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Solving the Terminology Conundrum

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This article discusses the terms "commissioning," "qualification," and "verification." Do the terms refer to the same or different ideas? How should the pharmaceutical and biotechnology industries use these terms in a consistent and meaningful way? This article provides a compilation of how these terms are used in regulations and by various industries, and provides a proposal for clear definitions to be used as ISPE updates and creates Baseline® Guides.

Introduction

In today's biopharma and pharmaceutical industries, three related, but distinct terms are in common use: commissioning, qualification, and verification. Inconsistent interpretation and application of these terms leads to misunderstandings and inefficiencies on the part of vendors, service providers, and manufacturing personnel from company to company. This article, through a review of the industry definitions and associated practices, is intended to stimulate discussion on resolving this terminology conundrum and provide key input to pending publications of ISPE Baseline® Guides.

In 2001, ISPE issued the Baseline® Guide Volume 5: Commissioning and Qualification, that provided definitions for two of these terms: Commissioning and Qualification. In 2007, ASTM E2500-07: A Standard Guide for the Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment was issued. This standard introduced the term "verification" as a new term for demonstrating suitability and fitness for intended purpose, in place of the terms commissioning and qualification.

The terms "verification" and "commissioning" are used in many industries and have a fairly consistent meaning. The term "qualification" has been used by the regulated pharmaceutical and biotech industries, and can be found in EU regulations, as well as US, EU, and ICH guidance documents. Do these terms mean the same thing (more or less) or do they convey three different necessary and unique meanings?

This article is divided into two parts:

1. definitions and use of the terms found in published regulatory and guidance documents
2. analysis of the terms in light of current practices

The authors invite readers to respond to this discussion, either through the ISPE Commissioning and Qualification Community of Practice (C&Q COP) discussion board, or via direct communication. Such input will be considered when any related updates to the Baseline® Guides are undertaken.

Part I – Definitions and Citations

Qualification

The term qualification, while not specifically found in US GMP regulations, is found in EU regulations, ICH Q7A, and ICH Q9, as well as WHO and other country regulations and guidance documents.

US – FDA

The US GMPs do not explicitly mention the term qualification – in that there is no specific regulatory requirement to produce documents labeled installation, operation, or performance qualification. However, there are clear expectations of a process that demonstrates fitness for intended use and assures proper performance.

US GMPs require that:

- *Facilities be "suitable... to facilitate cleaning, maintenance, and proper operation."*
- *Equipment is to "be of appropriate design... to facilitate operations for its intended use." (21 CFR 211.42, 211.63, 606.40, 606.60, 820.40, 820.60).*
- *Automated systems are required to be "checked according to a written program designed to assure proper performance" (211.68).*

The medical device regulations (21 CFR 820) require that: *"computer software programs shall be validated by adequate and documented testing" (820.61).*

21 CFR Part 11 requires [for those systems to

which Part 11 applies]: *"Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered record."*

The 1987 FDA guidance on process validation first introduced the term qualification in these terms:

Installation qualification studies establish confidence that the process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. After process equipment is designed or selected, it should be evaluated and tested to verify that it is capable of operating satisfactorily within the operating limits required by the process. This phase of validation includes examination of equipment design; determination of calibration, maintenance, and adjustment requirements; and identifying critical equipment features that could affect the process and product. Information obtained from these studies should be used to establish written procedures covering equipment calibration, maintenance, monitoring, and control. ***In assessing the suitability of a given piece of equipment*** *[emphasis added], it is usually insufficient to rely solely upon the representations of the equipment supplier, or upon experience in producing some other product. Sound theoretical and practical engineering principles and considerations are a first step in the assessment.*

The Food and Drug Administration's (FDA's) current thinking on the topic of Active Substances Used as Starting Materials is represented by the ICH Q7A guidance, which includes references to Qualification.

EU – EMEA

EU Volume 4: EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 15 (Qualification and Validation), while specifically referencing both qualification and validation, further outlines in its lead Principle Statement that:

"...manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations... A risk assessment approach should be used to determine the scope and extent of validation."

The Annex goes on to describe the following validation and qualification activities as:

- *The first element of the validation...* ***could*** *be design qualification.*
- *Installation qualification should be performed on new or modified facilities, systems, and equipment.*
- *Operational qualification should follow installation qualification.*
- *Performance qualification should follow successful completion of installation qualification and operational qualification.*

The annex includes specifics regarding the *content* and *execution* of qualification work. Content requirements include the items typically found in an IQ, OQ, or PQ protocol, such as installation verification, collection of equipment manuals, calibration, materials of construction, testing across operating ranges, etc. Execution requirements include:

- *Written protocol specifying critical steps and acceptance criteria.*
- *Protocol reviewed and approved (does not specify by whom).*
- *A report written summarizing results, including recommending changes necessary to correct deficiencies, and documenting changes with appropriate justification.*
- *Formal release to the next step in qualification or validation as a written authorization (does not specify by whom).*

ICH Q7A has been incorporated into the EU GMPs as **Part II: Basic Requirements for Active Substances used as Starting Materials**, which also includes specific references to qualification activities.

