Validation Group

ECA Foundation
Fostering harmonisation of GMP/GDP regulations

Good Practice Guide Qualification and Validation

A guide to effective qualification based on Customer - Supplier Partnership

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1 Introduction

The purpose of this guide is to enable effective and GMP-compliant Qualification and Validation (Q&V) projects by mutual understanding between pharmaceutical customers and suppliers on projects related to pharmaceutical manufacturing systems, including equipment, facilities and utilities.

This guide is about close involvement of suppliers of pharmaceutical technical equipment and projects to enable a more effective project execution by reducing multiple testing throughout the qualification activities and to enable a more integrated approach to qualification and validation. It must be emphasized that the ultimate legal responsibility for qualified equipment and validated processes cannot be delegated and shall be retained by the pharmaceutical customer.

The guide is following the principles as outlined in the Process Validation Guide from US Food and Drug Administration (FDA) (2011) and the European GMP Annex 15 on Qualification and Validation (2015). Both are based on the Quality Risk Management guideline ICH Q9, from International Council of Harmonisation (ICH). This guide is based on these regulations with main focus on Annex 15 and does not create new legal obligations for suppliers or for pharmaceutical customers beyond these regulations.

Traditionally pharmaceutical companies have used a qualification approach based on, e.g., Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ) and Process Validation (PV) phases. The EU GMP Annex 15 on Qualification and Validation from 2015 is flexible on the naming and combinations of qualification activities. Thus, the Qualification and Validation activities can be planned based on best practices and use supplier activities and documentation where appropriate.

The core principle of this guide is that a quality management system is already in place when suppliers are working on the design, construction and testing of any manufacturing system, including but not limited to a good and accurate documentation that supports qualification and related documentation. This is part of “Good Engineering Practice” (GEP). During the cooperation between pharmaceutical customers and suppliers both win most if they share knowledge in an integrated approach using the supplier’s understanding of their systems and the pharmaceutical customers of their products, requirements, and regulatory context of their application.

Suppliers are directly or indirectly affected by many of the GMP regulations and may have to follow some of the pharmaceutical customer’s procedures. Pharmaceutical customers have their individual quality systems, technical requirements and procedures and they may differ significantly between companies, thereby complicating the cooperation between pharmaceutical customers and suppliers.

The core concepts of this guide facilitate the cooperation by describing elements of an efficient cooperation approach that is based on principles of Good Engineering Practice (GEP). It is compatible with other standards and industry guide, including ASTM E2500 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment and supports qualification as required in GMP regulations.

The term *Supplier* is used throughout this guide as an "organisation that provides a product or a service" (ISO 9001:15) and may include relevant subcontractors, manufacturers etc. A good cooperation in projects gives a pharmaceutical company an opportunity to learn from the accumulated best practices and expertise from the suppliers without any confidential information being revealed. It enables suppliers to plan, execute and document their test and verification activities so it can be demonstrated that the manufacturing systems are fit for the intended use.

The term *manufacturing system* is used as umbrella term for facilities, equipment and utilities related to pharmaceutical manufacturing. The term is defined in the ASTM E2500 standard as "elements of pharmaceutical and biopharmaceutical manufacturing capability, including manufacturing systems, facility equipment, process equipment, supporting utilities, associated process monitoring and control systems and automation systems, that have the potential to affect product quality and patient safety".

The term *Commissioning* is used in the meaning "a planned, managed and documented approach to the setting to work, start-up, regulation and adjustment, and installation/operation/performance verification necessary to bring equipment, automation and systems to a fully operational state meeting safety and end-user requirements" (ASTM E2500). These activities may include acceptance testing, especially Factory Acceptance Test (FAT) and Site Acceptance Test (SAT).

The term *Verification* is used according to ISO 9000 as "confirmation, through the provision of objective evidence, that the specified requirements have been fulfilled" (ISO 9000:2015). In pharmaceutical context ASTM E2500 describes verification as "a broad umbrella term that includes specific actions to confirm, with a high degree of assurance, that a particular fabrication, configuration, installation, operation or performance specification has been satisfied and is suitable for its intended purpose. Verification actions can be of a variety of types, including physical inspection, structural or functional test, document review, performance monitoring etc. Commissioning and qualification activities are types of verification" (ASTM E2500). The approach in this guide is mainly focused on qualification of critical aspects of the manufacturing system and application of Good Engineering Practices.

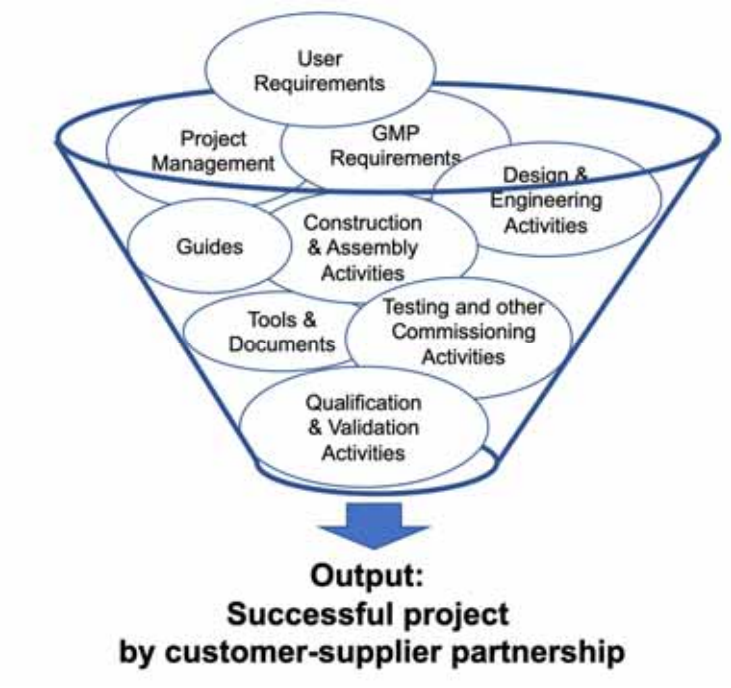
The term *Qualification* is used to the EU GMP Annex 15 on Qualification and Validation as 'documented verification'. This is also in accordance with the ASTM E2500 definition: "a systematic approach to confirming that manufacturing systems, acting singly or in combination are suitable (fit) for intended use with respect to patient safety and product quality. Qualification begins with defining suitability for use in a particular manufacturing context, typically based on process and quality risk control strategy, and ends with formal acceptance and release for manufacturing followed by life cycle continuous improvement."

The term *Critical Aspects* is used as intended in EU GMP Annex 15: "It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product". The ASTM E2500 definition is "typically functions, features, abilities and performance, or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety. They should be identified and documented based on scientific product and process understanding".

The intent of the guide is to meet the EU GMP Annex 15 expectations for Qualification and Validation without adding further requirements as well as to meet expectations from US FDA's Process Validation Guide and other regulatory guidance on qualification and validation. This includes the expectations on e.g. Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) as documented verification activities which may be organised based on Factory Acceptance Test (FAT), Site Acceptance Test (SAT) and other activities, as described in the following sections.

The approach of *Integrated qualification and validation* implies a science- and risk-based approach in cooperation with suppliers, based on quality risk management, scientific product and process understanding and use of GEP and GMP regulation in close cooperation between pharmaceutical customers and suppliers. The guide may be used together with other industry guides on both commissioning and qualification as well as on validation that are mentioned in the bibliography (see section 10). Qualification and validation activities may be integrated more than is common practice and this guide covers several activities and documents as illustrated below in figure 1.

Figure 1 Input to successful project and partnership



The aim of the guide is to enable fast and efficient activities with sufficient documentation to ensure:

- Increased understanding of the project, the process and the technical solutions involved
- Reduction of time and effort to achieve compliant systems
- Managed changes during design phase and testing phase
- Less need for expensive and time-consuming re-testing (no need for retesting unless for deficiencies that have been corrected)
- Reduced risk of creeping escalations of requirements by using established tools and methods

- Transparency in projects to ensure delivery on time, according to budget and the agreed quality standards
- Common language, terminology and documentation expectations

Although this guide has separate sections for involved parties (suppliers, customers) it is strongly recommended to have a complete reading in order to comprehend the approach for a successful project.

This guide is published by European Compliance Academy (ECA) by a Qualification and Validation Task Team which consists of pharmaceutical companies, pharma equipment, systems and solution suppliers, engineering and consulting suppliers that openly share experiences and knowledge to bring the industry forward - with mutual benefits for both parties. It has been reviewed by several individuals and organisations of which some are listed above. The Qualification and Validation Task Team thanks ECA and all involved individuals and organisations for their support.

2 Scope of this Guide

The guide is applicable to new manufacturing systems, including facilities, equipment and utilities and its principles may also be used for projects executed in existing factories with existing manufacturing systems such as upgrade or expansion projects. It can be applied for both, the manufacturing of drug substances and drug products.

