and data transferred to
- **Conversion to a Universal Data Format**: Data and metadata could be converted to an open format such as AnIML (Analytical Information Markup Language, https://www.animl.org/) for longer term storage followed by transfer to another application software for any reinterpretation. The process would need to be extensively validated with checks, like the data migration above, to see that the data content and meaning are preserved and the same decisions were taken in both systems.

12.10 Retirement of the Instrument or System

- Group B instruments can be retired relatively easily as they contain no GMP electronic records.
    - Depending on use the instrument may require decontamination.
    - The asset number needs to be removed from the company's records as well as any laboratory inventory.
    - The instrument can then be sold, disposed of or donated to an educational laboratory.
- Group C systems may need be virtualised to maintain proprietary records as described above. If not then the electronic records must be removed from the system.
    - Similar tasks are required to remove a Group C system from financial assets and laboratory inventories.
    - Many companies will destroy the computer hard drives to ensure no records can be read.
    - Demagnetising hard drives is another alternative but not for solid state device.
    - The analytical instrument could be recycled or retired.

13 How To Appendices

13.1 Introduction: Interpretation and Risk Management

In the these How to Appendices, the aim is to take the regulations, guidance and lifecycle principles outlined in Sections 2 – 12 and apply them to specific illustrative examples of apparatus, instruments and systems covering all three USP Groups and subgroups.

Note that these examples only focus on selective parts from Stage 1 (Specification and Selection) and Stage 2 (Qualification and Validation) and follow the various sections of the lifecycle shown in Section 9.1.1 and Figure 20

In applying these illustrative examples to a particular laboratory, Users must consider the risk assessment approach of their organisation or follow Section 8 of this Guide.

Note: These Appendices are illustrative suggestions only and not definitive answers to specific applications.

Table 5 Contents of How-to Appendices

Appendix / Section	USP Group	Apparatus / Instrument / System
Section14: Appendix 1	A1 A2	Vortex mixer Volumetric Glassware, Burette or Pipette
Section15: Appendix 2	B1 B2 B3	pH meter Autotitrator Dispenser Dilutor and Management of User Defined Programs
Section16: Appendix 3	B1 B2 B1 to C2	Analytical balance used for weighing samples and standards Analytical balance as above plus weight uniformity calculations Analytical balance connected to an instrument data system
Section17: Appendix 4	C1 C2	UV spectrometer validated by integrated validation document Biopharmaceutical instrumentation and software
Section18: Appendix 5	B1 C2 C2 C2	HPLC chromatograph Standalone Chromatography Data System Networked CDS CDS delivered by Software as a Service (SaaS)
Section19: Appendix 6	C3	NIR spectrometer for identification of raw materials using macros

14 Appendix 1: Group A; Apparatus

14.1 Appendix 1: Group A1; Vortex Mixer

General purpose laboratory vortex mixers are used as part sample preparation where solids are dispersed in a liquid phase or mixing liquids. The only variable is usually the rotation mixing speed which is usually up to 3000rpm. This is not a critical parameter as qualification each time the mixer is used is by observation.

For example, qualification is by observation:

- When using a vortex mixer to dissolve a substance in a test tube the analyst continues to use the mixer until the material appears to be fully dissolved.
- When using a vortex mixer to disperse a sample in a test tube, the analyst uses the mixer until the material appears vigorously dispersed for not less than 2 minutes.

14.2 Appendix 1: Group A2; Volumetric Glassware; Burette or Pipette

Titration is a common test in regulated laboratories that are outlined in USP <541> for Titrimetry [87] and EP 2.2.20 (Potentiometric Titration) [88] and can be conducted using either a glass burette or an autotitrator (see Section 16.2).

Stage 1 and 2 lifecycle tasks are minimal for standard volumetric glassware. The Risk Assessment classifies the volumetric glassware as Group A2. There is a metrological function which does not require user calibration. Grade A glassware is required and is purchased to specification and may also require a certificate of calibration in some circumstances.

Qualification is by observation:
Check that the burette or pipette is of the required grade and uniquely numbered for recording purposes.

- Check that the burette or pipette is undamaged before acceptance or use.

There are potential data integrity problems with using a burette in that only the analyst can see the start and end volumes and must record them accurately. A reviewer can only review the written record. An autotitrator may be a better alternative (see Section 15.2).

14.2.1 QR Coded Volumetric Glassware

An emerging trend with some volumetric glassware suppliers is to etch a unique QR code into the glass of the vessel. When used, each item can be scanned by an informatics application to automatically record the identity of each item of volumetric glassware used. This can be compared with information about each item that is contained in the application's database e.g. unique user identity, capacity, supplier, calibration certificate reference etc.

For each analysis this provides several advantages:

- Automatic acquisition of the identity of each item of volumetric glassware
- On-line verification that the right capacity is being used for the analysis: the analysis is paused until the correct item is used
- Avoiding transcription error entry by the analysis and reviewer

15 Appendix 2: Group B Instruments

Group B instruments typically will be qualified by testing with reference standards, certified reference materials or using calibrated test equipment. Regardless of the approach used, the tests must relate to the requirements and acceptance criteria documented in the URS. The end of supplier commissioning should also be considered as the start of the on-going instrument performance monitoring in Stage 3 of the lifecycle which should be trended as discussed earlier in this Guide.

Modern instruments have sophisticated firmware that can be used to define user accounts and access privileges including administrator roles, restrict access to the system clock to authorised individuals that avoid conflicts of interest.

Many instruments retain electronic records (see PIC/S PI-041 section 8.9.1 [36]) but users do not have access to them.

15.1 Appendix 2: Group B1; pH meter

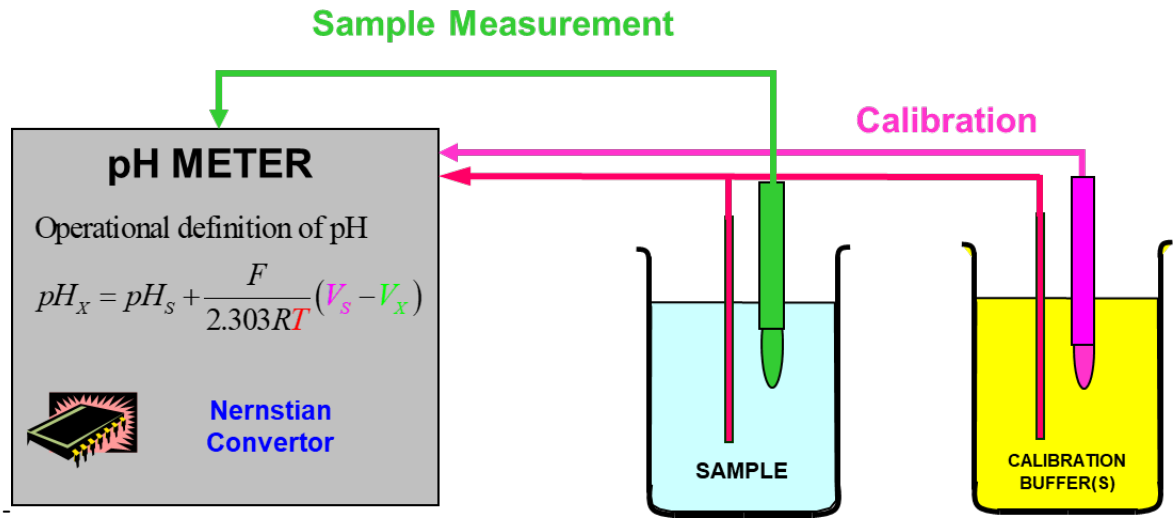
After weighing operations, the measurement of pH is usually the second most common analytical test.

As with the operation of a balance(discussed in Section 16, the pH measurement is linked to traceable standards and pharmacopeial requirements. Generally technical compliance will be required to USP General Chapter <791> [89]and Pharm. Eur General Chapter 2.2.3 [90]

However, the measurement of pH is dependent on two parameters namely voltage from an electrode and temperature. In its most basic form, a pH meter is really only a high impedance voltmeter with a temperature probe and some firmware to do the calculations.

A simple view of the requirements for the traceable measurement of pH are given in **Figure 30**

Figure 30 A simplified overview of calibration of a pH meter and measurement of a sample



The operational definition of pH is given by the Nernstian equation as shown which is contained in instrument firmware to convert these two voltages to the pH of the sample. These calculations are performed by the instrument and the user has no influence over them.

Ideally, it is necessary to assure both the accuracy of the voltage measurements and the temperature probe as well as verifying the conversion firmware. Generally, this is done holistically by using a traceable calibration buffer or buffers and confirmation against another traceable buffer used as a sample within predetermined acceptance limits over the operational range.

Table 6 Supplier and Laboratory Specifications for a simple B1 pH meter

Critical Instrument/System Controls and Parameters	SUPPLIER SPECIFICATION		LABORATORY URS	
	Operational Range	Tolerance	Operational Range	Tolerance
pH	0 to 14	±0.01	3 to 11	±0.05
Temperature	0 to 100°C	±0.5°C	15°C to 30°C	±0.5°C
Automatic Temperature Control	YES		YES	
Calibration protocol	3 points		3 points	
Printer output for calibration and sample data		YES		YES

Table 6 illustrates the USP <1058> statement that user requirements for commercial instruments should be minimal. Of note is the comparison of the supplier and laboratory operational range, the latter is smaller than that the supplier's but all that is necessary for the instrument's intended use. Confirmation of printer outputs will be obtained during commissioning and/or user acceptance testing.

Typical stage and phase tasks for a standalone pH meter with a printer are shown in Table 7.

Table 7 Typical Stage 1 and Phase tasks for a Group B1 pH meter

LIFECYCLE ACTIVITY Stage and Phase	Instrument
Stage 1: Specification and Selection	
Risk Assessment (RA)	✓
URS (define intended use)	✓
Evaluation and selection	✓
Supplier Assessment/Qualification	
ID Critical Inst & DI controls	
Selection Report	✓
Supplier SW asessment	✓
Purchasing specification & PO	✓
Stage 2: Qualification and Validation	
Plan work Required from RA	
Site Preparation	
Supplier install and integration	✓
Supplier commissioning	✓
Prototying and Configuration	
Update URS	
Requirements traceability	✓
User Acceptance Testing	✓
Write SOPs and training	✓
Instrumentation Log book	✓
Authorisation for use	✓

Although a full supplier qualification is clearly too much, some questions such as the availability of spare parts after the instrument is discontinued should be asked.

Because this modern pH meter has automated temperature control and that the calibration sequence has 3 traceable buffers the measurement of the 4th traceable buffer makes the confirmation of accuracy easy. However, the temperature measurement is important because the pH of CRM buffers is a function of temperature. Typical values are taken from the Pharm. Eur. 2.2.3 [90] as shown in **Table 8**.

Table 8 Reference standards for pH

Temperature °C	Potassium tetraoxalate 0.05 M	Potassium hydrogen tartrate saturated at 25°C	Potassium dihydrogen citrate 0.05 M	Potassium hydrogen phthalate 0.05 M	Potassium dihydrogen phosphate 0.025 M + disodium hydrogen phosphate 0.025 M	Potassium dihydrogen phosphate 0.0087 M + disodium hydrogen phosphate 0.0303 M	Disodium tetraborate 0.01 M	Sodium carbonate 0.025 M + sodium bicarbonate 0.025 M	Calcium hydroxide saturated at 25°C
	$C_4H_3KO_8$, $2H_2O$	$C_4H_5KO_6$	$C_6H_7KO_7$	$C_8H_5KO_4$	KH_2PO_4 + Na_2HPO_4	KH_2PO_4 + Na_2HPO_4	$Na_2B_4O_7$, $10H_2O$	Na_2CO_3 + $NaHCO_3$	$Ca(OH)_2$
15	1.67		3.80	4.00	6.90	7.45	9.28	10.12	12.81
20	1.68		3.79	4.00	6.88	7.43	9.23	10.06	12.63
25	1.68	3.56	3.78	4.01	6.87	7.41	9.18	10.01	12.45
30	1.68	3.55	3.77	4.02	6.85	7.40	9.14	9.97	12.29
35	1.69	3.55	3.76	4.02	6.84	7.39	9.10	9.93	12.13
$\frac{\Delta pH}{\Delta T}$	0.001	-0.0014	-0.0022	0.0012	-0.0028	-0.0028	-0.0082	-0.0096	-0.034
pH variation per °C									

15.2 Appendix 2: Group B2; Autotitrator

The problem with using a traditional burette for manual titrations is that only the analyst sees and manually records the titrant start volume and, after visual detection of the endpoint, the end volume which are a high-risk data integrity issues as a reviewer only has the analyst's handwritten entries in the QC batch record, controlled blank form or laboratory notebook to review that may include observation and typographical errors. Therefore, automating titration is one way to reduce data integrity risk in titration using technical controls, automatic calculation and provide objective evidence for second person reviewer to check the work faster.

In contrast, an autotitator removes these analyst manual operations as shown in Figure 29.

The Risk Assessment, based upon the URS, identifies a particular simple autotitrator with only display output of the titrant volume and/or calculated value as Group B2 and the typical Stage and Phase tasks are illustrated in Figure 28. Note that only the Instrument Lifecycle thread is necessary for this category.