ICH Q9 has recently been adopted by the EU as part of its Vol 4 GMPs as **Annex 20.**

ICH Harmonized Tripartite Guidelines

The ICH International guidance documents contain additional references to qualification. ICH Q7A, *GMPs for Active Pharmaceutical Ingredients* states that:

"Before initiating process validation activities, appropriate qualification of critical equipment and systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

- *Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended use.*
- *Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified.*
- *Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.*
- *Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.*

The recent ICH Q9, *Quality Risk Management*, includes an appendix of applications of quality risk management; Appendix II.4 describes how to use quality risk management for facilities, equipment, and utilities, including:

"We leave it to industry to debate these proposals; it is important that we achieve a consistent understanding and application of these terms. Once the debate is complete, it is for ISPE to incorporate the results into upcoming Baseline® Guides."

"...to determine the scope and extent of qualification of facilities, buildings, and production equipment..."

ISPE Baseline® Guide

The 2001 Commissioning and Qualification Baseline® Guide defines IQ, OQ, and PQ in similar terms:

- *Installation Qualification: the documented verification that all aspects of a facility, utility or equipment that can affect product quality adhere to approved specifications (e.g., construction, materials) and are correctly installed.*
- *Operational Qualification: the documented verification that all aspects of a facility, utility, or equipment that can affect product quality operate as intended throughout all anticipated ranges.*
- *Performance Qualification: the documented verification that all aspects of a facility, utility, or equipment that can affect product quality perform as intended meeting predetermined acceptance criteria.*

World Health Organization (WHO)

World Health Organization (WHO) Guidance on Validation defines Qualification as *"Action of proving and documenting that any premises, systems, and equipment are properly installed and/or work correctly and lead to the expected results."*

Commissioning

EU – EMEA

EU GMPs Annex 11, *Computerised Systems* positions commissioning as a component of computer validation:

[The computer validation life] "cycle includes the stages of planning, specifying, programming, testing, commissioning, documentation, operation, monitoring and modifying."

ISPE Baseline® Guide

The 2001 Commissioning and Qualification Baseline® Guide defines Commissioning as *"A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations."*

The material that follows this definition positions commissioning as a process that includes inspections, operational testing, and performance testing.

Commissioning as defined by non-drug industries:

- *Building commissioning provides documented confirmation that building systems function according to criteria set forth in the project documents to satisfy the owner's operational needs* (Building Commissioning Association).
- *Commissioning means to verify that the building's energy related systems are installed, calibrated and perform according to the owner's project requirements, basis of design, and construction documents* (LEED requirements).
- *Building commissioning is the process of ensuring that building systems and equipment are designed, installed, tested, and capable of being operated and maintained according to the owner's operational needs* (US Department of Energy).
- *Process of ensuring that new buildings and their systems perform as designed* (Oak Ridge National Laboratory).

Verification

US – FDA

21 CFR Part 820 (U.S. medical device quality system regulations) defines Verification to mean: *"confirmation by examination and provision of objective evidence that specified requirements have been fulfilled."* This definition may be contrasted with the Part 820 definition of Validation, *"confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled."*

EU – EMEA

EU Volume 4: EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 15 (Qualification and Validation), Glossary, includes the same definitions for DQ, IQ, OQ, and PQ as originated in the ICH Q7A document, which defines these activities in terms of a *"Documented Verification."*

ASTM E2500 defines *Verification* as: *"A systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification, verification, system validation, or other."*

According to ISO 9000:2000 Verification is defined as the: *"Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled." Objective evidence is defined as "data supporting the existence or verity of something."*

IEEE Standard 1012-2004, *Standard for Independent Verification and Validation*, defines Verification as: *"Process for determining whether the soft-*

ware products of an activity fulfill the requirements or conditions imposed on them in the previous activities."

Of note, the definition of Validation in IEEE standard 1012-2004 is: *Validation – process for determining whether the requirements and the final as-built system or software product fulfills its specific intended use.*

Part II – Analysis in Light of Current Practices

The question is, do these three terms – verification, commissioning, qualification – describe the same or different things?

The simplest term to analyze is *verification*. For the most part, the definitions of verification are consistent (as found in 21 CFR 820, ISO 9000, IEEE 1012-2004, and other sources). These definitions focus on the idea of "confirming, through objective evidence, that a specified requirement has been met (fulfilled)." ASTM E2500 defines Verification using the same base word: "to verify." The standard assigns a broader mission for verification, "a systematic approach to verify... systems and equipment are fit for intended use, properly installed, operating correctly... an umbrella term."