It covers the project expectations and requirements for both the pharmaceutical customer and the suppliers of manufacturing systems and solutions to the pharmaceutical industry as well as engineering and consulting suppliers for effective cooperation on commissioning, qualification and validation.

The main purpose of the qualification activities described in this guide is to demonstrate that a manufacturing system is fit for its intended use, including that it is installed and can be operated as intended throughout the range of the process, as described in EU GMP Annex 15 and in FDA's Process Validation guide.

The guide builds on existing guidelines, standards, and company case studies to improve understanding and best practice sharing. It does not specifically cover computerised systems because this subject is well covered in the GAMP®5 Guide (Good Automated Manufacturing Practices, 2nd edition) from ISPE. It includes qualification and validation based on other media than paper and also remote testing without physical presence. Many companies have experienced significant savings, improved documentation and reduced travel needs due to these methods.

3 Outline of the Approach

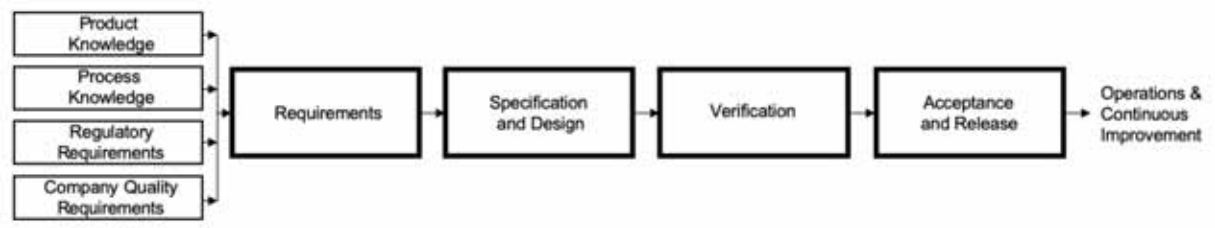
3.1 Introduction

Pharmaceutical companies must comply with Good Manufacturing Practice (GMP) regulations, including requirements concerning the quality management of the manufacturing process, including the involved manufacturing systems. This guideline is based on a project model that supports the following:

- An efficient, cooperative project management process
- Avoidance of duplications of tests by re-use of accepted results from previous testing, including those from suppliers
- Identification and testing of Critical Aspects of a manufacturing system based on quality risk management principles
- Use of Good Engineering Practice
- Use of Good Documentation Practice
- Integrated testing of equipment and process control
- Utilisation of punch list (open item list) for non-conformities
- Use of electronic documentation
- Remote testing

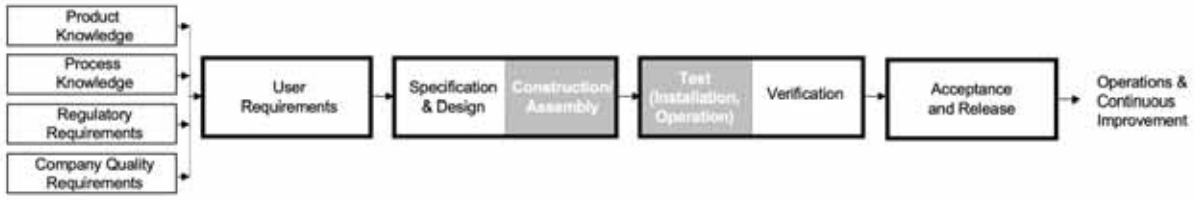
The overall project flow in this guide reflects the ASTM E2500 project life cycle model, as illustrated in figure 2, which is commonly used in several industry guides related to how commissioning and qualification activities can be aligned.

Figure 2 ASTM E2500 project life cycle model



To clarify the cooperation between pharmaceutical customers and suppliers this guide has enhanced the project life cycle with some typical supplier activities in order to illustrate the supplier-related activities during the project execution. Especially, the assembly and construction activities that follows specification and design and test activities that precede the verification activities have been added, as illustrated in Figure 3. Typical supplier activities (possibly in cooperation with the customer) are indicated in grey. These are typically supplier activities of importance for the cooperation between the pharmaceutical customer and the supplier.

Figure 3 Enhanced project life cycle model



3.2 Cooperation between Customer and Supplier

The cooperation between the pharmaceutical customer and supplier(s) of manufacturing systems may simplify qualification and validation activities significantly. Suppliers should be aware that there are specific pharmaceutical requirements and should ensure that they deliver good quality manufacturing systems in a broad sense, including comprehensive documentation and testing of their manufacturing system delivery. Well documented activities can be used by the pharmaceutical customer to demonstrate that the system is designed, built and tested in a way that ensures that it is “fit for the intended use”.

The cooperation and responsibilities of each activity should be agreed early in a project to make sure that the related measures and controls are established throughout the entire system life cycle and that documents, changes and deviation management follows good documentation practice.

Suppliers to the pharmaceutical industry generally have a very deep understanding of their equipment and its use from many customers. However, suppliers should understand that pharmaceutical customers might have different quality systems, different applications and different approaches to fulfil the GMP requirements.

An effective project typically benefits from the use of a variety of principles such as:

- **Customer-supplier partnership:** A good cooperation intent and team-spirit between the pharmaceutical customer and the supplier’s organisations should be based on clear contractual and commercial terms and may include mutual incentive elements to stimulate win-win solutions between pharmaceutical customer and supplier. The coordinated activities on both sides should start early and be continued throughout the project, including e.g., how to behave in a cleanroom environment during the installation process, how to operate in classified areas or how to ensure a clear transfer from project into operations.
- **Company standards and guidelines:** Many pharmaceutical companies have their own company specific standards and guidelines. If they are intended to be applied in a project, this should be agreed upon before the project execution starts. Companies may use this ECA guideline as a reference for mutual agreement on how to cooperate and document the project outcomes as part of the overall package.
- **Subject Matter Experts (SMEs):** Specialists, who cover the most important areas of expertise such as product, process, quality, qualifications and technical knowledge as well as members of the quality organisation should be involved in key roles, including both technical, pharmaceutical, and

quality-related areas of expertise. They should preferably be acting as a team and meet frequently at cross-functional project meetings for e.g., risk assessment, Design Review, qualification planning etc.

- **Cross-functional teamwork**: A good cross-functional cooperation on both the pharmaceutical customer organisation and the supplier organisation, especially an effective cooperation between the technical side (engineering/manufacturing/process etc.) and the quality side within the pharmaceutical customer's organisation. For example, the quality function may delegate activities to an internal engineering department or other areas of expertise within the company.

- **Good Engineering Practices** (GEP) consists of proven and accepted engineering methods, procedures and practices that provide appropriate and well-documented solutions to meet user-requirements and compliance with applicable regulations, including GMP regulations. It includes change management and deviation management, and it underpins activities in day-to-day operations and planning for a pharmaceutical business. Well documented activities can be the basis for verification and qualification activities. For a basic understanding see ISPE Good Practice Guide on Good Engineering Practice.

- **Good Documentation Practices:** Clearly understood and agreed practices should be used for both pharmaceutical customer and supplier activities. This enables technical solutions and technical documentation to be used in the pharmaceutical company's final qualification documentation. Handwritten entries should be made in clear, legible, indelible way and records should be made or completed at the time each action is taken, and any alteration made to the entry on a document should be signed and dated and permit the reading of the original information as well as the reason for the alteration should be recorded. In general, ALCOA principles should be considered. Raw data from test documentation should be kept for reference. For further description, see EU GMP volume 4, Part 1, Chapter 4 Documentation.

- **Single test approach:** The use of Good Engineering Practices, including Good Documentation Practices, is important to enable a single test approach where the quality activities and the related documentation is sufficient to be part of the overall qualification documentation that should demonstrate the "fitness for intended use" of the manufacturing system. Where single test approach is part of the qualification activities, the documentation and test executions need to comply with good manufacturing regulations.

- **Life cycle approach:** The pharmaceutical customer must control the critical aspects of their manufacturing systems during the full life cycle of the product and the manufacturing process; not just as a project with an end. Any planned changes concerning the manufacturing system and processes, which may affect the quality of the product, should be formally documented and the impact on the qualified and validated status etc. should be assessed. The life cycle may involve the supplier on issues such as spare parts, maintenance, service agreements etc.

In some cases, depending on the project, other special approaches may apply to support effective qualification and validation activities:

- **Worst Case Approach:** Tests should be planned with worst-case scenarios in mind based on a risk assessment with realistic worst-case situations on operational conditions and process parameters

(e.g., highest temperature, biggest volume etc.) as part of planning for an effective testing approach, as expected in EU GMP Annex 15, Qualification and Validation.