Figure 31 Manual versus autotitrator operations

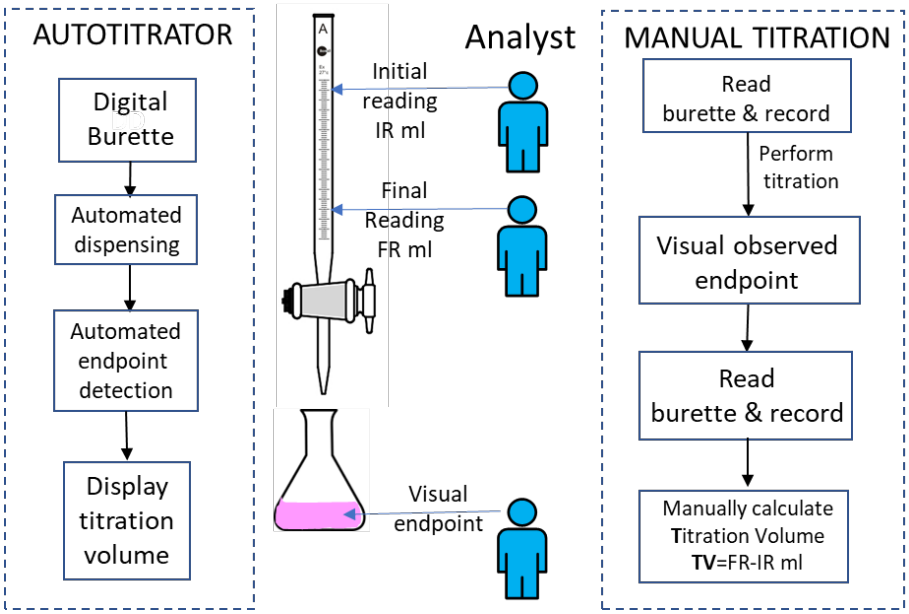


Table 9 Typical Stage and Phase tasks for a Group B2 Autotitrator

LIFECYCLE ACTIVITY Stage and Phase	Instrument
Stage 1: Specification and Selection	
Risk Assessment (RA)	✓
URS (define intended use)	✓
Evaluation and selection	✓
Supplier Assessment/Qualification	
ID Critical Inst & DI controls	
Selection Report	✓
Supplier SW asessment	✓
Purchasing specification & PO	✓
Stage 2: Qualification and Validation	
Plan work Required from RA	✓
Site Preparation	
Supplier install and integration	✓
Supplier commissioning	✓
Prototying and Configuration	
Update URS	
Requirements traceability	✓
User Acceptance Testing	✓
Write SOPs and training	✓
Instrumentation Log book	✓
Authorisation for use	✓

Assuming that the user required endpoint detection options are available, the critical metrological parameters are related to the burette as identified in Figure 27 and illustrated in Table 8

Table 10 Critical Instrument/System Controls and Parameters for the Group B2 Autotitrator

Critical Instrument/System Controls and Parameters	SUPPLIER SPECIFICATION		LABORATORY URS	
	Operational Range	Tolerance	Operational Range	Tolerance
Burette Accuracy	0 to 50ml	±0.03ml	10 to 30 ml	±0.05ml
Burette Repeatability		0.20%		0.25%

Calculations performed, as defined in the URS, and printouts are verified during Stage 2 user acceptance testing phase.

15.3 Appendix 2: Group B3; Dispenser Dilutor and Management of User Defined Programs

The last Group B instrument example is a dispenser dilutor with user defined programs. The system Risk Assessment, based upon the laboratory URS, categorises this system as Group B3.

15.3.1 Supplier and Laboratory Instrument Specifications

The two sets of specifications are shown in Table 11. The laboratory instrument specification is minimal as stated in USP <1058> [22] and it uses more relaxed acceptance criteria compared with the supplier's as the laboratory environmental conditions are not as highly controlled as the supplier's.

Table 11: Volumetric accuracy and precision requirements for the dilutor dispenser.

Critical Instrument/System Controls and Parameters	SUPPLIER SPECIFICATION		LABORATORY URS	
	Operational Range	Tolerance	Operational Range	Tolerance
Liquid handling performance	1µl to 5ml		10µl to 1500µl	
Diluter accuracy	10µl	± 1.75%	10µl	± 2%
Diluter precision	10µl	≤1%	10µl	≤1%
Diluter accuracy	1000µl	≤0.75%	1500µl	± 1%
Diluter precision	1000µl	± 0.3%	1500µl	≤1%

Note The tolerances specified in the Laboratory URS should have been specified to 2 significant figures not one for acceptance criteria to be set.

In addition, the laboratory URS will need to specify the ability to specify, build and verify User Defined Programs for the dilution and dispensing according to the process flow. There is no controlling computer with an application, as these programs are developed and stored within the instrument firmware and recalled by a user from memory when required. The ability to "program" is limited to automation of instrument functions and parameters and is not a recognised computer language per se. Therefore, the user requirement for writing user defined programs is very simple as it references an SOP for the task.

In general, simple dispenser dilutors may not have any electronic records of a task performed to confirm correct operation or enable troubleshooting, Backup may not be required as user programs are maintained in firmware or there may be the option to backup to a USB device which is not recommended by the PIC/S PI-041 guidance in Section 9.6 [36].

15.3.2 Lifecycle Stages and Phase Tasks for the Dispenser Dilutor

The typical Stage and Phase tasks are illustrated in Table 12.

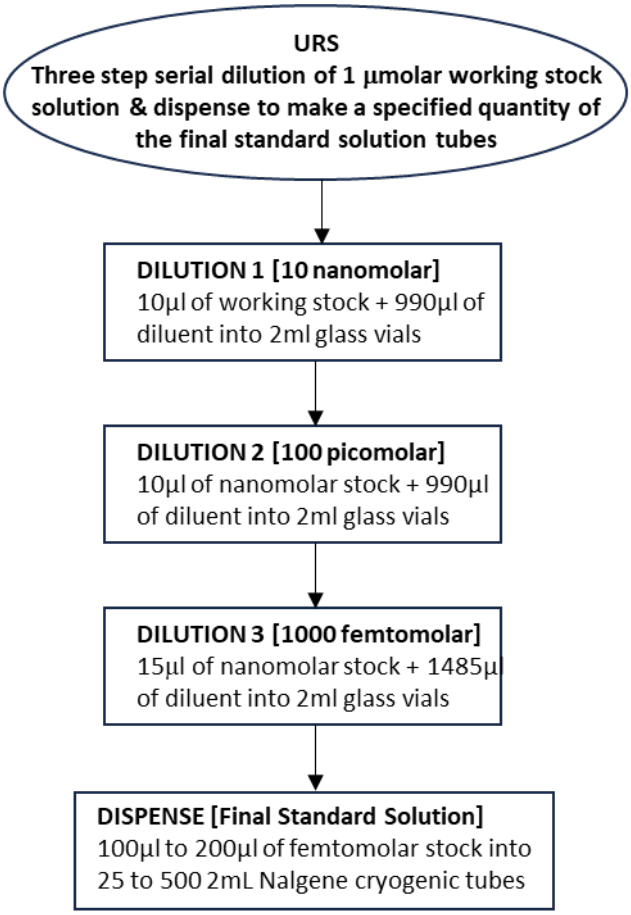
Table 12 Typical Stage and Phase tasks for a Group B3 dispenser diluter

LIFECYCLE ACTIVITY Stage and Phase	Instrument	System	Application	IT & Network
Stage 1: Specification and Selection				
Risk Assessment (RA)	✓	✓	✓	
URS (define intended use)	✓	✓	✓	✓
Evaluation and selection	✓	✓	✓	
Supplier Assessment/Qualification	✓	✓		
ID Critical Inst & DI controls	✓			
Selection Report		✓		
Supplier SW asessment	✓	✓		
Purchasing specification & PO	✓	✓		
Stage 2: Qualification and Validation				
Plan work Required from RA				
Site Preparation				
Supplier install and integration	✓	✓	✓	
Supplier commissioning	✓	✓		
Prototying and Configuration		✓		
Update URS		✓		
Requirements traceability	✓	✓		
User Acceptance Testing	✓	✓	✓	✓
Write SOPs and training	✓	✓		
Instrumentation Log book	✓	✓		
Authorisation for use	✓	✓		

To illustrate the process, Figure 32 shows a four-step process flow for standalone automated dilutor/dispenser instrument to prepare working standard solutions. Clearly the number of vials at each stage has to be predefined to allow adequate volumes at Dilution 3 for the dispensing operation. From an instrumental control viewpoint, the volumetric accuracy and precision of the multiple dilution steps are critical instrumental parameters and shown in Table 4. Depending on the system chosen and the syringe burette(s) available, the dilution step 3 might have to be performed in two operations and not one.

Any modifications to the established User defined programs must be done under change control and subsequent verification.

Figure 32: Process flow for the working standard preparation



15.3.3 Management of User Defined Programs

Management (e.g. specification development, verification and change) of user defined programs for Group B3 instruments requires a separate procedure that is outside the scope of the life cycle phases and threads in Section 9.1.2.

These can be developed and verified before the system goes live or at any time using the operational phase of the instrument. However, User defined programs cannot be released for operational use until each one has been verified to demonstrate that it meets the intended use requirements during user acceptance testing. Any modifications to the established user defined programs must be done under change control and subsequent verification.

For the example shown in Figure 32, the dilution of the sample is performed automatically.

16 Appendix 3: Analytical Balance Grouping is Dependent on Intended Use

This appendix aims to demonstrate that USP group classification of an analytical balance is dependent on the intended use. The same make and model of an analytical balance is used in this example with the same laboratory instrument specification used in the three examples.

The assumption made in these examples are that the environmental conditions e.g. base or table, air currents, temperature fluctuations etc. are the same to achieve the same measurement uncertainty.

It is important to understand that a change in the USP <1058> grouping could occur at any point throughout the lifecycle of an analytical instrument or system. The principle is demonstrated by an analytical balance but it could be applicable to any instrument or system.

16.1 Common Instrument Specification for all Examples

The analytical balance has the following specification with an attached printer as shown in Table 13:

Table 13: Supplier and Laboratory Specifications for an Analytical Balance

Critical Instrument/System Controls and Parameters	SUPPLIER SPECIFICATION		LABORATORY URS	
	Operational Range	Tolerance	Operational Range	Tolerance
Capacity	0 to 220g		0 to 160g	
Readability		0.1mg		0.1mg
Repeatability		0.1mg		0.1mg
Maximum Linearity deviation		0.2mg		N/S
Eccentricity at 100g load		0.2mg		N/S
Minimum weight USP <41>		82mg		Complies
Sensitivity temperature drift		0.00015%/°C		N/S

Note The Laboratory URS is deficient in that the Linearity and Eccentricity criteria are not specified.

There is also the capability to perform weight uniformity calculations built into the firmware of the instrument.

16.2 Analytical Balance Group B1

The intended use for an analytical balance in Group B1 with user access management capability enabled is for the weighing of reference standards and samples prior to analysis. The weighing process is as follows:

- Log onto the balance as an analyst
- Use external reference masses to ensure that the analytical balance meets acceptance criteria
- Weigh the weighing vessel or boat
- Tare the balance
- Weigh the sample or reference standard
- Print the weighing sequence with analyst name and a correct date and time stamp
- Complete the instrument log book

Although the balance has the capability to perform weight uniformity calculations, the function is not used in this example.

If the supplier installation and commissioning include testing the balance operating range and tolerance contained in the laboratory URS shown in Table 6, it can be released for operational use.

16.3 Analytical Balance Group B2

Now the intended use of the analytical balance changes as the laboratory now wants to perform weight uniformity calculations using the qualified instrument. A change request is completed and the laboratory URS is updated to include the pharmacopoeial calculation equation, number of units to be weighed, range of weights expected and acceptance criteria of the calculation. In addition, update the risk assessment as the instrument is now Group C2.

The USP <905> [91] and EP 2.9.5 [92] weight uniformity calculations are verified by weighing 10 dosage forms and the mean and average calculated by the balance and the accuracy of the balance calculation cross-checked by a second means e.g. validated spreadsheet. Further tests should look at testing calculations outside of the acceptance criteria i.e. testing to fail. As verification of the calculation is aim of the test just a single dose form should be used a documented assumption will states that the calculation applies to any dosage form.

If the verification results are acceptable, the balance can be released for performing weight uniformity calculations.

16.4 Analytical Balance Groups B1 and C2

If the balance is to be used in an automated system, the balance is specified as in Section 16.1 and qualified as outlined in Section 16.2. When complete, the qualified balance is installed into an automated system and instead of printing the weights, the weights are transferred automatically to the controlling informatics application.

The URS for the automated system will cross reference the balance URS and add additional requirements for the process that uses the balance along with the interface between the balance and the informatics application. In addition, the risk assessment needs to be reviewed and updated as the intended use has changed and the classification has now changed from Group B1 to C2. To aid sample identification and ensure data integrity a static bar code reader or RFID can be used.

The lifecycle threads and phases for the Group C2 system are shown in Table 14. The instrument thread omits the SOP for balance use as this is now a component of the overall system. An IT thread is also included for IT network access and support such as cybersecurity, user account management, configuration of the application, time synchronisation, backup and recovery etc.