The term *commissioning* is more complex – different organizations in our industry assign different meanings to commissioning. Some view it as the work that is necessary to make a piece of equipment ready to start, i.e., the pre-functional inspections and checks (sometimes referred to as pre-commissioning). Other organizations are more aligned with the 2001 Commissioning and Qualification Baseline® Guide definition, which positions commissioning as a project lifecycle activity that consists of a planned, managed, and documented approach to bringing equipment or systems to a full operational state, and demonstrating conformance with specifications and user requirements. Depending on system complexity, the start-up, setting to work, regulation and adjustments, cycle development, and related work can be significant, not to mention the actual inspections and testing activities. Using this idea of commissioning means it may include a number of diverse activities requiring significant planning and coordination. Other industries define commissioning in terms that emphasize the performance testing of a system or group of systems against end-user requirements.

Finally, *qualification*, as shown above, is specifically mentioned in EU regulations as well as ICH Q7A and ICH Q9. Although the word Qualification is not explicitly mentioned in US GMP regulations, the concept of equipment and facilities being ***suitable for their intended use*** is clearly referenced. Furthermore, US GMPs do contain a requirement to validate certain automation systems, and everyone recognizes that the typical current industry practice is to include installation, operation, and performance qualification.

How do we reconcile this *Terminology Conundrum*? Are we to adopt the stance that if one uses the term "verification," that this implies a science- and risk-based approach as defined by ASTM E2500, whereas use of the terms "commissioning" and "qualification" implies a more traditional approach not based on science and risk? Or do these three terms describe three different ideas or processes, each of which can have a useful place in our approach to delivering equipment, systems, and automation that are ***suitable for their intended use?***

1. Irrespective of an organization's regulatory compliance strategy of using either a program labeled "Verification" or "Qualification," facilities and equipment will still need to be *commissioned* as defined above. Therefore, a well planned, managed, and documented effort to start-up and place into service a system, equipment, or combination thereof, including automation, will need to be undertaken – *commissioning*. This phase includes safe start-up, setting to work, regulation and adjustment, cycle development, etc., which contribute to achieving a full operational state.

2. A significant amount of valuable verification work may occur during this commissioning process, e.g., physical inspections, documentation reviews, operational testing, and performance testing. Retention of the term *commissioning* for this complex process of placing equipment into operation may therefore be appropriate, and for this term to extend to and include, the verification work that may occur at this time.

3. Assignment of the term *verification* to the act of confirming, through objective evidence, that a particular specification has been met is appropriate, given the common understanding of the meaning of this term and its use by the medical device regulations, ICH guidance, etc. This confirmation can take many forms: physical inspection, operational testing, performance testing, as well as other methods such as review of a material certification document, software code inspection for conformance to programming standards, etc.

    a. This *verification could* occur at any point in the overall lifecycle of, design, fabrication, installation, pre-start-up, start-up, or initial operation of the overall system or process.

    b. This *verification should* occur at the most appropriate point in the overall lifecycle – as defined and justified though the Quality Risk Management (QRM) process.

    c. This *verification* work *may* occur during factory acceptance, site acceptance testing, installation, or formal commissioning phases of the project.

    d. This *verification* work is performed under *Good Engineering*

Practice (GEP), and executed by appropriate Subject Matter Experts (SME).

4. A common requirement of all of the regulatory references above is that facilities, equipment systems, and associated automation are documented and authorized as *suitable for the intended use*. The determination that systems are *suitable for their intended use* present a difficulty in ensuring that there is a clear understanding of what suitability means. Suitability for use can be defined in many ways, and there may be different possible design solutions, which will achieve a desired result. We strongly recommend that *suitability for use* is not equivalent to meeting a particular engineering design specification. Instead, we propose that *suitability for use* be defined in terms of ability to meet product and process requirements necessary to manufacture a quality product, and ability to provide sufficient control of risks to the patient (this is what ASTM E2500 has as its approach). Suitability for use is therefore linked to:

   a. A specific manufacturing process and product (or class of products).

   b. It is based on knowledge of the process and an analysis of risk to the patient.

Qualification should mean that equipment has been found to be suitable for its intended use, based on the design criteria (process requirements or equivalent) and the verification work that was performed throughout the delivery process, in particular including that which occurred during the commissioning phase. *Qualified* no longer means the completion of an IQ/OQ/PQ protocol as traditionally formulated – leveraged or otherwise, but is instead a state or condition of certified suitability for use. Graphically, these three terms relate as illustrated in Figure 1.