- **Fast Track Projects:** In fast-track projects where the project time is on high priority, the user requirement specifications, test methods and documentation standards are always on the critical path of the project. An early agreement on these may have significant advantages for the overall timeline of the project. Also, close cross-functional cooperation between production, engineering, quality etc. in the pharmaceutical customer organisation is very important to ensure an effective project execution under fast-track conditions. When running a project on a fast track, GMP requirements shall not be compromised.

3.3 Risk Management in the Project

Pharmaceutical companies are expected to use risk-based approaches in their quality activities. This is done on their regular business as well as within investment projects for new systems or processes. The regulatory expectations have evolved towards science- and risk-based principles based on a scientific understanding of the pharmaceutical product and processes and quality risk management. This guide follows a risk-managed approach based on commissioning, qualification and validation activities that goes 'hand in hand': The stepwise risk-managed model enables concurrent remediation of errors and deviations with follow-up verification as an integrated part of the commissioning, qualification and validation activities.

The approach to commissioning, qualification and validation in this guide is aligned with the Quality Risk Management principles of the ICH Q9 Quality Risk Management guideline:

- *The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and*
- *The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.*

The EU GMP Annex 15 on Qualification and Validation states the following regulatory expectation:
"It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process".
Annex 15 states in addition: *"A quality risk management approach should be applied throughout the life cycle 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."*

This guide applies these principles and the concept of pharmaceutical quality risk management, also in a supplier context. Annex 15 states: *"Data supporting qualification and/or validation studies which were obtained from sources outside of the manufacturers own programmes may be used provided that this approach has been justified and that there is adequate assurance that controls were in place throughout the acquisition of such data."*
Quality risk assessment typically starts during the development activities of the pharmaceutical product(s) to be manufactured. The pharmaceutical customer should at least identify the Critical

Quality Attributes (CQA) of the pharmaceutical product and the Critical Process Parameters (CPPs) of the manufacturing process and other attributes that are Critical to Quality (CTQ) as described in Section 5.2. In this guide these are identified by an initial Quality Risk Assessment by the pharmaceutical customer, preferably long before a project starts.

Quality Risk Management may be supplemented with other risk management activities for issues such as project risk, environmental, health and safety (EHS) related risk etc.

3.4 Roles and Responsibilities

The pharmaceutical customer, namely the head of production is responsible for qualification and validation activities even if it is done with support of the supplier.

Within a pharmaceutical company the overall responsibility for a project related to a manufacturing system involves members representing the quality function. Based on the principles of quality risk management the responsibility for certain areas of a project can be delegated to other subject matter experts.

Within a supplier company the contact persons and their responsibilities in the project should be defined to facilitate the cooperation between subject matter experts on the pharmaceutical customer and the supplier side.

Subject Matter Experts (SMEs) can take a lead role in the design, construction, assembly, commissioning, qualification and validation activities within their area of expertise and responsibility. Subject matter experts within similar areas of expertise can facilitate the cooperation between the pharmaceutical customer and supplier within their area of expertise on e.g., mechanical issues, automation issues etc. Generally, the pharmaceutical customer's head of production and SMEs have responsibility for the overall qualification and validation planning and execution whereas the supplier`s SMEs have focus on detailed design, construction and verification activities to ensure that the system meets the user requirements and is tested to ensure correct installation and function as intended.

Typical examples of SME roles are:

- Quality SME: e.g., pharmacist or other experts with product- and process know-how and experience with the pharmaceutical quality system, the production principles, quality risk management etc.
- Qualification SME: e.g., engineer, chemist, pharmacist, etc. involved in the planning and execution of the qualification and validation activities, working with suppliers etc.
- Process SME: e.g., chemist, pharmacist, process engineer etc. involved in process aspects, including process know-how, material selection, overall design, risk management etc.
- Technical SME or Equipment SME: e.g., mechanical, utility or HVAC engineer with special knowledge in utilities, cleanrooms, risk management etc.
- Automation SME: e.g., experts in design, implementation, testing and documentation of automation- and IT systems, including network, data integrity, configuration management for computerized systems etc.
- Production SME: e.g., manufacturing personnel with knowledge concerning the operation including sampling, writing of SOPs (Standard Operating Procedures), training of operators, etc.

The subject matter experts, their roles, responsibilities and areas of expertise should be documented on both the pharmaceutical customer and supplier side and the cooperation should be described, for

example as RACI matrix of Responsible, Accountable, Consulted, and Informed stakeholders in the project.

4 Essential Joint Activities

4.1 Overview

In order to ensure an effective project execution, it is important that some activities are executed in close cooperation between pharmaceutical customer and supplier, including the following:

- **User Requirement Specification (URS)**: The URS is the starting point of the qualification activities and should be a point of reference throughout the project. It is the pharmaceutical customer's responsibility and should reflect the pharmaceutical customer requirements for the manufacturing system in scope of the project. The URS issued by the pharmaceutical customer may be updated to a final, *agreed* URS which is supported by and agreed with the supplier. An *agreed* URS for the manufacturing system is the starting point for the supplier activities to ensure a successful project. The URS is further described in sections 5 and 6 as well as in Appendix 2.

- **Risk Management:** Risk management and especially Quality Risk Management (QRM) activities including risk assessment and risk mitigation should start with the pharmaceutical customer's risk assessment, especially regarding the product and the processes in scope. Risk mitigation should be reflected in the URS where applicable and it is typically useful to involve the supplier in the identification, assessment and management of risk in order to build on the supplier's experience from similar applications. Several quality risk management methods and tools are described in the ICH Q9 document on Quality Risk Management. See section 5.4. and Appendix 4.

- **Project Quality Plan (PQP):** Pharmaceutical customer and suppliers should agree on a common Project Quality Plan which is typically developed by the supplier. Often both, pharmaceutical customers and suppliers have separate plans for their quality activities. A PQP should be agreed as basis for the common quality activities of the project, depending on the size and complexity of the project. See section 6.2. and Appendix 6.

- **Project Management:** The core element for a successful project execution is a close cooperation between pharmaceutical customer and supplier and both should be jointly involved in project management activities, e.g., scheduling, progress tracking, documentation, deviation and change management.

- **Design Review**: Design Reviews are typically performed to investigate how the requirements outlined in the URS or the GMP guides are reflected in design and can be implemented in the layout, the infrastructure, the construction and assembly of the manufacturing system.

- **Design Qualification** should ensure and evident how the specifications from the URS are met in the design specification of the supplier. Even the DQ is under the responsibility of the pharmaceutical customer, the DQ can be a highly interactive work process between customer and supplier (s. above Design Review), which is finalised by customer's DQ report.

- **Commissioning and Acceptance Testing (FAT and SAT):** Factory Acceptance Test (FAT) is executed in the supplier's factory before shipping to the pharmaceutical customer and Site Acceptance Test (SAT) is executed at the pharmaceutical customer's site after transportation and installation. These

are examples of commissioning activities and should be clearly defined and agreed, including the documentation requirements, procedures and acceptance criteria.

The test documentation may be fully or partly used by the pharmaceutical customer to support Installation Qualification (IQ) and Operational Qualification (OQ) or the pharmaceutical customer may decide to do additional activities and/or call them IQ, OQ or IOQ activities, depending on company preferences. Special attention should be given in case activities e.g., FAT are done remotely or generally based on electronic systems. See section 6.9. and Appendix 8.

An important part of this is the availability of the supplier documentation as outlined in the original project scope agreement e.g., in the form of a Supplier Turnover Package that is handed over from the supplier to the pharmaceutical customer at the end of the project, containing design documents (as built status), material certificates, calibration certificates, manuals etc. including documentation necessary for the life cycle management of the manufacturing system. Special attention should be given to documents that are required legally, such as instruction manuals, EU Declaration of Conformity etc.

4.2 Contracting Manufacturing System Qualification by Suppliers

4.2.1 Roles, Responsibilities and Tasks

As mentioned in chapter 5.1, a written contract is needed between the pharmaceutical customer and the supplier to ensure a unique understanding of roles, responsibilities, and tasks, when manufacturing system qualification is outsourced to the supplier. This is also a fixed requirement as e.g., stated in the EU GMP, Volume 4, Part I, Chapter 7 “Outsourced Activities”. It is stated there, that for “any activity covered by the GMP Guide” (which includes the qualification & validation activities), such a contract is needed.

While the Project and Quality Plan (PQP acc. Chapter 6.2) is part of the deliverables and is created once the supplier is onboard, the contract as described here, is a written legal agreement established prior to project execution. Other than Quality Assurance Agreements (QAA), typically set-up for contract manufacturers and solely dealing with assignment of QA tasks, the supplier contract in most cases is a mixture of commercial and quality related aspects, also focusing on performance and guaranty values, for which the supplier finally should be responsible, and payment is based on. Depending on the scope of supplies, deliverables and responsibilities even may include the quality of the product produced at a certain process stage with a specific and highly complex (e.g., fully automated) manufacturing system. In this case, even additional contracts may become necessary to cover all details of task and responsibility sharing.