Table 14 Risk assessment of a Group B1 Analytical Balance in a Group C2 System

LIFECYCLE ACTIVITY Stage and Phase	Instrument	System	Application	IT & Network
Stage 1: Specification and Selection				
Risk Assessment (RA)	✓	✓	✓	
URS (define intended use)	✓	✓	✓	✓
Evaluation and selection	✓	✓	✓	
Supplier Assessment/Qualification	✓	✓		
ID Critical Inst & DI controls	✓			
Selection Report		✓		
Supplier SW asessment		✓		
Purchasing specification & PO		✓		
Stage 2: Qualification and Validation				
Plan work Required from RA				
Site Preparation				
Supplier install and integration	✓	✓	✓	
Supplier commissioning	✓	✓		
Prototying and Configuration		✓		
Update URS		✓		
Requirements traceability	✓	✓		
User Acceptance Testing	✓	✓	✓	✓
Write SOPs and training		✓		
Instrumentation Log book	✓			
Authorisation for use		✓		

16.4.1 Point of Use Analytical Balance Checks

A common question is should an analytical balance performance be checked using the internal calibration function of the balance or using calibrated external masses? For example, daily internal calibration check with a weekly external mass check. The best answer to this question can be found on the FDA web site in a Level II guidance [93].

3. **Many leading analytical balance manufacturers provide built-in "auto calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should the schedule for calibration be?**

   The auto-calibration feature of a balance may not be relied upon to the exclusion of an external performance check (21 CFR 211.68). For a scale with a built-in auto-calibrator, we recommend that external performance checks be performed on a periodic basis, but less frequently as compared to a scale without this feature. The frequency of performance checks depends on the frequency of use of the scale and the criticality and tolerance of the process or analytical step.

   Note that all batches of a product manufactured between two successive verifications would be affected should the check of the auto-calibrator reveal a problem. Additionally, the calibration of an auto-calibrator should be periodically verified—a common frequency is once a year—using National Institute of Standards and Technology (NIST)-traceable standards or NIST-accredited standards in use in other countries.

17 Appendix 4: Group C Systems

17.1 Group C1; Standalone UV-Visible Spectrometer Using an Integrated Validation Document

This example of a Group C1 system consists of a UV-Vis spectrometer controlled by GAMP© Category 3 software operating on a separate PC. In this example, the instrument and software application has been installed by the supplier and qualified over the operating range specified by the laboratory. The outcome of the risk assessment is that the entire system can be validated using the integrated validation document (IVD) described in Section 8.8.

17.1.1 Spectrometer Specification

The supplier's instrument specification is shown in Table 15: Comparison Between a Supplier Specification and a Laboratory URS for a UV-Vis Spectrometer which is used as the basis for the laboratory URS section of the Integrated Validation Document. Note that the acceptance criteria for the instrument are linked to the respective USP and EP general chapters rather than document them in the URS. Although this appears simpler, a process owner taking this approach will need to keep current with any changes in the respective general chapters.

Table 15: Comparison Between a Supplier Specification and a Laboratory URS for a UV-Vis Spectrometer

Critical Instrument/System Controls and Parameters	SUPPLIER SPECIFICATION		LABORATORY URS	
	Operational Range	Tolerance	Operational Range	Tolerance
Wavelength range	190 to 1100 nm		220 to 700nm	
Absorbance range	0-3 A		0.1 to 2.0 A	
Spectral bandwidth nm	1.0nm			
Absorbance accuracy		+/-0.0015 A		
Absorbance precision		+/-0.0005 A		
Wavelength accuracy		±0.1nm		
Wavelength precision		±0.1nm		
Stray Light @198nm		<1%T		
Stray Light @340 & 400nm		<0.02%T		
Photometric Drift		<0.0003 A/hr		

The contents of the integrated validation document for the instrument is system are presented in Table 16 As the system performs two functions a sample scans over a defined wavelength range or determination of absorbance at a single wavelength, the requirements for these functions are relatively simple. However, the controlling workstation and application software, including application configuration, must also be specified and these areas are included with the intended user requirements as shown in Table 14. Each requirement is uniquely numbered and has a column for traceability to an SOP, supplier installation and commissioning documents or test procedure within the IVD.

One key area for any software validation are the assumptions, exclusions and limitations of testing. This allows contemporaneous documenting of the rationale why tests were designed and conducted as well as why certain requirements were not tested specifically. This is very useful during audits and inspections to explain and justify the approach taken to validate the software.

Table 16: Content of an Integrated Validation Document for a UV-Vis Spectrometer

IVD Section	Description
Introduction	• Purpose of Document
System Description	• Intended Purpose and Major Components including software name and version A data flow diagram is an option
Referenced Documents	• Company and system procedures Supplier installation and commissioning documents Applicable regulations and guidance documents
User Requirements with Traceability	• System Qualification and Calibration • Application, Security and Access Control Configuration Settings • Functional Requirements • Regulatory and data integrity requirements (e.g. GMP, Annex 11 and 21 CFR 11) for the system • IT Support
Test Preparation	• Preparation reagents and samples • Assumptions, Exclusions and Limitations of test approach e,g, password expiry will not be tested
Test Procedures	1. Confirmation of Configuration Settings, Security and Access Control Test log, documented evidence and acceptance criteria 2. Single Absorbance Reading: Test log, documented evidence and acceptance criteria 3. Wavelength Scan: Test log, documented evidence and acceptance criteria 4. Audit Trail Entries (Generated during Tests 1-3) Test log, documented evidence and acceptance criteria 5. Backup and Restore: Test log, documented evidence and acceptance criteria • Test Execution Notes • Test Summary Log
Release Statement	• Validation Summary Proforma and Release Statement

17.2 From Group C1 to C3; Bioassay Analysis Software

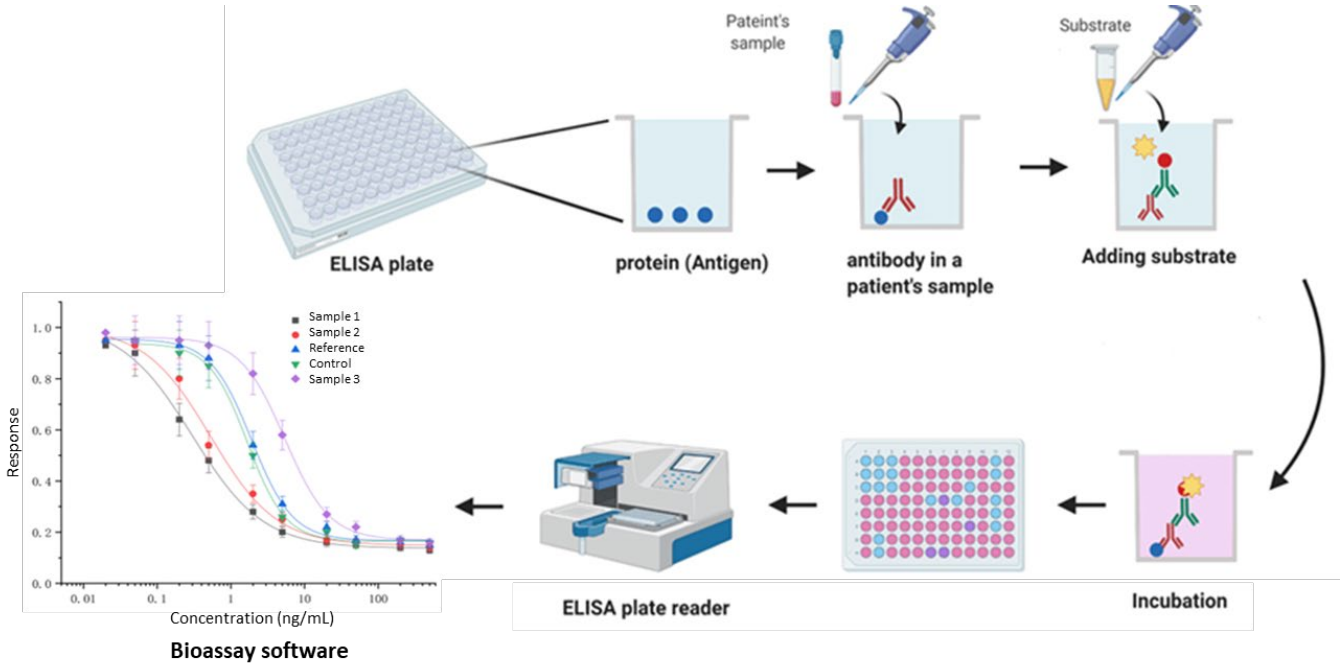
This section has been written by Margarita Sabatier, the authors acknowledge her input.

A bioassay is a biochemical test to estimate the potency of a sample. Usually, this potency can only be measured relative to a reference standard. A typical bioassay involves a stimulus (e g. drugs) applied to a test item (e g. animals, tissues, cells, antigens). The corresponding response (ex. Binding, proliferation, activation, staining intensity) of the test item is thereby triggered and measured either as quantal observations (e.g. staining score) or as quantitative observation (e.g. absorbance, luminescence). One of the most common types of bioassay is immunoassay, also known as ELISA. ELISA is a quantitative analytical method that measures absorbance of colour change from antigen-antibody reaction (ex. Direct, indirect, sandwich, competitive). ELISA is used to measure a variety of substances in the human body, and as potency test for biopharmaceutical products.

Common for bioassays using cells or antigens as test items is that they use microtiter plates where the cells or antigens are absorbed and drugs react creating a response. This response is measured by a multi-modal microplate reader.

The response generated in a bioassay is usually fitted to a non-linear model (e.g. 4 parameter logistic model) by a biostatistical software. These activities (measuring generated response and statistical analysis) can be separated. A typical process workflow is illustrated in Figure 32.

Figure 33: Process flow for a typical immunoassay with associated bioassay analysis



17.2.1 Lifecycle Phases for the Instrument and Bioassay Analysis Software

17.2.2 Two Examples

The examples used in this section are:

- W = Standalone software installed on a benchtop workstation without instrument control
- N = Software installed on-premises controlling single or multiple instruments

The example W consists of a GAMP Category 4 software operating on a separate PC. In this example, the software application has been installed by the supplier. Data integrity controls are qualified by the laboratory. User defined protocols are configured and verified by the laboratory. The outcome of the risk assessment is that software should be fully validated.

Table 17 Risk Assessment for a standalone Bioassay analysis software

LIFECYCLE ACTIVITY Stage and Phase	Application
Stage 1: Specification and Selection	
Risk Assessment (RA)	✓
URS (define intended use)	✓
Evaluation and selection	✓
Supplier Assessment/Qualification	✓
ID Critical Inst & DI controls	✓
Selection Report	✓
Supplier SW asessment	(✓)
Purchasing specification & PO	
Stage 2: Qualification and Validation	
Plan work Required from RA	✓
Site Preparation	
Supplier install and integration	✓
Supplier commissioning	✓
Prototying and Configuration	(✓)
Update URS	
Requirements traceability	✓
User Acceptance Testing	✓
Write SOPs and training	✓
Instrumentation Log book	
Authorisation for use	✓

The example N consists of a Group C2 system consisting of a multi-modal reader (e.g. UV-Vis spectrometer capable of measuring microtiter plates) controlled by GAMP Category 4 software operating on a separate PC. In this example, the instrument and software application has been installed by the supplier and qualified over the operating range specified by the laboratory. User defined protocols are configured and verified by the process owner or authorised persons. The outcome of the risk assessment is that the entire system can be validated using the integrated validation document (IVD) described in Section 8.8. Refer to example in 17.1 for the instrument part of the system.

However, in its simplest form, the application software may use pre-defined analytical protocols standardized for specific test e.g. as in the case of insulin analysis on a blood analyzer and would be categorized as Group C1. The outcome of the risk assessment is that the entire system can be validated using the integrated validation document (IVD) described in Section 8.8. Refer to example in 17.1 for an example of IVD.

Both W and N systems can be further enhanced through networking or cloud-based solutions, where data transfer and instrument control become the key elements to be qualified.

For W, avoid the use of USB devices for data transfer as recommended by PIC/S PI-041 Section 9.5.6 and data transfer must be secure as required by Section 9.4.1 and validated [36].

Table 18 Risk Assessment for a multi-modal reader with associated Bioassay analysis software

LIFECYCLE ACTIVITY Stage and Phase	Instrument	System	Application
Stage 1: Specification and Selection			
Risk Assessment (RA)	✓	✓	✓
URS (define intended use)	✓	✓	✓
Evaluation and selection	✓	✓	✓
Supplier Assessment/Qualification			✓
ID Critical Inst & DI controls	✓	✓	
Selection Report		✓	
Supplier SW asessment			(✓)
Purchasing specification & PO		✓	
Stage 2: Qualification and Validation			
Plan work Required from RA	✓	✓	✓
Site Preparation		✓	
Supplier install and integration	✓	✓	✓
Supplier commissioning	✓	✓	✓
Prototying and Configuration		✓	(✓)
Update URS		✓	
Requirements traceability		✓	
User Acceptance Testing	✓	✓	✓
Write SOPs and training	✓	✓	✓
Instrumentation Log book	✓		
Authorisation for use	✓	✓	✓

17.2.3 User Requirements Specification

The critical document in any computer validation project is the URS as it defines the intended use.

Table 19: Suggested High-Level Content of a Bioassay software URS

Section	Content
Introduction	• Laboratory and high-level function of the system • System details: supplier, application and version number • Referenced documents
Computer Platform	• Hardware • Database, operating system, peripherals
System Scope	• Number of users • Number of predefined analysis protocols • Data formats • Connectivity for instrument control • Supplier and assessment
Regulatory Compliance	• Applicable regulations • User identities, user roles and passwords • Configuration settings • Audit trail(s) • Electronic signature use • Time settings and time zones if applicable
Operations, Calculations and Statistical Functions	• Folder or project naming conventions and settings • Method development and validation • Instrument control including Acquisition Processing • Requirements for statistical analysis • Calculation and reporting of results
IT Support	• User account management • System administration • Backup and recovery, disaster recovery • Change control: patching and updating • Cybersecurity
Interfaces	• For each system interfaced outline the data flows and transfers (If applicable)
Data Migration	• Migration from one version to another (If applicable)

17.2.4 Management of User Defined Protocols

Management (e.g. specification development, verification and change) of user defined protocols for Group C2 instruments/GAMP category 4 software requires a separate procedure that is outside the scope of the life cycle phases and threads in section 9.1.2.