The question is, can we adopt this

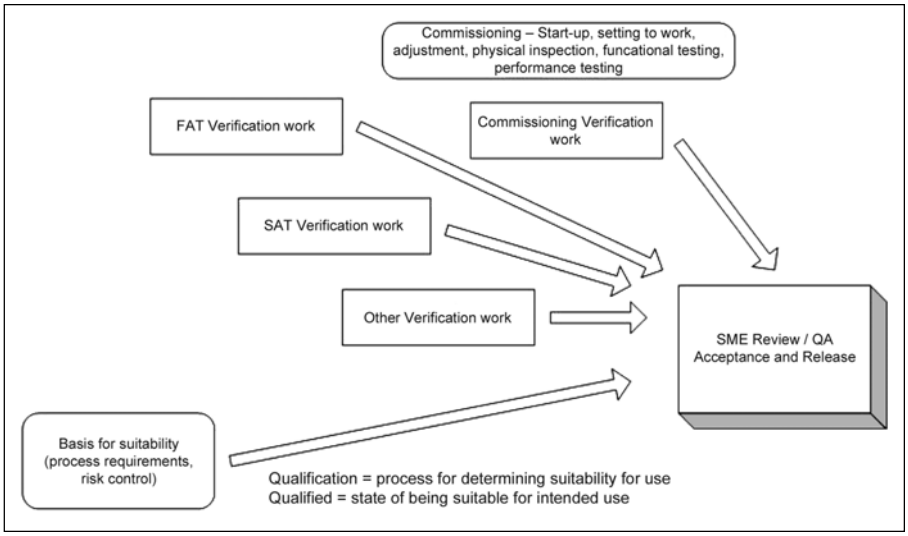

Figure 1. Relationships between the concept of verification, commissioning, and qualification.

use of the word *qualification* without invoking the non-value added practices of the past? Can people get past the habit of creating separate IQ, OQ, and PQ protocols, and instead adopt the idea that qualification is a "state" achieved as shown above? Or should we adopt a different definition? Or drop the use of the term altogether (as ASTM has done), and leave it to the operating company to explain how their program nonetheless meets the intent of EU and other global regulations?

For those who feel the need to have some form of qualification documentation, the determination that equipment is suitable for its intended use could be equivalent to either the Acceptance and Release phase described in ASTM E2500 or to the Qualification Summary Report phase currently undertaken in many traditional compliance programs, as illustrated in Figure 2.

Both these representations and the relationship of the terminology meet the intent of all regulations for demonstrating *Suitability for Use* and do not present non-compliance concerns within the ICH or EU regulated regions. Design qualification also can fit into this scheme should that be desired. Therefore, the idea that suitability for use can be determined based on patient risk

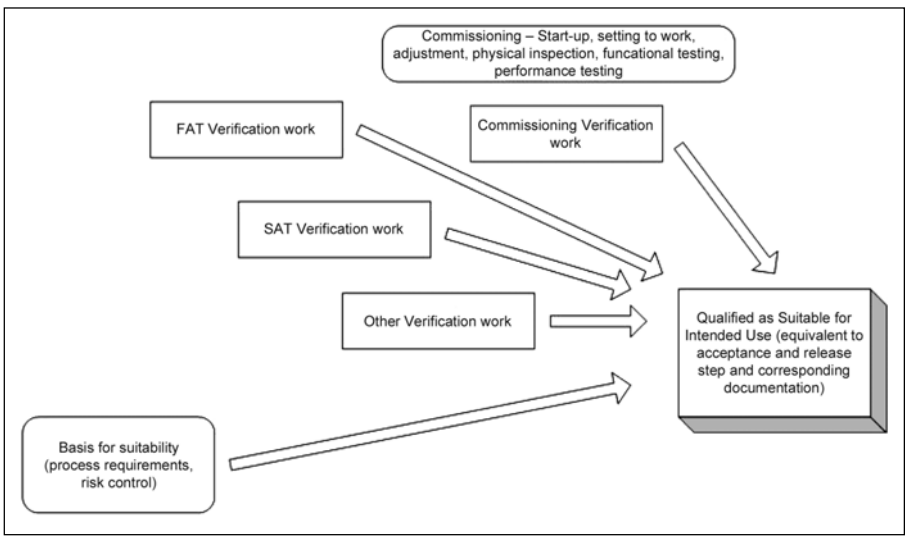

Figure 2. Verification, commissioning, and qualification as distinct steps. Note that in this model, there is no extra qualification-related field work or documentation when compared to the ASTM E2500 process. It is simply a repackaging of the acceptance and release phase for those organizations that require a document labeled "qualification protocol/ report."

and process requirements is well grounded in EU regulations and ICH documents, and is supported by US regulations and guidance documents.

We leave it to industry to debate these proposals; it is important that we achieve a consistent understanding and application of these terms. Once the debate is complete, it is for ISPE to incorporate the results into upcoming Baseline® Guides.

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