Talking about GMP, qualification and validation responsibilities, the EU GMP Guide Part I for medicinal products states that the heads of production and quality control should “ensure the qualification and maintenance of their departments, premises and equipment and to ensure that the appropriate validations are done” (2.7 and 2.8).

In practice the responsibility for qualification cannot be delegated but qualification tasks may be delegated, also to outside parties, provided there is quality oversight of the tasks.

4.2.2 Content of a Contract

Dependent on the size of a project, such contracts can be extensive and may include descriptions of scope and details of deliverables, timelines for deliverables, milestone plans, prices, payment terms, liabilities and many more. Regarding qualification activities, contracts moreover include the scope of qualification support and phases of qualification to be supported. Also, in many cases it is regulated how the qualification work of a supplier will finally be integrated into the pharmaceutical customer's overall qualification system. This may be the way to fully accept the supplier's qualification documents or only to accept the test plans and records, while the qualification cover sheets are those of the pharmaceutical customer.

For this part of the contract – the outsourced qualification – it is important to regulate in detail, who is doing what to which extend and how in details the documentation should look like and who is going to sign the documents for which role of responsibility.

The checklist in Appendix 10 provides help to check a contract for completeness of quality and qualification related aspects, which should be regulated between the pharmaceutical manufacturer and the supplier.

5 Customer Activities

5.1 Introduction

Within the pharmaceutical customer's organisation, a qualification and validation project is typically managed according to a Validation Master plan (VMP) as described in EU GMP Annex 15. It outlines the qualification and validation activities for the project.

Suppliers typically receive a Request for Proposal (RfP) document with an initial User Requirement Specification (URS) and other documents related to the scope of the project and its commercial terms. The initial URS should be negotiated and adapted as an *agreed* User Requirement Specification which is a common point of reference throughout the qualification project.

The pharmaceutical customer's initial requirements, especially regarding the pharmaceutical products and processes are an important starting point for Quality Risk Management activities of the project and especially the identification of the Critical Aspects of the manufacturing systems in scope.

The pharmaceutical product and process requirements are proprietary knowhow of the pharmaceutical company and as such highly confidential. Some pharmaceutical companies use a "Product and Process User Requirement Specification" (PPURS) as an overview document. It also reflects the marketing authorization/product registration aspects. The PPURS is an overview with the essential product and process information for a specific product across all its manufacturing steps typically including a quality risk assessment summary of the product and processes. This serves as the initial quality risk assessment for the product and the process in scope. The PPURS is normally not shared with suppliers but used as basis for the URS requirements for each manufacturing system, based on the product- and process-related requirements and associated quality risk assessments. As soon as sensitive information is exchanged a non-disclosure agreement should be in place. Appendix 2 includes an overview of a typical structure of a PPURS.

Before selecting and contracting the supplier there should be a thorough supplier assessment as described in section 5.3 and appendix 3.

Once the supplier is identified the project activities should be negotiated and agreed, e.g., in one or more joint workshops. It is important that the customer's initial URS and information needed to identify, assess and control critical aspects of the manufacturing systems is discussed with the supplier(s) and adapted as a mutually agreed and understood set of project requirements und put into an *agreed* URS as the point of reference throughout the rest of the whole project.

There must be a written contract between the pharmaceutical customer and the supplier which clearly establishes the roles and responsibilities of each party (see sections 4. 2 and 6.2). The pharmaceutical customer is responsible for assessing suitability and the competence of the supplier as well as for ensuring that the principles and guidelines of GMP are followed and the results are reliable, including aspects of data integrity. Also, the mutual understanding of terminology and definitions between supplier and pharmaceutical customer is essential for project success, including impact of key regulatory terminology. The pharmaceutical customer should clearly define which regulations will be applied (EU, FDA regulation or others) and prepare for early input in the project, preferably as part of a Project Quality Plan (PQP). A template example of a PQP is in Appendix 6.

The pharmaceutical customer activities described in this guide should be conducted with a life cycle perspective and the project life cycle should be described in PQP, e.g., design, review, construction, testing etc. involving the supplier's quality system and relevant guidelines, standards etc. as Good Engineering Practices.

Depending on the scope of services agreed between the pharmaceutical customer and the supplier the European GMP regulations regarding outsourced activities need to be considered as applicable. The regulatory expectation is that the pharmaceutical customer is responsible for any outsourced activities, incorporating quality risk management principles.

5.2 User Requirement Specification

The requirements concerning manufacturing systems should be defined in a User Requirement Specification (URS) that describes what is needed in terms of function, features, abilities and performance characteristics for the systems to fulfil the intended use. It is a regulatory expectation that essential elements of quality requirements related to the pharmaceutical product and the manufacturing process are defined as well as requirements related to the mitigation of GMP-related risks to an acceptable level. Where the marketing authorization holder and the manufacturer are not the same, appropriate arrangements should be in place taking into account the requirements of the marketing authorization.

The URS should be based on the intended use of the equipment and should be a point of reference throughout the project life cycle. Especially for the Design Qualification and the final Performance Qualification the URS is important to demonstrate that the user requirements can be met, and that the manufacturing system is fit for intended use.

The URS should be well structured, clear, and precise on what has to be accomplished ('must have') and outline the activities or documentation to be delivered.

The agreed URS should be part of the contract. It may be combined with other specifications, e.g., general technical and GMP-related requirements, company standards and guidelines etc. Appendix 2 contains a template example of an URS.

5.3 Supplier Assessment

The supplier selection should include an assessment of the supplier's ability to deliver the expected technical scope of supply and related services. This selection should be part of the Quality Risk Management. The Quality Unit and associated departments of the pharmaceutical customer should run the supplier evaluation in a systematic manner and therefore, are responsible to assess, approve and monitor providers of outsourced activities.

This assessment should include, but is not limited to, the supplier's capabilities for provision of expected technical documents, design documentation, test protocols, test execution, deviation management and change management as addressed by Good Engineering Practice. These activities and documents may be part in the supplier's quality management system. Therefore, the supplier selection is an important part of the pharmaceutical customer's responsibilities and the assessments of suppliers and their capabilities should be documented.

Especially if suppliers are using their own format for test documentation it is important that they follow a quality system that ensures consistency, traceability and good documentation practice. For ISO 9001 certified suppliers this is part of their quality system certification and should be easily assessable.

The pharmaceutical customer should involve relevant subject matter experts in the supplier evaluation, depending on the scope of the project. This may involve quality, engineering, automation, production or other areas of subject matter expertise. Supplier assessment often requires auditing the supplier's facilities, processes and organisation. The intensity and scope of assessment can vary and be influenced by the quality impact of supplier's scope of delivery.

The outcome of the supplier assessment should be used to determine:

- Which parts of the supplier's quality system to use and/or supplement in the project
- Expected extent to suppliers testing and documentation may be used as part of the qualification
- Expected level of oversight and participation that the pharmaceutical customer or 3rd parties should perform
- Expected level of additional testing and documentation to be performed by the pharmaceutical customer or 3rd parties

These conclusions should be reflected in the Project Quality Plan. After the selection of the supplier there should be a quality agreement for the project, typically in an agreed Project Quality Plan (PQP) written by the supplier.

Appendix 3 includes a list of issues to be considered in a supplier evaluation.

5.4 Quality Risk Assessment and Critical Aspects

The Quality Risk Assessments are part of the Quality Risk Management activities that in context with commissioning, qualification and validation should identify and manage risks primarily associated with product quality finally linked to the end user's (patient) safety and therefore requiring the thorough assessment of

- product quality attributes
- ability to maintain the process in the state of control during routine commercial production.
- compliance with general regulatory and GMP requirements
- other technical and operational aspects with potential impact on product quality.

For pharmaceutical product quality the quality risk management activity typically starts with the Critical Quality Attributes (CQA) of the product and the related Critical Process Parameters (CPP) of the production process in scope of a project. For recently approved pharmaceutical products these are defined in the Marketing Authorisation or in regulatory approval documents. For older (legacy) products, they should be identified by the pharmaceutical company. In either case these critical attributes are assessed in a first Quality Risk Assessment, called QRA 0 in this guide, which is followed by subsequent risk assessments named QRA 1, etc.

Any deviation from predefined limits may have a potential impact on safety, efficacy and quality. CQAs are typically linked to the product specifications considering assay, impurities, potency and any other chemical, physical or microbial properties. For more explanation of CQA and CPP please see EU GMP Annex 15 or ICH Q8 Pharmaceutical Development.

Product quality and related CQAs are influenced by the manufacturing process. The identification and control of CQAs and CPPs are essential for keeping a process reproducible and thus to allow production of the pharmaceutical products according to their specification and approval.