These must be developed and verified by testing before the system goes live and updated at any time using the operational phase of the instrument. However, user defined protocols cannot be released for operational use until each one has been verified to demonstrate that it meets the intended use requirements during user acceptance testing. Any modifications to the established user defined protocols must be done under configuration and change control and subsequent verification.

18 Appendix 5: Chromatography From Group B Instrument to Group C Networked System

In this section we will look at specification for an isocratic liquid chromatograph and then consider the system aspects when a CDS is used to control the instrument. The CDS options discussed here are standalone, networked and SaaS CDS options.

18.1 Group B Type 1: Liquid Chromatograph Specification

18.1.1 Isocratic Chromatograph: From Supplier's Specification to Laboratory URS

The supplier's specification for an HPLC isocratic chromatograph is shown in Table 20 on the left-hand side of the table and the corresponding laboratory URS is shown on the right-hand side. USP <1058> notes that suppliers should produce meaningful specifications [22]. The supplier's specifications are measured under extremely well controlled environmental conditions that you will be very unlikely to reproduce in your laboratory. For example:

- The pump range is 0.05 – 10.0 mL min^{-1}. From experience, likelihood of an analytical method with a flow rate greater than 2 mL min^{-1} is low and therefore the URS reflects intended use in the laboratory.
- The flow rate tolerance value for the supplier's specification is ± 0.02 but the laboratory has been practical set a tolerance of ± 0.2.
- You can see further examples of how the supplier's specification has been adapted to the laboratory's requirements in Table 10.
- The specification may also consider failure of the instrument and how one would be detected [94]

Is the laboratory's URS adequate? Yes, as USP <1058> says a URS for a commercial instrument is expected to be minimal as shown in Table 20.

Table 20: Comparison Between a Supplier Specification and a Laboratory URS for a Liquid Chromatograph

Component	SUPPLIER SPECIFICATION		LABORATORY URS	
	Range	Tolerance	Operational Range	Tolerance
Isocratic pump; ml min^{-1}	0.05-10.0	± 0.02	1.0-2.0	± 0.2
Autosampler vial capacity	100	N/A	50	N/A
Injection volume; µL	1-1000	± 1	20-100	± 2
Column Temperature; °C	25-100	± 2	40-50	± 2
UV detector wavelength; nm	190-800	± 1 (UV) ± 3 (VIS)	210-280	± 1 (UV)

The wavelength range in the table is 210 – 280nm. Many laboratories and suppliers use caffeine as a wavelength standard (it is not traceable) but it could be used to commission the detector, if so it would be worth updating the instrument specification to 205nm. The specification has no statements for drift over time.

18.1.2 Considerations for a Gradient Liquid Chromatograph

For a gradient LC the following should be considered:

- Binary or quaternary gradient (most routine gradients are binary but the quaternary chromatograph provides options for automated pre and post analysis conditioning and washing of the column).
- High pressure or low pressure gradient mixing

Do these options matter? Yes, because if you have a mixture of mixing options available, consistency between instruments within a laboratory matters because you may not get consistency of results from a heterogeneous mix of LC instruments. Moreover, technology transfer is made more difficult if a method was developed on a high-pressure mixing instrument and transferred to a low pressure mixing one or vice versa.

Of course, it is unlikely that a laboratory would purchase a chromatograph without the controlling Chromatography Data System (CDS) application and the rest of this appendix discusses the validation of the CDS application software including qualification of interfaced chromatographs.

18.2 Lifecycle Phases for the Instrument and CDS

18.2.1 Three CDS Examples

The examples used in this section are:

- W = Standalone CDS installed on a benchtop workstation controlling a single LC
- N = Networked CDS installed on-premises controlling multiple chromatographs
- S = SaaS CDS installed in the cloud with a service provider remote from the laboratory

18.2.2 Lifecycle Phases and Threads for Three CDS Modes

The lifecycle phases and threads for the three types of CDS are presented in Table 21. The worst situation is where there is a standalone CDS operating in a laboratory and where the chromatographers are responsible for managing the application configuration and the IT support. This is a potential disaster zone are there could be failure to meet ALCOA++ criteria e.g.:

- Users sharing the same account
- Conflicts of interest where laboratory users could have administrator functions
- Laboratory users responsible for regularly backing up the data and application don't
- Time synchronisation may not be considered
- Manual transfer of data using USB drives

In addition, there are practical problems with a standalone system:

- Keyboard contention: conducting a data review stops the next analysis from being set up
- Single points of failure within the workstation: disk drive, disk drive controller, power supply etc.
- Data transfer may be via USB drive or manually entering data from printouts from the CDS into a spreadsheet

Table 21: Lifecycle Phases and Threads for three types of Chromatography Data System (CDS)

LIFECYCLE ACTIVITY Stage and Phase	Instrument	System	Application	IT & Network
Stage 1: Specification and Selection				
Risk Assessment (RA)		✓		
URS (define intended use)	✓	✓	✓	N, S
Evaluation and selection		✓		
Supplier Assessment/Qualification	✓			
ID Critical Inst & DI controls	✓	✓	✓	
Selection Report		✓		
Supplier SW asessment				
Purchasing specification & PO		✓		
Stage 2: Qualification and Validation				
Plan work Required from RA		W, N, S		
Site Preparation	✓			
Supplier install and integration	✓	S, N	W, N	N, S
Supplier commissioning	✓	✓	✓	
Prototying and Configuration		W, N, S		
Update URS		All		
Requirements traceability		All		
User Acceptance Testing		All		
Write SOPs and training		All		
Instrumentation Log book	✓			
Authorisation for use		All		

18.2.3 User Requirements Specification

The critical document in any computer validation project is the URS as it defines the intended use. If the validation project is to select a new CDS there will be a minimum of two and more likely three versions of the URS:

- **Version 1: Generic URS to select the system**.
  The application, version number and supplier will be unknown but the main functional (control of chromatographs and analytical process) and non-functional requirements (IT platform, compliance and IT support requirements) can be specified.
- **Version 2: Specific to the Application and Version Number**.
  The supplier and software has been selected and the key users trained, the URS then must be updated to match the functions to be used by the laboratory.
- **Version 3 (or more): Update of the URS following writing some testing documents**.
  Inevitably, the version 2 URS will contain missing elements, misunderstood functions etc that require the URS to be updated. This is normal and expected.

Table 22: Suggested High-Level Content of a Chromatography Data System URS

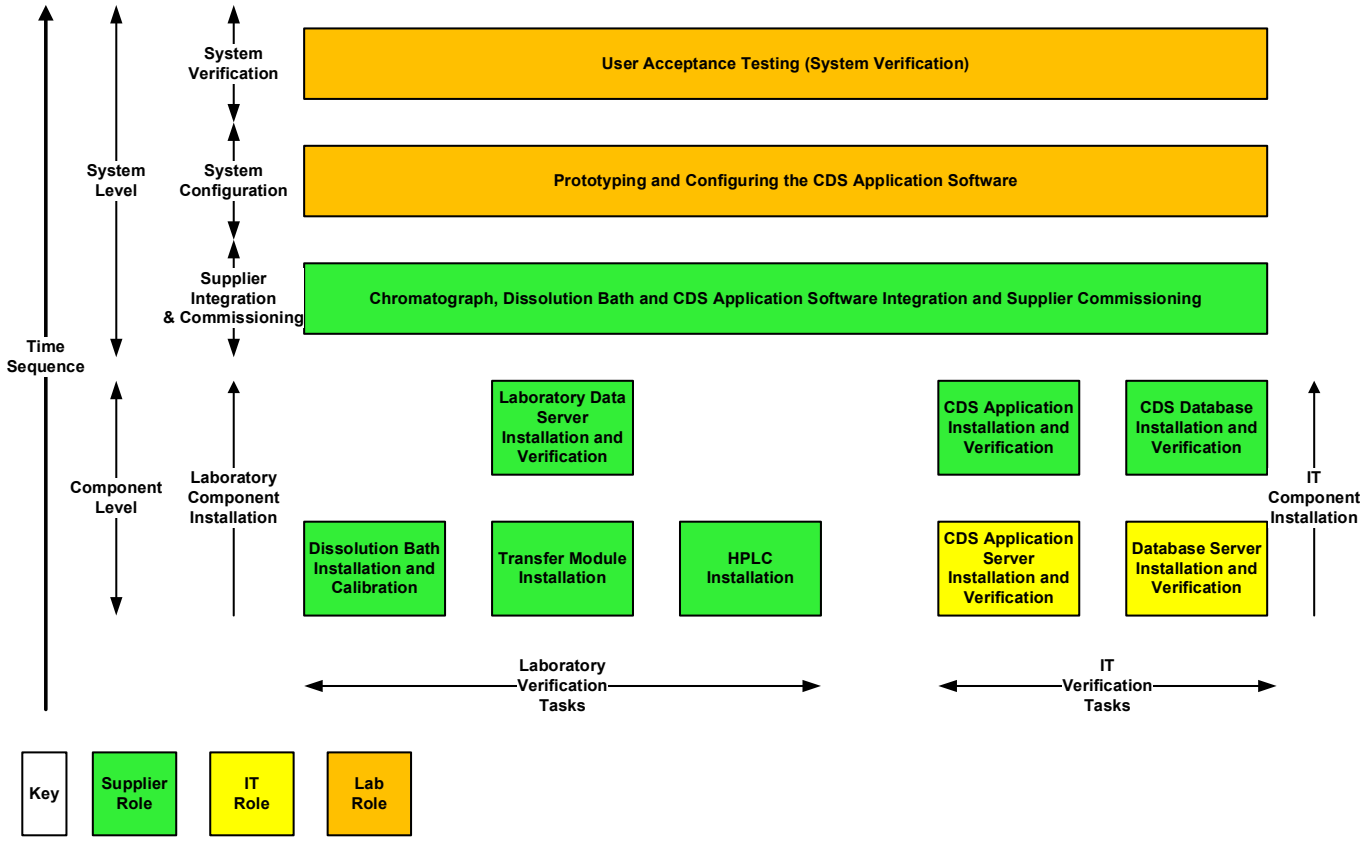
Section	Content
Introduction	• Laboratory and high-level function of the system • System details: supplier, application and version number • Referenced documents
Computer Platform	• IT hardware • Database, operating system, peripherals
System	• Number of users • Number of chromatographs • Laboratory data servers for instrument control • Supplier and assessment
Regulatory Compliance	• Applicable regulations • User identities, user roles and passwords e.g. Analyst, Supervisor, LabAdmin, QA, Service, ITAdmin etc • Configuration settings • Audit trail(s) • Electronic signature use • Time settings and time zones if applicable
Chromatography Functions	• Folder or project naming conventions and settings • Chromatograph specifications • Method development and validation • Requirements for chromatographic analysis: Sequence file Instrument control including Acquisition Processing Calculation and reporting of results • SOP for use missing (also in the previous example)
IT Support	• User account management • System administration • Backup and recovery, disaster recovery • Change control: patching and updating • Cybersecurity
Interfaces	• For each system interfaced outline the data flows and transfers (If applicable)
Data Migration	• Migration from one version to another (If applicable)

Table 22 shows an example of the high-level content for a CDS URS. The document should be adapted to suit the type of CDS e.g. standalone, networked or SaaS. As required by EU GMP Annex 11 clause 4.4 requirements should be traceable throughout the life cycle [21] and therefore should be uniquely numbered.

18.2.4 Group C Type 2: On-Premises Installation of a Networked CDS

When installing, integrating and commissioning an on-premises network CDS there are several layers of qualification to consider such as the IT hardware that the application will run on as well as the chromatographs and data servers for the laboratory. There are also several responsibilities involved in the process for individual items and the integration into a working system. Figure 34 illustrates the process of installation, integration, qualification of components, prototyping the workflow and validation of the overall system. This is based on a case study where there were chromatographs as well as an integrated automated dissolution and LC analysis modules.

Figure 34: Layers of Qualification and Responsibilities for a Networked CDS



There are three roles involved in the overall qualification and validation of this system.