There can be other production issues than CPPs that can affect the product quality. Some pharmaceutical companies use the term Critical to Quality (CTQ) for such aspects (e.g., the environmental conditions).

The control of CQAs and CPPs as well as other CTQs may be affected by the manufacturing systems with certain functions, features, and performance elements, which in general are called Critical Aspects (CA) as defined in the ASTM E2500 standard. The identification of CAs is essential in quality risk management activities for a manufacturing system and should be addressed during the course of the manufacturing system risk assessment (QRA 1 etc.).

Table 1 illustrates a Critical Aspects project example for a formulation tank system where the uniformity of the product is ensured by controlled agitation. From the product and process development the product uniformity is identified as a CQA, and it depends on two CPPs: the agitation speed and agitation time.

During the Design Review (in QRA 1) it may be decided to mitigate risk to the product uniformity by adding measures to prevent failure on the product (risk control mechanism) and measure to detect the failure (risk detection) such as agitator control or alarm on agitator speed. ISPE's Baseline Guide for Commissioning and Qualification, revision 2 uses the term "Critical Design Elements (CDE)" to identify critical aspects risk control in the design. Other measures may be procedural controls (SOPs) for the agitation process.

Table 1 Example for link between CQA/CPP and Critical Aspects (CQA) and Critical Design Elements (CDE)

CQA	**CPP**	**Quality risks**	**Critical Aspects**	
			Risk control	**Risk detection**
Product uniformity	Agitation speed Agitation time	Agitator speed failure Agitation time failure	Speed Control system (CDE) Speed agitation system (CDE) Work instruction (SOP)	Alarm on speed deviation (CDE) Recording of agitation time (CDE)

Identification of CAs should be part of the risk assessment of the manufacturing system, as described in section 5.5 Critical Aspects Risk Management.

In case that CQA and CPPs are not know in early phases of a project, e.g., development for the product is not completed, it is necessary to make assumptions for CQAs and CPPs and document them.

5.5 Critical Aspects Risk Management

Once the critical aspects are identified, the associated risk management activities during project execution should be executed and documented. A useful tool for this is a matrix for Critical Aspects Risk Assessment (CARA) as described in Appendix 1. The CARA matrix is used to document the quality risk management activities of the Critical Aspects during QRA 1, 2 and 3. It lists all the critical aspects of the manufacturing systems, their failure modes, the identified risk control mechanisms and related activities of the project execution. The CARA matrix is a life cycle document that is updated stepwise as the project is executed.

The Critical Aspects Risk Assessments may use the risk management method called “Failure Mode, Effects and Criticality Analysis” (FMECA) or similar method for each manufacturing system. It should identify all Critical Aspects, related to CQA, CPP or other CTQ aspects as described in section 5.4. As illustrated in the example in Appendix 1, the CARA matrix includes the risk analysis with failure modes, possible risk mitigation changes and the associated verification activities. It is typically prepared during design phase and can be used for Design Qualification Each update should be approved by the quality assurance function of the pharmaceutical customer.

The Critical Aspects should be identified early and included in the URS, so they are shared with the supplier during design, review and verification activities. That means that CARA can be used to document the iterative process to identify risks to critical aspects, determine how to control them and improve the design until the point, where all risks to the quality of the product have been controlled to an acceptable level.

There may be several Design Review meetings during a project depending on its scope and approach. There should be a clear conclusion on that the design meets its intended use and related GMP requirements so the design has been qualified (see also 5.6 Verification and Qualification). For complex systems, a formal design freeze or design approval may be agreed by supplier and customer.

The Design Reviews may be supported by a **Requirement Traceability Matrix (RTM**), which links all the URS requirements with relevant design information for each requirement. This is useful to ensure that all URS requirements are met and may also be used to plan verification activities.

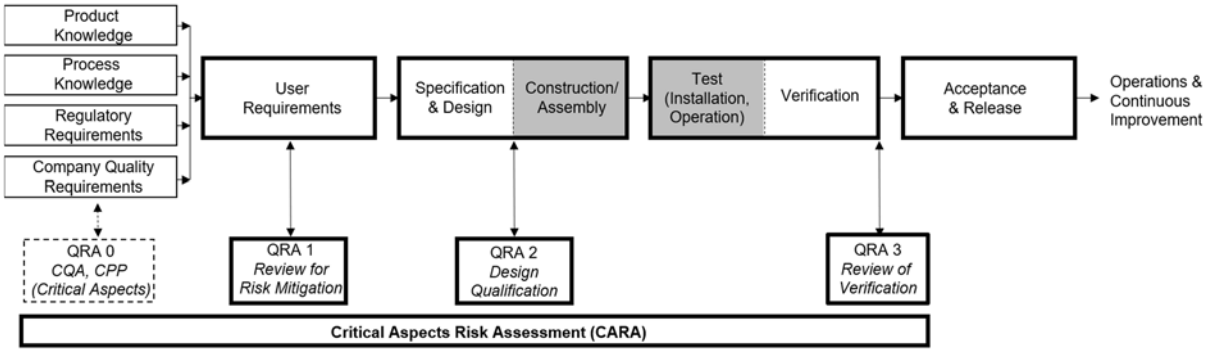
It may be useful in larger project to list all tests for the URS requirements (both those related to Critical Aspects and all others) in a separate **Test Matrix (TM)** to plan if they are to be done in FAT, SAT, or other testing activities. Appendix 4 also includes a template example of a TM. The TM and the RTM may be combined in one document.

These tools can be used to streamline the qualification activities and support a good cooperation with mutual understanding between customers and suppliers and to avoid multiple testing throughout the qualification activities.

Figure 4 (based on the ASTM E2500 standard with addition of the supplier involvement on Construction/Assembly and Test [Installation, Operation], marked in grey) illustrates a science- and risk-based qualification approach where the starting point is the initial quality risk assessment associated with the pharmaceutical product and process, based on the development of the pharmaceutical product and process (QRA 0). Follow-up risk management activities are the Critical Aspects Risk Identification (QRA 1), the Design Qualification (QRA 2) and the Qualification Completion Risk Assessment (QRA 3). The risk management approach may be adapted according to the project specific needs.

Risk management activities should be carried out by a team of SMEs within key areas such as quality, process, engineering, automation/IT, equipment design etc.

Figure 4 Enhanced project life cycle approach with Quality Risk Management activities



Quality Risk Assessment 0 (QRA 0): Product and Process Critical Requirements

The initial Quality Risk Assessment 0 (QRA 0) should be started during the pharmaceutical company's process development, ideally based on the control strategy as described in Section 5.4. This includes the CQAs of the pharmaceutical product, Critical Process Parameters CPPs of the production process and other requirements that are CTQ aspects of the pharmaceutical product. QRA 0 should define the "Severity" as the consequence of a hazard impacting the CQA.

CTQ aspects (incl. CQAs and CPPs) may be part of a Product and Process User Requirement Specification (PPURS) in some pharmaceutical companies (see Section 5.1), thus linking to the market authorisation of the pharmaceutical product.

Quality Risk Assessment 1 (QRA 1): Critical Aspects Identification

The *agreed* URS for a manufacturing system should be reviewed and possibly adjusted to ensure that risk mitigation and GMP compliance have been addressed sufficiently in the URS, and that all critical aspects as outlined in QRA 0 are reflected.

Quality Risk Assessment 2 (QRA 2): Design Qualification

The design of the manufacturing systems should be reviewed by the pharmaceutical customer and supplier for sufficient quality risk mitigation and GMP compliance, including formal acceptance of residual risk elements. This may raise new requirements in the URS, based on identified risk mitigations by change to design or functionality (or by procedural measures in e.g., Standard Operational

Procedures (SOPs) for the operation of the production). If the risk cannot be mitigated to an acceptable level, the design should be changed or appropriate procedures (SOP) need to implemented to mitigate risk. Based on this the detailed test execution and acceptance criteria for at least Critical Aspects and other GMP aspects should be established and documented as part of the overall qualification plan. Output of this QRA phase is the DQ report. This is a customer responsibility and may be supported by the supplier.

Quality Risk Assessment 3 (QRA 3): Qualification Completion Risk Assessment
After the completion of the testing activities, the test results are reviewed and documented to accept and release the system for subsequent Process Validation activities. When all tests are passed and the test documentation acceptable, the verification review conclusion may be documented in a System Acceptance and Release Report.

5.6 Verification and Qualification

Design Qualification should be completed prior to construction and building of each individual equipment. Design Qualification shall be completed prior to testing (for details see CARA 2 and 6.5).

Qualification should verify that the manufacturing system meets the requirements regarding installation, operation and performance requirements, including that it is fit for its intended use for the specific process of the customer.

All testing activities should be pre-defined, and the test results documented in such a way, that they can be used as documented evidence as described in section 3.2 Good Engineering Practice. During testing Change Management (section 6.3) and Deviation Management (section 6.4) should be applied to ensure the validity of the test and documentation.

Appendix 5 includes template example for deviation management. Both supplier and pharmaceutical customer should agree on how to manage open issues. Typically, deviations related to Critical Aspects should involve the quality assurance function of the pharmaceutical company.

The combination of commissioning and qualification is explained in section 6.8. Appendix 7 shows a qualification documentation template example.

5.7 Integration Testing

Integration testing is recommended and may involve all manufacturing systems and utility systems in scope and is typically done under production-like conditions with all auxiliary equipment and associated environment to demonstrate that the systems can operate in accordance with the process requirements. The testing is typically done based on GEP and should include all anticipated operating ranges of routine production as well as interventions, and start-up and stoppage.

Many pharmaceutical companies require integration testing to be completed before starting the Performance Qualification. Some do integration testing and Performance Qualification (PQ) of each manufacturing system with an “interim release” before the overall, integration test of all systems incl. utilities.

5.8 System Acceptance and Release Report

The completed testing and verification activities may be concluded in a System Acceptance and Release Report (SARR) to document that the inspection and test activities for all manufacturing systems are completed. In the event, that several manufacturing systems forms a production line, SARR must consider each single equipment as well as the entire production line. It may refer to the Project Quality Plan and other supporting documents such as Test Matrix, CARA, and others.

It should be approved by the pharmaceutical company's quality assurance function and should include a clear conclusion on whether the manufacturing system is fit for its intended use, as specified in the URS. It may include verification that the pharmaceutical company's quality system is feasible for the operation of the manufacturing system(s), including relevant SOPs, training etc. It typically marks the formal release of the manufacturing system from qualification to the subsequent Process Validation activities.

5.9 Process Validation

5.9.1 Introduction

Process Validation activities are required by the regulatory authorities worldwide and the expectations for a successful Process Validation are a precondition for the permission to produce a pharmaceutical product commercially. The regulations of Process Validation generally follow the core concept of Quality Risk Management and a robust process development so the activities for Process Validation should be based on the same Quality Risk Assessments including the Critical Quality Attributes of the product, the Critical Process Parameters of the process and other Critical Parameters as described in Section 5.5 Critical Aspects Risk Management.

The fundamental purpose of the Process Validation is to demonstrate that the process, when operating within established parameters can effectively and reproducibly produce a product meeting its predetermined specifications and quality attributes. In pharmaceutical terminology it must be shown that all critical quality attributes of the product and all critical process parameters are consistently met during manufacturing and that operating ranges can be maintained during routine production by the developed control strategy consisting of the master batch record, the in-process controls, the sampling and specifications.

Process Validation requires qualification of the manufacturing systems to demonstrate that they are fit for their intended use. Besides, Process Validation should build on knowledge from the process development, and it should be followed by an ongoing evaluation of the process performance during commercial production. The terminology is slightly different between US FDA's Process Validation Guide (2011) and the EU GMP Annex 15 on Qualification and Validation (2015) but the expectations are very similar.

Thus, Process Validation has become a continual effort to be performed throughout the entire life cycle of the process, called Ongoing Process Verification (OPV) (US FDA's Process Validation Guide uses the term Continued Process Verification while the EU GMP Annex 15 is using Ongoing Process Verification for similar regulatory requirements). The OPV program should include the use of statistical

tools to support the conclusions regarding control of the process and product quality with the established manufacturing process, where applicable as part of an ongoing program.
Pharmaceutical companies subjected to US FDA approval may notice that in contrast to the US FDA Process Validation guide, the EU regulations have no sharp boundary between the stages of validation (US: Stage 1 is development of the process design; Stage 2 is process Performance Qualification (initial Process Validation); Stage 3 is continued process verification).

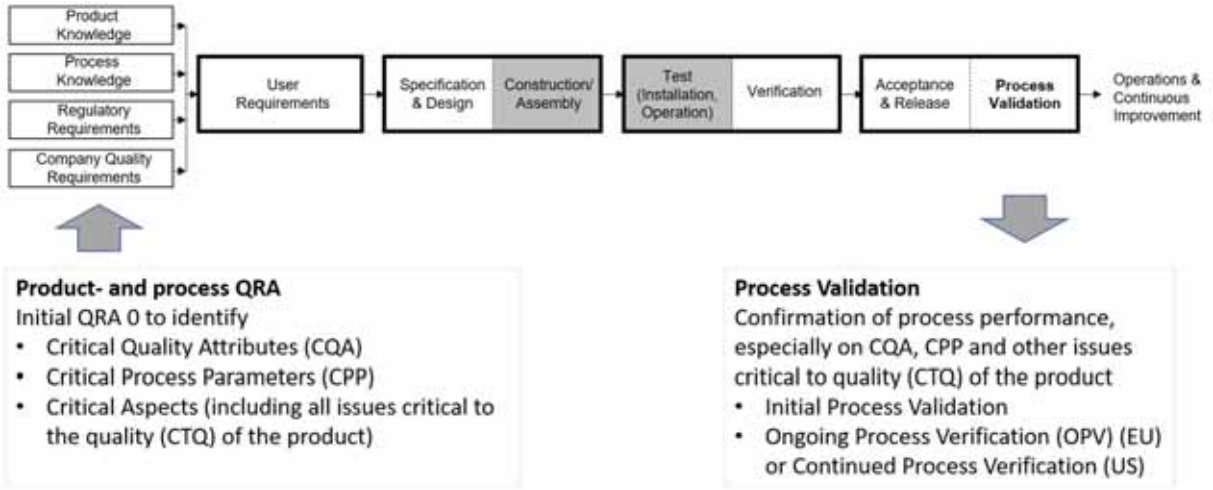
The EU GMP Annex 15 mentions three approaches to Process Validation: 1. Traditional Process Validation, 2. Continuous Process Validation and 3. Hybrid approach, which is a mix of 1 and 2. For all three approaches to Process Validation the ongoing process verification is required during life cycle.

In both EU and US regulations validation activities should be based on the product- and process knowledge when deciding test parameters, sampling frequency, amount and a statistical evaluation on the process performance, number of validation batches to be manufactured and related acceptance criteria. EU GMP Annex 15 states that “A Process Validation protocol should be prepared which defines the critical process parameters (CPP), critical quality attributes (CQA) and the associated acceptance criteria which should be based on development data or documented process knowledge”. Thus, the quality risk assessment and related identification of CQA, CPP, etc., which is used for qualification should serve as a basis for the Process Validation activities and documentation in an integrated qualification and validation approach.

Before commercial distribution of a product can begin, all involved manufacturing systems must be qualified and all processes must be validated to demonstrate that they are fit for their intended use and can produce the product robust and reliably throughout its lifetime. The ongoing process verification effort will continue as long as the product is produced and distributed commercially.

There are several industry guidelines about the Process Validation activities as a separate activity. There should be a link between the qualification and validation activities. Ideally, they are based on the same initial Quality Risk Assessments and the Critical Aspects of the qualification activities should be consistent with the Process Validation activities. In many pharmaceutical companies’ qualification and validation activities are managed by different departments and different SMEs (as outlined in section 3.4 Roles and Responsibilities). So, a cross-functional cooperation is important to achieve synergies between qualification and validation activities.

Figure 5 Input and output from integrated Qualification and Validation



5.9.2 Involving Suppliers in Process Validation Activities

The cooperation between the pharmaceutical customer and the supplier may extend into the Process Validation activities, although the cooperation traditionally ends with the System Acceptance and Release. There may be an overlap between the Performance Qualification and the Process Validation activities, but the Process Validation must be done on real products with all necessary support systems, utilities, personnel, SOPs etc. whereas Performance Qualification may be done on a simulated product.

Advanced manufacturing systems which include a high degree of process and product knowledge, e.g., for continuous manufacturing or other emerging technologies or to implement in an early stage the precondition for a high-level process control strategy, encourage such cooperation since the supplier typically assist in setting up the process model and formulas that the process will be using. The Process Validation for such systems may include online measurement of important product attributes by Process Analytical Technology (PAT) and this can be used for a continuous process verification approach that may require a very close involvement of the supplier during both qualification and validation of the manufacturing system. The same purpose belongs to the continued or ongoing process verification which requires, implementing as high-level model, interface functions for export of CPPs or online measurements for CQAs for the monitoring program to demonstrate that the process remains capable. This phase can be supported by the supplier based on an agreement fixed in a service contract.

Example: A CQA of a typical blistering process is the tightness of the blister. This CQA is influenced by 3 CPPs for the sealing process: Time, Temperature and Pressure. The CQA and the CPPs were identified in the initial quality risk assessment (QRA 0) as part of developing a robust sealing process with stable performance.