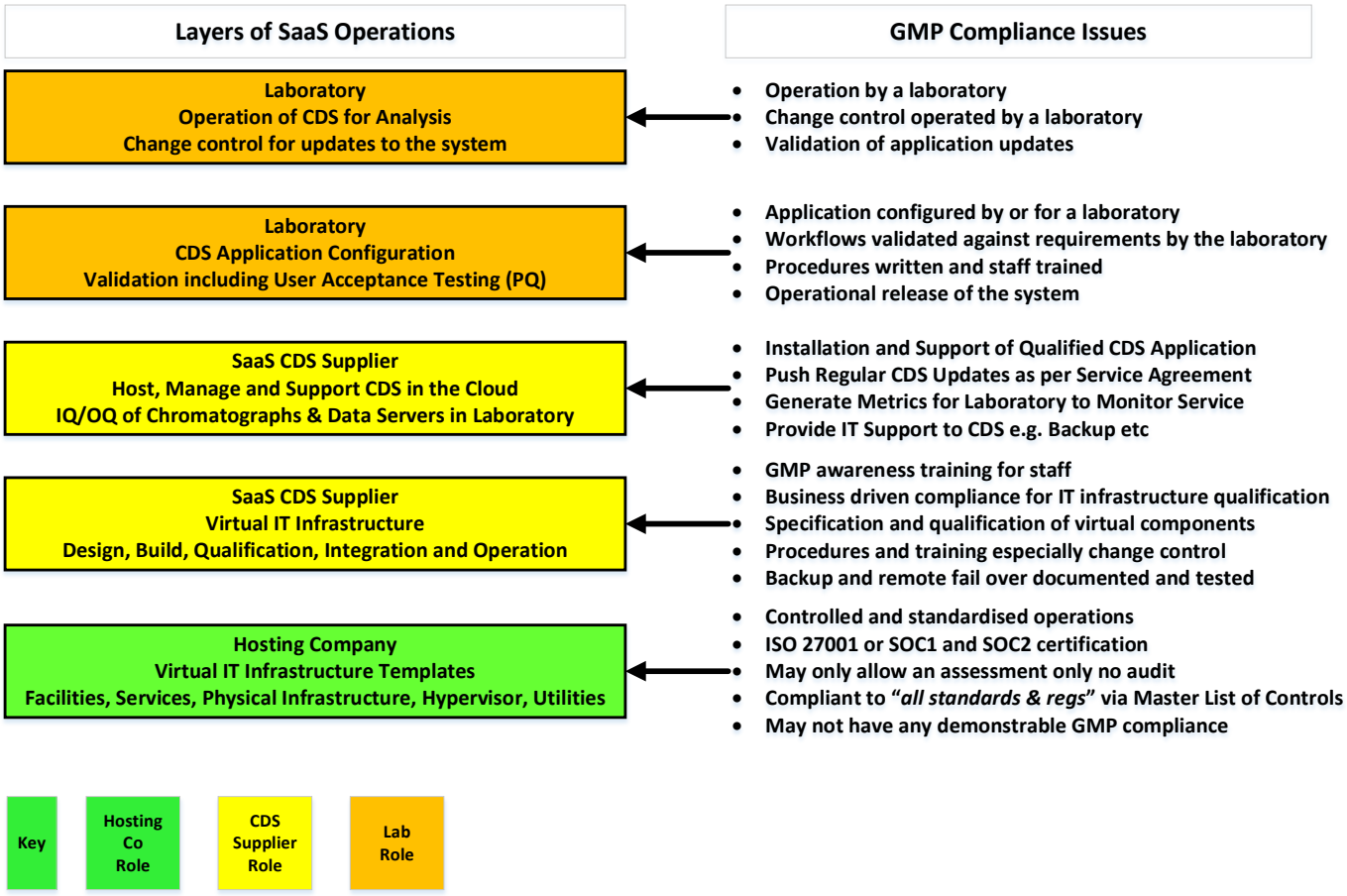
- **IT Department**:
  Responsible for specifying and qualifying the IT platform that the application will run on. This can be physical or virtual but will involve input from the supplier of minimal specifications to run the application. Usually this will be exceeded to ensure that there is sufficient computing power and data storage to function for 2 – 3 years before change. This is shown in yellow in Figure 32. Not shown is the requirement for sufficient network access points in the laboratory and network capacity especially if large files such as DAD or MS files have to be transferred across the network.

- **CDS Supplier**:
  Responsible for the installation and qualification of the software components of the CDS on the servers as well as the individual chromatographs, dissolution baths and transfer modules and laboratory data servers. All must be integrated together and commissioned by the supplier.
- **Laboratory**:
  Once the unconfigured system is handed over by the supplier, the key laboratory users will prototype the workflows: incorporation of calculations instead of using a spreadsheet, use of electronic signatures to eliminate paper printouts etc. When complete, configuration specifications can be completed as part of the validation documentation ready for the user acceptance testing to be undertaken. When necessary, the URS and configuration specification should be updated.

18.2.5 Group C Type 2: CDS Software as a Service (SaaS)

If a laboratory is considering a CDS SaaS option, the risk involved need to be understood. Instead of the computer system be installed and operated by the organisation's IT department it is outsourced to the CDS supplier and their hosting company as shown in Figure 35. In essence SaaS is the laboratory's data on someone else's computer. Your IT department is now the CDS supplier and their proxy the hosting company.

Figure 35: Responsibilities and GMP Compliance Issues with a SaaS CDS



We will discuss the three roles involved in a SaaS CDS installation in Figure 35:

- **Hosting Company**:
  A cloud service provider is typically certified to ISO 27001 [95]1 and SOC1 and/or SOC2 standards [96, 97] that provides a data centre where the physical computers are installed with N+1 services to ensure that the systems can still operate if there is a fault.
- The hypervisor application is installed on the physical hardware and virtual servers and IT infrastructure templates are developed by the hosting company for a supplier to use. The hosting company is not seen by the laboratory unless there is a major problem. The key is the Service Level Agreement (SLA) that the CDS supplier has with the hosting company including a failover remote from the main site. This is critical as data centres can catch fire and an automatic failover to a remote location is critical to ensure that you can still operate and no GMP data are lost. It may not be possible for an assessment of the hosting company can be carried out, all that may be provided are statements of compliance with ISO 27001 and/or SOC2 standards.
- **CDS SaaS Provider**
  Welcome to your new IT Department. The CDS supplier's IT staff will provide the virtual infrastructure that the application will operate on and this will be part of an assessment of the supplier as to GMP compliance:
  - Are staff trained including GMP awareness with records?
  - Is the IT infrastructure qualified?
  - Is change control and configuration management in place and working?
  - Are backup and recovery working with a remote failover location?
  - Do the supplier's staff have access to your chromatography data?

  The problem with SaaS is the frequency of updates, typically every three or four months that will trigger partial revalidation of the system. As this will be a contractual obligation, it means that it will be relatively easy to determine the amount of requalification work required if the supplier provides detailed release notes listing the enhancements and bug-fixes together with their impact on the system in each release. This will enable the laboratory to plan the amount of revalidation work required.
- **Laboratory**
  The work required is like that shown and discussed earlier in Figure 34. Prototyping and validation. Ideally, the SaaS supplier will provide a test environment to assess the changes and allow time to write any revalidation tests. In some cases all that may be required is to reprocess data already acquired to show that the same results are generated before and after the upgrade.

18.3 Service Level Agreement with an IT or SaaS Service Provider

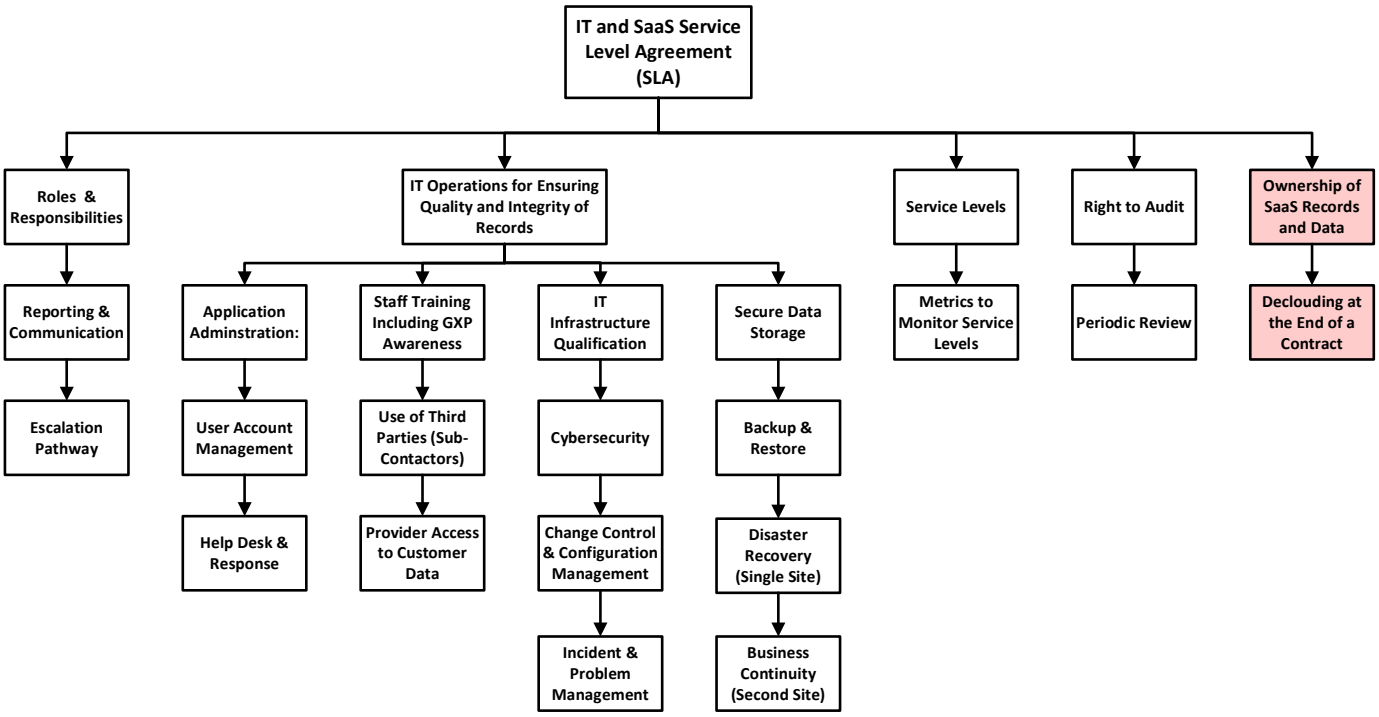
For Group C systems connected to the network and Group B instruments connected to informatics applications there will be IT involvement. Annex 11 clause 3.1 requires an agreement between an IT service provider (in-house, external or SaaS) and the laboratory for the services provided [21]. Figure 36 provides an overview of such an agreement with some explanatory test that follows. The scope of this section has been modified from a draft Cloud Computing Supplement to OCED GLP No 17 [98] and adapted for any IT service provider. As with any suggestions in this Guide, each individual organisation is responsible for tailoring this advice to their own needs.

18.3.1 Roles and Responsibilities

- All roles and responsibilities of both the organisation and the IT or cloud service provider should be clearly described.

- The accountability for outsourced services and the records of their work to enable GMP compliance remains with the laboratory and the process owners of the systems being run by IT or SaaS service providers.
- If an IT or cloud service provider subcontracts work to third-party suppliers, this should be addressed in the SLA with a list of subcontractors, subcontracted activities, GMP awareness training and associated responsibilities. Knowing who is involved is critical for ensuring compliance with GMP as many external service providers can be opaque.

Figure 36: Components of an IT Service Level Agreement between a Laboratory and an IT or SaaS Service Provider



18.3.2 Communication and Escalation Routes

- The communication lines between the regulated user and the IT or cloud service provider must be described in the SLA. Specific named individuals and deputies should be identified along with their contact details.
- There should be agreement as to what information is to be shared from the service provider e.g. problem and incident management, change control requests, can the supplier access company data? L
- Both parties should cooperate to ensure the compliant and valid operation of the system and IT infrastructure to maintain the qualified and validated state of the system. Due diligence of the IT and cloud service provider needs to be performed to ensure that Quality Management System and associated procedures and records are adequate. This is especially so as the current proposal to update Annex 11 suggests that cloud service providers help the regulated user support inspections [64].

18.3.3 IT Platform Qualification and Support

- The SLA should describe the duties of both the regulated user and cloud service provider (and any subcontractor(s)) during the life cycle of the supported systems. At a minimum, following areas should be covered to ensure the integrity and security of the data and records held:
    - Qualified physical and virtual IT infrastructure
    - Security and cybersecurity measures
    - Limiting access to authorised individuals of the service provider to data; no data deletion allowed unless authorised by company management and documented.
    - Secure data storage.
    - Change control and configuration management.
    - Problem and incident management.
    - Back-up and restore, Disaster recovery and Business continuity
    - Data ownership and management
    - Archiving and disposal of data
    - Data privacy

18.3.4 SaaS Application Updates

- For a SaaS provider, the provision of regular updates, typically quarterly, must be accompanied by thorough release notes containing the changes contained in the latest update and their impact on the system. The implications of updates or patches of the operating system must also be considered.
- These must be provided to the regulated user in sufficient to understand the impact of the changes and update any validation documentation.
- A test environment should also be provided for hands on checks before cut over to the new version.