The initial Process Validation data can be used as basis for the continued / ongoing process verification acceptance criteria (e.g., by statistical Control Chart SPC) or for periodic activities, e.g., re-calculation of the capability indices, or trend evaluation. The approach to calculate process capabilities can be used for follow-up qualification assessments as well, e.g., to calculate machine capabilities.

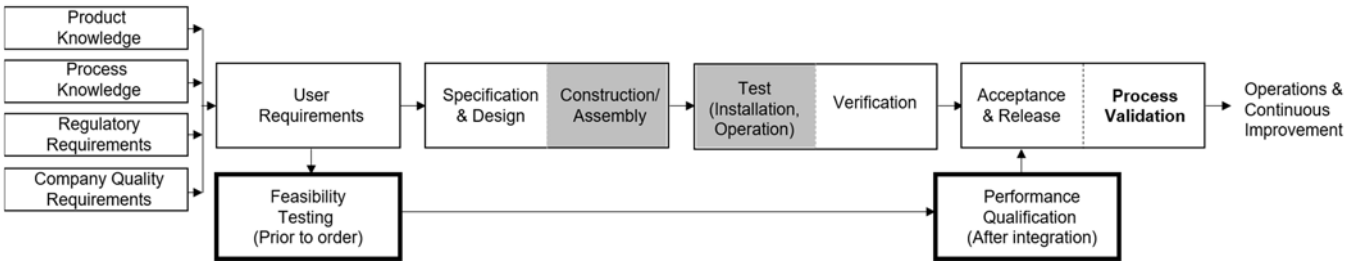
Overall, the effort of qualification and validation, including the optional involvement of suppliers in Process Validation activities, should bear in mind that a regulatory GMP inspection scope is broader than the qualification and validation and involves registration documents with the following requirements:

- descriptions of the fundamental manufacturing process
- the design of the equipment used
- details of the in-process controls
- the risk assessments for determining the scope of validation

5.9.3 Involving Suppliers in Feasibility Testing

For standard equipment or configured standard equipment (see section 7) it may be useful to test the feasibility of the manufacturing system before proceeding with the equipment. This typically involves the supplier in feasibility tests with the real product or a simulated product prior to order. For economic reasons alone, FAT feasibility studies are often carried out at the supplier's premises before a purchase contract is concluded. If such tests are to be used for a later qualification, the client must ensure in good time that the EU-GMP-requirements with regard to test design and documentation are complied with. The early cooperation between the pharmaceutical customer and the supplier could streamline the overall qualification and validation activities, e.g., for sterilisation or freeze-drying cycles, grinding processes, packaging processes etc. as illustrated in figure 6.

Figure 6 Initial feasibility testing and final performance testing



6 Supplier Activities

6.1 Introduction

Generally, suppliers make significant effort in comprehensive testing of their products and solutions to demonstrate that they deliver manufacturing systems of good quality. If the supplier's Good Engineering Practice is matching GMP requirements with regard to procedures, acceptance criteria and documentation including data integrity, then the pharmaceutical customers may use the outcome of these supplier activities to support demonstrating that the manufacturing system is designed, constructed, and tested to fulfil the requirements.

If this is the aim of a pharmaceutical customer and it is made clear at a very early stage of a project, it is possible to avoid testing the same attributes multiple times in various stages of acceptance tests. The aim of a 'single-test qualification' approach is to use testing results throughout the complete project.

6.2 Agreed URS and Project Quality Plan (PQP)

The supplier's quality activities start from an *agreed* User Requirement Specification as described in section 5.2. Some suppliers have templates or examples for their specific equipment which may be a good starting point or useful inspiration for the development of a URS. The pharmaceutical customer has the knowledge about the product, the process, the GMP requirements and other important requirements that can be understood by the supplier by means of a clear and comprehensive cooperation. The supplier input is an important contribution to the final and agreed URS as part of the contractual agreements including also scope of supply, services, timelines, and other supporting documents.

A separate Project Quality Plan (PQP) may be agreed with an overview of the project and the quality activities, possibly as attachment to the contract. It typically includes the project scope, organisation, reference to supplier's quality system, document list and distribution, approval matrix, Design Reviews, sub-contractor management, procedures related to construction, overview of testing activities, change management, deviation management, storage, and shipping, as well as reference to relevant principles, procedures, standards and applicable guidelines. This document is normally created by the supplier and agreed with the pharmaceutical customer. Appendix 6 includes a PQP template example.

6.3 Change Management

The project change management activities are an important part of the project management activities but also of the planning and execution of the related review, inspection and test activities. The handling should be described in the PQP to ensure that relevant requirement documents, design documents etc. are updated to reflect agreed changes. Changes should be documented so they can be tracked, and they should be linked to Quality Risk Management.

At this point, it should be pointed out, that the supplier should not make unauthorized changes, outside the terms of the Contract, which may adversely affect the quality of the outsourced activities

for the client. The distinction between an "engineering change" and a GMP-related change should not be left to the supplier alone.
Normally suppliers have an internal change management process, based on their quality management system. The link between the project change management and the supplier's internal change management is important, especially in the follow-up on deviations, non-conformities etc. during review and testing. It is typically associated with a so-called 'open punch list' or 'open items list' as exemplified in Appendix 5.

The supplier is also expected to have change management to ensure that all parts of the design, hardware and software and other outcomes are kept up-to-date and that subsequent changes are cascaded to all relevant elements of design etc.

It may be useful to distinguish between the engineering change management and GMP-related change management of the supplier. For GMP related changes it can be necessary to involve the pharmaceutical customer's quality function (e.g., when related to Critical Aspects). Appendix 5 includes a template example of Project Change Management with further explanation.

6.4 Deviation Management

The management of deviations and non-conformities should be agreed including documenting deviations and non-conformities as well as the correction of errors. It should cover deviations from agreed procedures and methods. This is important for the project progress and workload whether identified defects are recorded on the punch list for GEP correction or on a list involving formalised deviation management, typically to be approved by the pharmaceutical customer's quality function. This should be addressed in the PQP of the project.

Defects resulting from mistakes and errors (typical punch list items) should preferably be corrected during the review, inspection and test activities. For deviations it should be agreed between pharmaceutical customer and supplier how deviations and changes will be managed, especially if they involve scope changes and approvals.

Appendix 5 includes a template example regarding Change Management and Deviation Management.

6.5 Design Activities, Engineering Activities

Engineering is the phase in technical projects, where work on the design and technical details is done. A number of design documents are prepared based on the URS and discussed among pharmaceutical customers, suppliers and engineering companies, if involved. The creation of the design drawings, specifications, component lists and other design documents is the initiation of a system with quality built in.

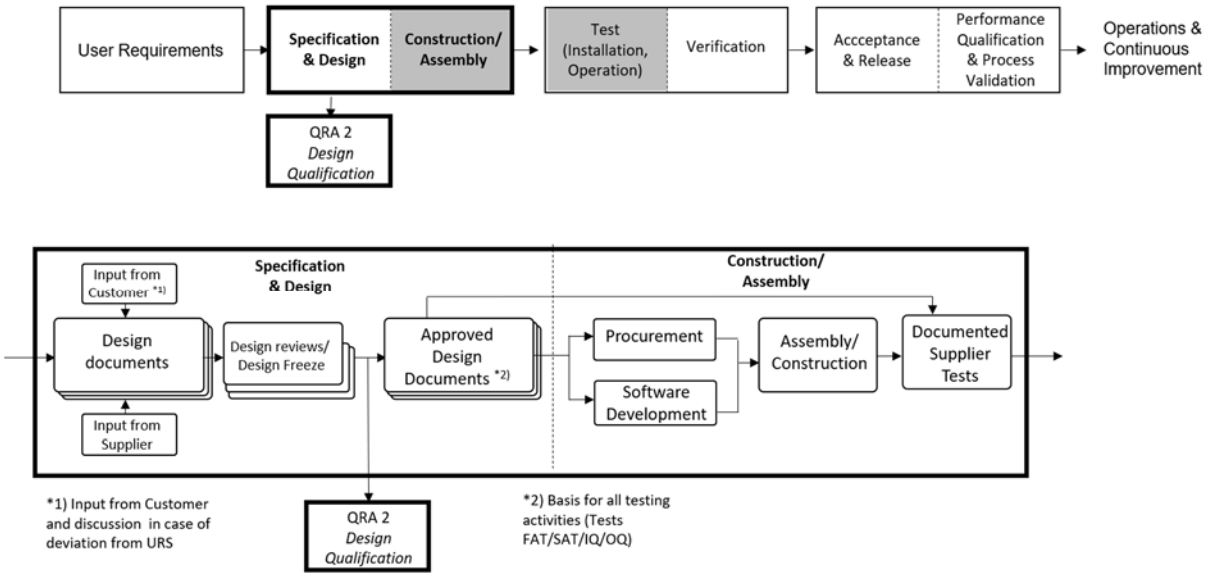
The cooperation between supplier and pharmaceutical customer during the design phase can be described as a combination of engineering activities (where initial functional specifications, P&IDs etc. are developed by the supplier or the engineering company and subjected to internal Design Reviews) and design qualification activity (where the initial engineering documents are reviewed and approved by the pharmaceutical customer).