18.3.5 Audits and Periodic Reviews

- The service provider should allow audits of their activities and this must be in a provision in the SLA
- Help in conducting periodic reviews of systems should also be defined in the SLA and the company QA programme

18.3.6 Exit Strategy

This is shown in light red in Figure 36:

- The SLA should clearly state the company's ownership of the data.
- It should also describe company's right to obtain all data and meta-data (including audit trails) in a readable and convertible format, in case the contract with the cloud service provider is terminated
- Negotiate this before the SLA and contract is signed and verify how your records would be made available: trust but verify it works

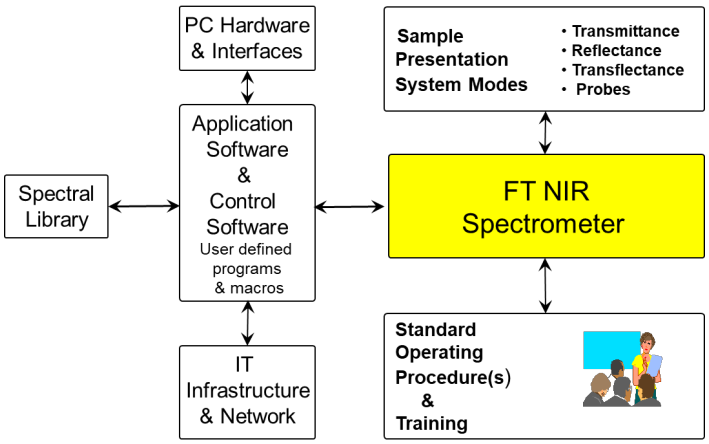
18.3.7 Review and Approval of the SLA

- Draft SLA should be reviewed by purchasing, legal and QA before finalising. The latter is responsible to ensuring GMP requirements are included in the agreement.
- Approval of the SLA will depend on the policies of the organisation and the overall scope of services provided

19 Appendix 6: Group C3 NIR spectrometer for identification of raw materials using macros

The application of a FT-NIR (Fourier Transform Near Infra Red) spectrometer for the identification of raw materials is a common application. The system does not use spectral libraries but the simple compare function in the software. The overall system is complex even at a high level as is illustrated in Figure 37

Figure 37 High level overview of an FT-NIR system for the identification of raw materials



The Risk Assessment requires all threads to be considered as shown in Table 23

Table 23 Risk Assessment for an FTNIR system for the identification of raw materials

LIFECYCLE ACTIVITY Stage and Phase	Instrument	System	Application	IT & Network
Stage 1: Specification and Selection				
Risk Assessment (RA)	✓	✓	✓	✓
URS (define intended use)	✓	✓	✓	✓
Evaluation and selection	✓	✓	✓	✓
Supplier Assessment/Qualification		✓		
ID Critical Inst & DI controls	✓	✓	✓	✓
Selection Report		✓		
Supplier SW asessment			(✓)	
Purchasing specification & PO		✓		
Stage 2: Qualification and Validation				
Plan work Required from RA	✓	✓	✓	✓
Site Preparation		✓		✓
Supplier install and integration	✓	✓	✓	
Supplier commissioning	✓	✓	✓	
Prototying and Configuration		✓	✓	
Update URS		✓		
Requirements traceability	✓	✓	✓	✓
User Acceptance Testing	✓	✓	✓	✓
Write SOPs and training	✓	✓	✓	✓
Instrumentation Log book	✓			
Authorisation for use	✓	✓	✓	✓

A simplified list of critical instrumental parameters is given in Table 24

Table 24 Typical critical instrumental parameters for a FTNIR system

Critical Instrument/System Controls and Parameters	SUPPLIER SPECIFICATION		LABORATORY URS	
	Operational Range	Tolerance	Operational Range	Tolerance
Wavelength scale range	780 nm to 2500 nm		780 nm to 2500 nm	Meets Pharm. Eur. Requirements & USP Requirements
Wavelength scale accuracy in all modes		± 1nm at 1200 nm, ± 1 nm at 1600 nm and ±1.5 nm at 2000 nm		
Wavelength scale precision in all sample presentation modes		<0.1cm^{-1}		
Photometric linearity in all sample presentation modes		1.00 ± 0.05 for the slope and 0.00 ± 0.05 for the intercept [95% confidence intervals]		
High flux RMS noise		Average <0.3×10^{-3} and no RMS noise >0.8×10^{-3}		
Low flux RMS noise		Average<1.0×10^{-3} and no RMS noise >2.0×10^{-3}		

An overall process is shown in Figure 38.

The critical element here is that during User Acceptance Testing it was discovered that the standard functionality of the commercial application software did not provide a method for assessing within container batch uniformity as required by the URS and accepted by the supplier.

However, the application had a macro language which allowed the required functionality to be programmed. However, this custom software was GAMP© Category 5 and required not only black box testing but also white box testing together with a fully documented code review. Hence the Supplier software development function assessment was required.

This was not a simple exercise and required considerable technical expertise to perform and was not available to the end user. Such macro programs should be avoided unless essential to meet user requirements.

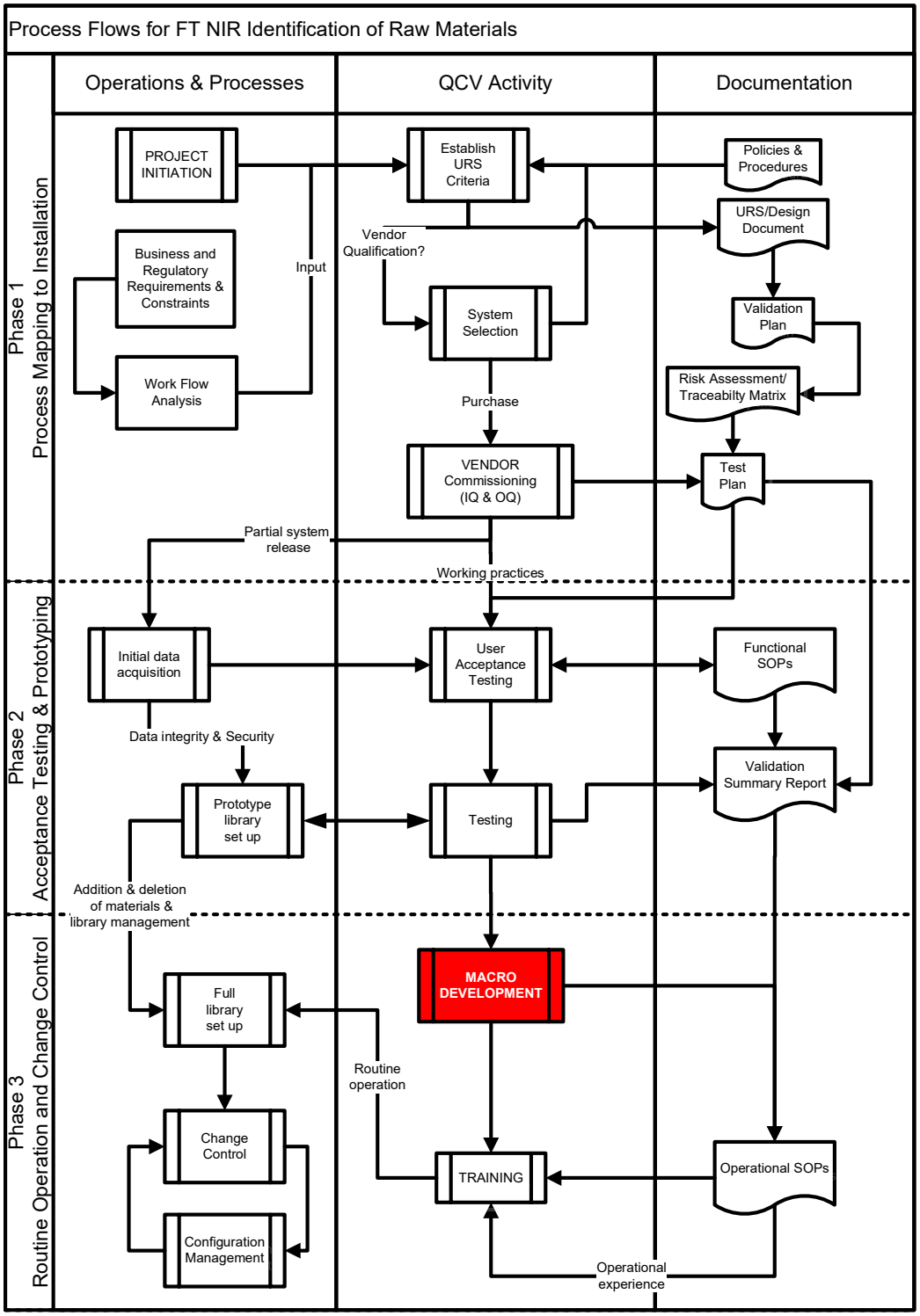
This functionality was included in the next release of the application software as standard.

19.1 Management of User Defined Macros

Management (e.g. specification development, verification and change) of macros for instruments & systems requires a separate procedure that is outside the scope of the life cycle phases and threads described in Section 9.1.2.

However, these can be developed and verified before the system goes live or at any time using the operational phase of the instrument. Macros cannot be released until each one has been specified, developed and verified to demonstrate that it meets the intended use requirements. Release should require a simple release statement or change control form.

Figure 38 Overall FTNIR process flow



20 Technical Glossary

This glossary is adapted from [59]. The terms presented here are quoted from several sources that can be found in the references at the end of this Guide. In some cases, a term may have several definitions from various sources to illustrate the differences between regulatory authorities. Also, an authority may have published two or three versions of guidance over time and the same term may have different definitions from the same authority that are included here, this is deliberate so that readers can see how the definition of a single term has evolved over time. Note, that detailed references are not given for all terms in this glossary as the focus is on data integrity terms.

20.1 Terms

Term	Meaning
Acceptance Criteria	The criteria a system must meet to satisfy a test or other requirement [99]
ALCOA.	A commonly used acronym for "attributable, legible, contemporaneous, original and accurate" [34].
ALCOA+	A commonly used acronym for "attributable, legible, contemporaneous, original and accurate", which puts additional emphasis on the attributes of being complete, consistent, enduring and available – implicit in the basic ALCOA principles [34]. ALCOA being Attributable, Legible, Contemporaneous, Original, and Accurate and the '+' referring to Complete, Consistent, Enduring, and Available. ALCOA was historically regarded as defining the attributes of data quality that are suitable for regulatory purposes. The '+' has been subsequently added to emphasise the requirements. There is no difference in expectations regardless of which acronym is used since data governance measures should ensure that data is complete, consistent, enduring and available throughout the data lifecycle [33].
ALCOA++	The same 9 criteria of ALCOA+ with the addition of Traceable [62]. The Guide refers to the acronym ALCOA++ rather than ALCOA or ALCOA++ Further reading on this subject is also available [63].
Analytical Instrument Qualification (AIQ)	AIQ is the collection of documented evidence that an instrument performs suitably for its intended purpose. Use of a qualified instrument in analyses contributes to confidence in the validity of generated data [22].
Application	Software installed on a defined platform/hardware providing specific functionality [74].
Application Configuration	See configuration specification

Term	Meaning
Archival	Archiving is the process of protecting records from the possibility of being further altered or deleted, and the storing these records under the control of independent data management personnel throughout the required retention period. Archived records should include, for example, associated metadata and electronic signatures [34].
Archive	Long term, permanent retention of completed data and relevant metadata in its final form for the purposes of reconstruction of the process or activity [100]. A designated secure area or facility (e.g. cabinet, room, building or computerised system) for the long term, permanent retention of complete data and relevant metadata in its final form for the purposes of reconstruction of the process or activity [101]. A designated secure area or facility (e.g. cabinet, room, building or computerised system) for the long term, retention of data and metadata for the purposes of verification of the process or activity [33].
Archivist	An independent individual designated in good laboratory practice (GLP) who has been authorized by management to be responsible for the management of the archive, i.e. for the operations and procedures for archiving [34].
Audit	An audit is a formal, independent, disciplined and objective review activity designed to assess the performance of a process or system with regards to established regulations and procedures. There are internal audits, second party audits (between two companies) and third-party audits (using an independent auditor).
Audit Trail	GMP/GDP audit trails are metadata that are a record of GMP/GDP critical information (for example the change or deletion of GMP/GDP relevant data), which permit the reconstruction of GMP/GDP activities [100]. A secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record. An audit trail is a chronology of the “who, what, when, and why” of a record. Electronic audit trails include those that track creation, modification, or deletion of data (such as processing parameters and results) and those that track actions at the record or system level (such as attempts to access the system or rename or delete a file) [102]. Audit trail means a secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record. An audit trail is a chronology of the “who, what, when, and why” of a record [34].

Term	Meaning
Audit trail (continued)	Audit trails are metadata that are a record of critical information (for example the change or deletion of relevant data) that permit the reconstruction of activities [101] The audit trail is a form of metadata containing information associated with actions that relate to the creation, modification or deletion of GXP records. An audit trail provides for secure recording of life-cycle details such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record regardless of its medium, including the "who, what, when and why" of the action [33]
Back-up	A copy of current (editable) data, metadata and system configuration settings (e.g. variable settings which relate to an analytical run) maintained for the purpose of disaster recovery [100]. A true copy of the original data that is maintained securely throughout the records retention period (for example, § 211.180). The backup file should contain the data (which includes associated metadata) and should be in the original format or in a format compatible with the original format [102]. A copy of one or more electronic files created as an alternative in case the original data or system are lost or become unusable (e.g. in the event of a system crash or corruption of a disk). It is important to note that backup differs from archival in that back-up copies of electronic records are typically only temporarily stored for the purposes of disaster recovery and may be periodically overwritten. Such temporary back-up copies should not be relied upon as an archival mechanism [34]. A copy of current (editable) data, metadata and system configuration settings (variable settings which relate to a record or analytical run) maintained for the purpose of disaster recovery [101]. A copy of current (editable) data, metadata and system configuration settings maintained for recovery including disaster recovery [33]. FDA uses the term backup in § 211.68(b) to refer to a true copy of the original data that is maintained securely throughout the records retention period (for example, § 211.180). The backup file should contain the data (which includes associated metadata) and should be in the original format or in a format compatible with the original format. This should not be confused with backup copies that may be created during normal computer use and temporarily maintained for disaster recovery (e.g., in case of a computer crash or other interruption) [102].
Bespoke/ Customized Computerised System	A computerised system individually designed to suit a specific business process [21]

Term	Meaning
Boundary Value	A minimum or maximum input, output or internal data value, applicable to a system [99]
Branch Testing	Execution of tests to assure that every branch alternative has been exercised at least once
Calibration	The demonstration that a particular instrument or device results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements [103]. An operation that, under specified conditions, in a first step, establishes a relation between the quantity values, with measurement uncertainties provided by measurement standards, and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication. Note that: 1. A calibration may be expressed by a statement, calibration function, calibration diagram, calibration curve, or calibration table. In some cases, it may consist of an additive or multiplicative correction of the indication with associated measurement uncertainty. 2. Calibration should not be confused with adjustment of a measuring system, often mistakenly called “self-calibration”, or with verification of calibration. 3. Often, the first step alone in the above definition is perceived as being calibration [22].
Change	The addition, modification or removal of approved, supported or baselined hardware, network, software, application, environment, system, desktop build or associated documentation (ITIL).
Change Advisory Board	A group of people who can give expert advice to change management on the implementation of changes. This board is likely to be made up of representatives from all areas within IT and representatives from business units (ITIL).
Change Control	A formal monitoring system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status to determine the need for corrective action that would assure that the system retains its validated state [5]
Change History	Auditable information that records, for example, what was done, when it was done by who and why (ITIL)
Change Management	Process of controlling Changes to the system or any aspect of services, in a controlled manner, enabling approved Changes with minimum disruption (ITIL).
Configuration – 1	The arrangement of a computer system or component as defined by the number, nature, and interconnections of its constituent parts (IEEE).
Configuration – 2	Changing the business process automated by an application by modifying the parameters within the software provided by the supplier (also known as parameterisation).

Term	Meaning
Configuration Baseline	Configuration of a system established at a specific point in time, which captures the structure and details of the system and enables that system to be rebuilt at a later date (ITIL).
Configuration Item (CI)	Component of an infrastructure or system or an item such as Request for Change which is under the control of Configuration Management. Configuration Items may vary widely in complexity, size and type – from an entire system (including all hardware, software and documentation) to a single module or a minor hardware component (ITIL)
Configuration Management	A system for identifying the configuration of hardware, software, firmware or documentation of a computerised system at discrete points in time with the purpose of systematically controlling changes to the configuration and maintaining the integrity and traceability of the configuration throughout the system life cycle
Corrective Action and Preventative Action (CAPA)	System for implementing corrective actions and preventative actions resulting from the investigation of non-conformances, deviations, audits, regulatory inspections and findings [104]. Actions taken to improve an organization's processes and to eliminate causes of non-conformities or other undesirable situations. CAPA is a concept common across the GXPs (good laboratory practices, good clinical practices and good manufacturing practices), and numerous International Organization for Standardization business standards [34].
COTS Software	Commercial off the shelf software application is used as is without altering the basic program Configurable off the shelf software applications that can be configured to specific user applications by "filling in the blanks" without altering the basic program. **Note:** This term is not used in this Guide and GAMP© software categories are used instead.
Controlled Function	A process and any related equipment controlled by a computer system
Customisation	Changing the business process automated by an application by writing software modules to add to an existing commercial application. Note enhancement of an application via a supplier language is the equivalent to custom code.
Code of Federal Regulations (CFR)	The codification of the general rules of the United States of America published in the Federal Register by the executive departments and agencies of the Federal Government. Divided into 50 titles that represent the areas regulated by the US Government.
Commercial off the shelf software	Software commercially available, whose fitness for use is demonstrated by a broad spectrum of users. [21] **Author note**: this term can be abused and can be used to confuse. GAMP© software categories should be used instead.

Term	Meaning
Commissioning	The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, specified in the user requirements specification, and capacities specified by the designer or developer. Commissioning is carried out before qualification and validation (WHO GMP).
Computer Hardware	Various hardware components in the computer system, including the central processing unit, printer, screen and other related apparatus
Computer System	Computer hardware components assembled to perform in conjunction with a set of programs, which are collectively designed to perform a specific function or group of functions A group of hardware components and associated software designed and assembled to perform a specific function or group of functions [21].
Computerised System	A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control [74] People, machines, and methods organized to accomplish a set of specific functions. Computer or related systems can refer to computer hardware, software, peripheral devices, networks, cloud infrastructure, operators, and associated documents (e.g., user manuals and standard operating procedures) [105]. A computerised system collectively controls the performance of one or more automated processes and/or functions. It includes computer hardware, software, peripheral devices, networks and documentation, e.g. manuals and standard operating procedures, as well as the personnel interfacing with the hardware and software, e.g. users and information technology support personnel [34].
Computerised System Specification	A document or set of documents that describe how a computerised system will satisfy the system requirements of the computer related system
Computerised System Validation	Establishing documented evidence which provides a high degree of assurance that a specific computer related system will consistently operate in accordance with predetermined specifications [99]. Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled [11].
Configuration Specification	Document containing the current application settings for security, system policies, data integrity, user roles with access privileges for each role etc.

Term	Meaning
Control Strategy	A planned set of controls, derived from current protocol, test article or product and process understanding, which assures protocol compliance, process performance, product quality and data reliability, as applicable. The controls should include appropriate parameters and quality attributes related to study subjects, test systems, product materials and components, technologies and equipment, facilities, operating conditions, specifications and the associated methods and frequency of monitoring and control [34].
Data	Facts, figures and statistics collected together for reference or analysis [100]. Data means all original records and true copies of original records, including source data and metadata and all subsequent transformations and reports of these data, which are generated or recorded at the time of the GXP activity and allow full and complete reconstruction and evaluation of the GXP activity [100]. Facts and statistics collected together for reference or analysis. Data governance measures should also ensure that data are compete, consistent and enduring throughout the lifecycle [101]
Data Governance	The sum total of arrangements to ensure that data, irrespective of the format in which it is generated, is recorded, processed, retained and used to ensure a complete, consistent and accurate record throughout the data lifecycle [100]. The totality of arrangements to ensure that data, irrespective of the format in which they are generated, are recorded, processed, retained and used to ensure a complete, consistent and accurate record throughout the data life cycle [101]. The sum total of arrangements to ensure that data, irrespective of the format in which it is generated, is recorded, processed, retained and used to ensure a complete, consistent and accurate record throughout the data lifecycle [101]. The arrangements to ensure that data, irrespective of the format in which they are generated, are recorded, processed, retained and used to ensure the record throughout the data lifecycle [33].

Term	Meaning
Data Integrity	The extent to which all data are complete, consistent and accurate throughout the data lifecycle [100]. Data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA) [102]. With ALCOA++, traceability is added as a 10th criterion [62]. Data integrity is the degree to which data are complete, consistent, accurate, trustworthy and reliable and that these characteristics of the data are maintained throughout the data life cycle. The data should be collected and maintained in a secure manner, such that they are attributable, legible, contemporaneously recorded, original or a true copy and accurate. Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices [34]. The extent to which all data are complete, consistent and accurate throughout the data lifecycle [32]. Data integrity is the degree to which data are complete, consistent, accurate, trustworthy, reliable and that these characteristics of the data are maintained throughout the data life cycle. The data should be collected and maintained in a secure manner, so that they are attributable, legible, contemporaneously recorded, original (or a true copy) and accurate. Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices [33].

Term	Meaning
Data Lifecycle	All phases in the life of the data (including raw data) from initial generation and recording through processing (including transformation or migration), use, data retention, archive / retrieval and destruction [100]. All phases of the process by which data are created, recorded, processed, reviewed, analysed and reported, transferred, stored and retrieved and monitored until retirement and disposal. There should be a planned approach to assessing, monitoring and managing the data and the risks to those data in a manner commensurate with potential impact on patient safety, product quality and/or the reliability of the decisions made throughout all phases of the data life cycle [34]. All phases in the life of the data (including raw data) from initial generation and recording through processing (including analysis, transformation or migration), use, data retention, archive / retrieval and destruction [32]. All phases in the life of the data from generation and recording through processing (including analysis, transformation or migration), use, data retention, archive/retrieval and destruction [33].
Data Processing	A sequence of operations performed on data in order to extract, present or obtain information in a defined format. Examples might include: statistical analysis of individual patient data to present trends or conversion of a raw electronic signal to a chromatogram and subsequently a calculated numerical result [33].
Data Quality	The assurance that data produced is exactly what was intended to be produced and fit for its intended purpose. This incorporates ALCOA [33].
Data Retention	Data retention may be classified as either archive (protected data for long term storage) or backup (dynamic data for the purposes of disaster recovery) [101].
Data Review	There should be a procedure that describes the process for the review and approval of data. Data review should also include a review of relevant metadata, including audit trails [101].
Data Transfer / Migration	Data transfer is the process of transferring data and metadata between storage media types or computer systems. Data migration changes the format of data to make it usable or visible on an alternative computerised system. Data transfer/migration should be designed and validated to ensure that data integrity principles are maintained [101].

Term	Meaning
Dynamic Data / Record	Dynamic data means that the record format allows interaction between the user and the record content e.g. interpretation of a chromatography data file for integration of the peaks of interest [106]. Records in dynamic format, such as electronic records, that allow for an interactive relationship between the user and the record content. For example, electronic records in database formats allow the user to track, trend and query data; chromatography records maintained as electronic records allow the user (with proper access permissions) to reprocess the data and expand the baseline to view the integration more clearly [34]. Information that is originally captured in a dynamic state should remain available in that state [33].
Design Qualification (DQ)	The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose [5]. DQ is the documented collection of activities that define the functional and operational specifications of the instrument, including the criteria for selection of the supplier, based on the intended purpose of the instrument. DQ states what the laboratory wants the instrument to do and shows that the selected one is suitable [107]. 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 one is suitable [22].
Developer	The company, group or individuals responsible for developing a system or some portion of a software application.
Electronic Signature	A signature in digital form (bio-metric or non-biometric) that represents the signatory. This should be equivalent in legal terms to the handwritten signature of the signatory [33].
Excluding Data	Data may only be excluded where it can be demonstrated through sound science that the data is anomalous or non-representative. In all cases, this justification should be documented and considered during data review and reporting. All data (even if excluded) should be retained with the original data set, and be available for review in a format that allows the validity of the decision to exclude the data to be confirmed [101].
Exception Report	A validated search tool that identifies and documents predetermined ‘abnormal’ data or actions, which requires further attention or investigation by the data reviewer [100].

Term	Meaning
Flat File	A 'flat file' is an individual record which may not carry any additional metadata with it, other than that which is included in the file itself [100]. A 'flat file' is an individual record which may not carry any additional metadata with it, other than that included in the file itself [101].
Firmware	A software program permanently recorded in a hardware device such as a chip or EPROM. Typified by GAMP© software category 2 or USP <1058> Group B analytical instruments [22].
Fully-electronic Approach	This term refers to use of a computerized system in which the original electronic records are electronically signed [34].
Functional Requirements	Statements that describe functions a computer related system must be capable of performing
Functional Specification	Statements of how the computerised system will satisfy functional requirements of the computer related system. Typically for a CDS validation, this is replaced by a configuration specification.
Functional Testing	A process for verifying that software, a system or a system component performs its intended functions
Good Data and Record Management Practices.	The totality of organized measures that should be in place to collectively and individually ensure that data and records are secure, attributable, legible, traceable, permanent, contemporaneously recorded, original and accurate and that if not robustly implemented can impact on data reliability and completeness and undermine the robustness of decision-making based upon those data records [34].
Good Documentation Practices	The measures that collectively and individually ensure documentation, whether paper or electronic, is secure, attributable, legible, traceable, permanent, contemporaneously recorded, original and accurate [34].
GXP	Acronym for the group of good practice guides governing the preclinical, manufacturing, testing, storage, and distribution for regulated pharmaceuticals, biologicals and medical devices, such as good laboratory practice, good clinical practice and good manufacturing practice [34].
Harm	Physical injury or damage to the health of people, or damage to property or the environment. Note this is for a medical device; this needs to be interpreted as the consequences of a software error or malfunction of the system [108].
Hazard	A potential source of harm [108].

Term	Meaning
Hybrid System	The use of a computerized system in which there is a combination of original electronic records and paper records that comprise the total record set that should be reviewed and retained. The hybrid approach requires a secure link between all record types, including paper and electronic, throughout the records retention period [34].
Inspection	The action by a regulatory authority of conducting an official review of facilities, documents, records, systems and any other resources to determine compliance with applicable regulations
Installation Qualification (IQ)	Documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations [5]. IQ is the documented collection of activities necessary to establish that an instrument is delivered as designed and specified, and is properly installed in the selected environment, and that this environment is suitable for the instrument [107]. 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 [22].
Instrument	Instrument includes any apparatus, equipment, instrument, or instrument system used in pharmacopoeial analyses [22].
IT Infrastructure	The hardware and software such as networking software and operating systems, which makes it possible for the application to function [21]
Life cycle (Computerised System)	All phases in the life of the system from initial requirements until retirement including design, specification, programming, testing, installation, operation, and maintenance [21]
Maintenance	Actions performed to keep an analytical instrument in a state of proper function so that it continues to operate within the boundaries set during qualification or validation [22].

Term	Meaning
Metadata	Data that describe the attributes of other data, and provide context and meaning [100]. Metadata is the contextual information required to understand data. A data value is by itself meaningless without additional information about the data. Metadata is often described as data about data. Metadata is structured information that describes, explains, or otherwise makes it easier to retrieve, use, or manage data [102]. Metadata are data about data that provide the contextual information required to understand those data. These include structural and descriptive metadata. Such data describe the structure, data elements, interrelationships and other characteristics of data. They also permit data to be attributable to an individual. Metadata necessary to evaluate the meaning of data should be securely linked to the data and subject to adequate review [34]. Metadata are data that describe the attributes of other data and provide context and meaning. Typically, these are data that describe the structure, data elements, inter-relationships and other characteristics of data e.g. audit trails. Metadata also permit data to be attributable to an individual (or if automatically generated, to the original data source). Metadata forms an integral part of the original record. Without metadata, the data has no meaning [33].
Ongoing Evaluation	The dynamic process employed after a system's initial validation to maintain its validated state.
Operating Environment	Those conditions and activities interfacing directly or indirectly with the system of concern, control of which can affect the system's validated state.
Operating System	A set of software programs provided with a computer that function as the interface between the hardware and the applications program
Operational Qualification (OQ)	The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges [5]. Operational Qualification (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 of purpose for the user's ways of working, and should reflect the contents of the DQ document [107]. 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 the contents of the DQ document [22].

Term	Meaning
Original Data	Link to raw data
Out of Specification (OOS) Result	A reportable result outside of specification or acceptance criteria limits. As we are dealing with specifications OOS results can apply to test of raw materials, starting materials, active pharmaceutical ingredients and finished products but not for in-process testing. If a system suitability test fails this will not generate an OOS result as the whole run would be invalidated, however, the needs to be an investigation of the failure [109].
Out of Trend (OOT) Result	Not an out of specification result but does not fit with the expected distribution of results. This can include a single result outside of acceptance limits for a replicate result used to calculate a reportable result. If investigated the same rules as OOS should be followed
Outsourced Activities	Activities conducted by a contract acceptor under a written agreement with a contract giver [104].
Performance Qualification (PQ)	The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification [5]. The documented verification that the integrated computerised system performs as intended in its normal operating environment i.e. that computer related system performs as intended [99]. Performance Qualification (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 performance qualification [22, 107].
Policy	A directive usually specifying what is to be accomplished
Process	Structured activities intended to achieve a desired outcome
Process owner	The person responsible for the business process [21]
Prospective Validation	Validation carried out before routine use of the system [5]

Term	Meaning
Qualification	Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification [74]. Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation [103]. Action of proving that any instrument works correctly and delivers the expected results; demonstration of fitness for purpose [22].
Qualification Protocol	A prospective experimental plan that when executed is intended to produce documented evidence that a system or subsystem has been qualified properly
Quality	The degree of which a set of properties of a product, system or process fulfils requirements [110].
Quality Assurance	The sum total of organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained [103].
Quality Control	Checking or testing that specifications are met [103].
Quality Unit	An organisational unit independent of production which fulfils both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QC and QA units or a single individual or group depending on the size of the organisation [103].

Term	Meaning
Raw Data	Original records, retained in the format in which they were originally generated (i.e. paper or electronic), or as a 'true copy'. Raw data must be contemporaneously and accurately recorded by permanent means. The definition of 'original records' currently varies across regulatory documents. By its nature, paper copies of raw data generated electronically cannot be considered as 'raw data'. Raw data must permit the full reconstruction of the activities resulting in the generation of the data. In the case of basic electronic equipment which does not store electronic data, or provides only a printed data output (e.g. balance or pH meter), the printout constitutes the raw data [31]. Raw data is defined as the original record (data) which can be described as the first-capture of information, whether recorded on paper or electronically [33]. Raw data means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study 21 CFR 58.3(k) [24].
Recording Data	Companies should have an appropriate level of process understanding and technical knowledge of systems used for data recording, including their capabilities, limitations and vulnerabilities [31].
Reportable Result	The term reportable result as used in this document means a final analytical result. This result is appropriately defined in the written approved test method and derived from one full execution of that method/procedure, starting from the sample. Compared with the specification to determine pass/fail of a test [109].
Retrospective Validation	Validation of a process or system after it has become operational [103].
Requalification	A repeat of all or part of the instrument qualification following preventative maintenance or repair to provide assurance that changes made to the instrument introduced in accordance with change control procedures do not adversely affect the instrument performance.
Revalidation	A repeat of all or part of the validation to provide assurance that changes in the system introduced in accordance with change control procedures do not adversely affect the system operation or data integrity.
Risk	Combination of the probability of occurrence of harm and the severity of that harm [108].

Term	Meaning
Risk analysis	The systematic use of available information to identify hazards and estimate the risk [108].
Risk assessment	The overall process of a risk analysis and risk evaluation [108].
Risk evaluation	Judgement, on the basis of risk analysis, of whether a risk that is acceptable has been achieved in a given context [108].
Risk management	The systematic application of management policies, procedures and practices to the tasks of analysing, evaluating and controlling risk [108].
Self-Inspection	An internal evaluation of compliance with applicable regulation in relevant regulated areas [34].
Senior Management	Person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilize resources within the company or site [34].
Severity	Measure of the possible consequences of a hazard [108].
Software Configuration	Adaptation of software functions to a business process using tools provided within the application by the supplier of the software [22].
Software Customisation	Changing the way software automates a business process by the addition of externally custom coded software modules using a recognized programming language or the development of macros within the application software [22].
Standard Operating Procedure	Instructions that specify how an activity or process is to be performed
Static Data / Record	Static record format is used to indicate a fixed-data document such as a paper record or an electronic image [102]. A static record format, such as a paper or pdf record, is one that is fixed and allows little or no interaction between the user and the record content. For example, once printed or converted to static pdfs, chromatography records lose the capability of being reprocessed or enabling more detailed viewing of baselines [34].
Structural Integrity	Software attributes reflecting the degree to which source code satisfies specified software requirements and conforms to contemporary software development.
Structural Verification	An activity intended to produce documented assurance that software has the appropriate structural integrity.

Term	Meaning
Supplier	The company or group responsible for developing, constructing and delivering a software application, computerised system or part of a system This term is used generically and can mean the manufacturer, a vendor, a service agent, or a consultant, depending on the circumstances [22].
System Owner	The person responsible for the availability, and maintenance of a computerised system and for the security of the data residing on that system [21].
Third Party	Parties not directly managed by the holder of the manufacturing and/or import authorisation [21].
True Copy / Certified Copy / Verified Copy	A true copy is a copy of an original recording of data that has been verified and certified to confirm it is an exact and complete copy that preserves the entire content and meaning of the original record, including, in the case of electronic data, all essential metadata and the original record format as appropriate [34]. A copy of original information that been verified as an exact (accurate and complete) copy having all of the same attributes and information as the original. The copy may be verified by dated signature or by a validated electronic signature. A true copy may be retained in a different electronic file format to the original record, if required, but must retain the equivalent static/dynamic nature of the original record [101]. A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original [33].
User	The company or group responsible for the operation of the system
User access / system administrator roles	Full use should be made of access controls to ensure that people have access only to functionality that is appropriate for their job role, and that actions are attributable to a specific individual. Companies must be able to demonstrate the access levels granted to individual staff members and ensure that historical information regarding user access level is available. Controls should be applied at both the operating system and application levels. Shared logins or generic user access should not be used. Where the computerised system design supports individual user access, this function must be used. This may require the purchase of additional licences [101]. Thoughts on adding user / elevated role Power User, Supervisor, etc? this role would be limited to a few people within the organization with capabilities of creating and updating method / protocols, instrument parameters

Term	Meaning
Validation – for intended purpose	Computerised systems should comply with regulatory requirements and associated guidance and be validated for their intended purpose. This requires an understanding of the computerised system's function within a process. For this reason, the acceptance of vendor-supplied validation data in isolation of system configuration and intended use is not acceptable. In isolation from the intended process or end user IT infrastructure, vendor testing is likely to be limited to functional verification only, and may not fulfil the requirements for performance qualification.
Validation Master Plan	A document providing information on the company's validation work programme. It should define details of and timescales for the validation work to be performed. Responsibilities relating to the plan should be stated [111].
Validation Plan	A document that identifies all systems and subsystems involved in a specific validation effort and the approach by which they will be qualified and the total system will be validated; includes the identification of responsibilities and expectations
Worst Case	Requirements or set of requirements that can include upper and lower limits and circumstances for a computerised system. Typically represent the limits of use within a specific laboratory

20.2 Abbreviations

Abbreviation	Meaning
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALCOA+	Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available
ALCOA++	Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available, Traceable
ANSI	American National Standards Institute
API	Active Pharmaceutical Ingredient
ASTM	American Society for Testing and Materials
ATP	Analytical Target Profile
BCP	Business Continuity Plan
CAPA	Corrective Action and Preventative Action
CBER	Center for Biologics Evaluation and Research (FDA)
CDER	Center for Drug Evaluation and Research (FDA)
CDRH	Center for Devices and Radiological Health (FDA)
CDS	Chromatography Data System
CE	Capillary Electrophoresis
CFR	Code of Federal Regulations (e.g. 21 CFR 11)
CMO	Contract Manufacturing Organisation
COTS	Commercial / Configurable Off The Shelf (Software) This term is not recommended for use as it is confusing when not defined. Define software type using GAMP© software categories.
CPG	Compliance Program Guide Compliance Policy Guide
CRO	Contract Research Organization
cGMP	current Good Manufacturing Practices
COA	Certificate of Analysis

Abbreviation	Meaning
COTS	Commercial / Configurable Off The Shelf Software
CS	Configuration Specification
CSF	Critical Success Factor
CSV	Computer System Validation
DI	Data Integrity
DG	Data Governance
DQ	Design Qualification
DR	Disaster Recovery
DS	Design Specification
ECD	Electron Capture Detector
EDMS	Electronic Document Management System
EIR	Establishment Inspection Report
ELN	Electronic Laboratory Notebook
EMA	European Medicines Agency
EMEA	European Agency for the Evaluation of Medical Products (now EMA)
EP	European Pharmacopoeia (Ph.Eur)
EU	European Union
FDA	Food and Drug Administration
FID	Flame Ionisation Detector
FMEA	Failure Mode and Effects Analysis
FOI (A)	Freedom of Information (Act)
FR	Federal Register
FS	Functional Specifications
FT	Fourier Transformation
GAMP©	Good Automated Manufacturing Practice guidelines
GC	Gas Chromatography

Abbreviation	Meaning
GdocP	Good Documentation Practice
GLP	Good Laboratory Practice
GRDP	Good Records and Documentation Practice
GXP	Good X Practices (where X can be clinical, laboratory and/or manufacturing)
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis Critical Control Point
HPLC	High Pressure Performance Liquid Chromatography
IaaS	Infrastructure as a Service
ICH	International Conference on Harmonisation (1990 – 2015) International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (from October 2015)
ICP	Inductively Coupled Plasma
IEEE	Institute of Electrical and Electronic Engineers, Inc
IND	Investigational New Drug Application
IQ	Installation Qualification
IP	Internet Protocol
IR	Infra-Red
ISO	International Organization for Standardization
ISPE	International Society of Pharmaceutical Engineers
IT	Information Technology
ITIL	IT Infrastructure Library
ITT	Invitation to Tender
KPI	Key Performance Indicator
LAN	Local Area Network
LES	Laboratory Execution System
LIMS	Laboratory Information Management System

Abbreviation	Meaning
MHLW	Ministry of Health, Labour and Welfare (Japan)
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MOU	Memorandum of Understanding
MRA	Mutual Recognition Agreement
MS	Mass Spectrometer
NCE	New Chemical Entity
NDA	New Drug Application
NIR	Near Infra-Red
NIST	National Institute of Standards and Technology (Gaithersburg, Maryland, USA)
NMR	Nuclear Magnetic Resonance
OECD	Organization for Economic Cooperation and Development
OOE	Out Of Expectation
OOS	Out Of Specification
OOT	Out Of Trend
OQ	Operational Qualification
ORA	Office of Regulatory Affairs (FDA)
OTS	Off The Shelf (refers to software – use is not recommended)
PaaS	Platform as a Service
PAI	Pre-Approval-Inspection
PDA	Parenteral Drug Association
PDF	Portable Document Format
Ph.Eur.	European Pharmacopoeia
PIC	Pharmaceutical Inspection Convention
PIC/S	Pharmaceutical Inspection Convention/Scheme
PKI	Public Key Infrastructure
PPQ	Procedure Performance Qualification

Abbreviation	Meaning
PPV	Procedure Performance Verification
PQ	Performance Qualification
PQS	Pharmaceutical Quality System
QA	Quality Assurance
QAU	Quality Assurance Unit
QC	Quality Control
QMS	Quality Management System
QP	Qualified Person
QRM	Quality Risk Management
R&D	Research and Development
RAID	Redundant Array of Inexpensive Disks
RFC	Request for Change
RFID	Radio Frequency Identity
RFP	Request for Proposal
RSD	Relative Standard Deviation
SaaS	Software as a Service
SAN	Storage Area Network
SDLC	System Development Life Cycle
SILC	System Implementation Life Cycle
SLA	Service Level Agreement
SOP	Standard Operating Procedure
SPC	Statistical Process Control
SQA	Society for Quality Assurance
SRS	System Requirements Specification (equivalent to URS)
SST	System Suitability Test
TMU	Target Measurement Uncertainty

Abbreviation	Meaning
UAT	User Acceptance Testing
UPS	Uninterruptible Power Supply
URS	User Requirement Specifications
USB	Universal Serial Bus
USP	United States Pharmacopoeia
UV	Ultraviolet
VMP	Validation Master Plan
VSR	Validation Summary Report
WAN	Wide Area Network
WI	Work Instruction
WHO	World Health Organisation

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