The agreement between supplier and customer with the approval of the design is very important for both supplier and pharmaceutical customer since it is the basis for consecutive supplier activities such as detail design, procurement, assembly, software development etc. and particularly the mutual basis for the Design Qualification (see section 5.6).

Larger engineering projects typically follow three stages of design: Conceptual design, Basic design and Detailed design or a variation of these. **Conceptual Design** is a very general summary of the overall layout, design principles and project scope, **Basic Design** handles the overall equipment or system level, whereas during the **Detailed Design,** all parts, components, modules, and programming details are specified.

In the cooperation between the pharmaceutical customer and supplier the supplier typically has a number of activities that does not involve the pharmaceutical customer, but the joint activities and decision points should be described in the PQP. Figure 7 illustrates a cooperation example where activities of Specification & Design and Construction/ Assembly are described in more detail from a supplier perspective with the link to the customer's Design Qualification (DQ).

Figure 7 Activities of Specification & Design and Construction/Assembly phases from a supplier perspective.



As soon as a design document is completed and the requirements of the URS and the other requirements have been considered and there is a common understanding between pharmaceutical customer and supplier, the design is considered "frozen". This implies that design documents are approved and released within the supplier's organisation for subsequent detail design, procurement, manufacturing etc. Individual design documents may have their own individual design freeze. The term "design freeze" is typically a project *milestone*, the action related to this milestone is the *document approval* and the documents related to this milestone are the "*approved design documents*".
There are many types of design documents, e.g., Functional Specifications, Software Design Specifications, Technical Design Documents, P&IDs, Component Specifications etc. They should document the intended design and function of the relevant manufacturing system and should contain

enough details to form the basis for Design Review activities. They must be version controlled, reviewed and agreed as outlined in the PQP. Updates of requirement and design documents and their intervals should be agreed beforehand between pharmaceutical customer and supplier and documented in the PQP. Changes should be managed as agreed.

The Functional Specification is one important document among many others that a supplier will develop during the design & engineering phase where pharmaceutical customer, supplier and possibly an engineering company typically collaborate. It describes the detailed functions of the manufacturing system, i.e., 'what the system will do'.

In general, it is helpful to use suppliers' standard design documents, test documents etc. to make best use of the supplier's capabilities.

In case the supplier involves any engineering company as a third party, the tasks and responsibilities of the third party shall be described in a contract and PQP respectively to ensure that information and knowledge are made available in the same way as between the client and supplier.

6.6 Design Review and its Link to Design Qualification (DQ)

Technical and compliance reviews of the engineering documents, called Design Reviews, are important elements in the design process, especially when they are used for the pharmaceutical customer's Design Qualification as described in Section 5. Design Review and review meetings should be planned into the design process and typically includes both internal supplier reviews and review meetings with the pharmaceutical customer.

6.7 Activities during Assembly/Construction

Depending on the manufacturing system in scope, the pharmaceutical customer's knowledge concerning the supplier and the supplier's capabilities, a pharmaceutical customer may want to carry out inspections during the assembly activities. Sometimes it is appropriate and important to perform testing activities during the building or assembly of the manufacturing system. Activities such as verification of material certificates, instrument certificates, welding, surface treatment, gaskets, piping drainability, and other technical solutions can be done effectively and efficiently at this phase of the project. Their documentation, including certificates, photos and other inspection documents is an important part of the documentation of the verification and qualification activities.

It is expected that the supplier performs necessary checks or testing activities during the assembly and construction to ensure that the design is realized with the right level of quality. This is especially important when using sub-suppliers for significant parts of the work. The pharmaceutical customer may also like to perform supervision in key stages or for specific elements like welding, material selection, calibration etc.

6.8 Commissioning and Qualification Testing

6.8.1 Introduction

Most suppliers have developed or adapted specifications, drawings, material management procedures, testing and inspections in acceptable formats and methods as agreed with the

pharmaceutical customer to make the supplier documentation useful for the qualification activities. The purpose for testing is to identify errors and correct them as soon as possible. Overall, the testing should confirm that the system is implemented as designed and performs as intended so that it may be concluded that it is fit for intended use. Particularly when engineering and pharmaceutical activities overlap, it must be clear which tests are to be carried out and documented in accordance with EU-GMP-Guidelines. This can be described in the PQP.

Some companies use the term commissioning for these activities to emphasize that they are engineering activities in the meaning "a planned, managed and documented approach to the setting to work, start-up, regulation and adjustment, and installation/operation/performance verification necessary to bring equipment, automation and systems to a fully operational state meeting safety and end-user requirements." (ASTM E2500). These activities may include acceptance testing, especially Factory Acceptance Test (FAT) and Site Acceptance Test (SAT). Before this testing and qualification, the supplier may conduct internal tests, some of which may go beyond the tests that the pharmaceutical customer has specified.

6.8.2 Installation Testing and Qualification

The installation testing follows the installation and assembly of the manufacturing system and verifies that all parts of the manufacturing system, such as components (e.g., valves, pumps, pipes etc.), software modules, wires, etc. are mechanically and electrically installed and connected as specified.

These activities depend very much on the type of manufacturing system and include both technical and GMP-related aspects such as material types, piping slope, drainability, airlocks, dead-legs, cleanability of surfaces and many other technical aspects that are covered in several industry standards and guidelines related to Good Engineering Practice of pharmaceutical manufacturing systems. Generally, installation testing is a prerequisite for operational testing and for some activities, for example input/output testing and calibration of instruments.

Some of the installation tests are typically part of the Factory Acceptance Test (FAT), especially for those parts of manufacturing systems that are not disassembled for transportation to the pharmaceutical customer's site. Installation tests where components, have to be dismantled after FAT due to transportation, as well as other tests, which could have been influenced by transportation, have to be repeated. Such repetitions may be described in the Test Matrix, see Appendix 1.

Site Acceptance Test (SAT) is performed after the manufacturing system has been installed in the pharmaceutical customer's facility. FAT and SAT typically address both the installation and the function of the manufacturing system, and they should be executed and documented as agreed.

The documented tests may be used by the customer to support Installation Qualification (IQ), as mentioned in some GMP regulations, e.g., EU GMP Annex 15 on Qualification and Validation.

6.8.3 Operational Testing and Qualification

Operational testing is focusing on functional aspects and is intended to demonstrate that the manufacturing system's functions are performing as specified in URS or design documents such as functional specifications and/or software design specifications.

Some of the operational tests may be performed as part of the Factory Acceptance Test (FAT), especially for those parts of manufacturing systems that are not disassembled for transportation to the pharmaceutical customer's site.

The documented functional tests may be used by the customer to support Operational Qualification (OQ), as mentioned in some GMP regulations, e.g., EU GMP Annex 15 on Qualification and Validation.

6.8.4 Remote Testing

Travel rules during, e.g., pandemic restrictions have increased acceptance of remote testing without physical presence at, e.g., the suppliers' premises during FAT. Also, broad experience with on-line video conferencing tools has increased the understanding that remote testing offers saving resources and cost and can be a good contribution to limit travel and improve sustainability.

When using this for e.g., FAT, the customer can participate in a test execution even when not being at supplier's site. Since this is a rather new approach it requires upfront preparation, such as checking of the IT Infrastructure on both ends, enhanced communication and common understanding of the limits. A risk assessment should be performed and documented as basis for the decision of using remote testing in each case.

A description of activities that can contribute to a successful remote testing is included in Appendix 8.

7 Support by Categorisation

7.1 Introduction

When planning the qualification approach in a project, it has proven useful to use a simple equipment categorisation approach. Similar approaches are used for software categories according to GAMP 5 and to analytical equipment according to USP <1058>, which distinguish between standard systems, configurable systems, and customised systems.
In short, a standard system is used without modifications, a configurable system is set up for each specific application (e.g., an autoclave sterilisation program) and a customised system is built for its specific purpose (e.g., a bioreactor). See more examples below.
The categorisation approach should be used with caution and should also take other aspects into consideration, e.g.

a) The manufacturing system is sourced by a supplier, who
   - Has established processes and follow them (e.g., ISO 9000ff)
   - Is using well known supportive standards or guidelines (e.g., from ASTM, ECA, ISPE)
   - If software is involved Is following the GAMP Approach
   - Is open for audits and accepts them as a possibility for continual improvement
   - has a fundamental understanding of “GMP Thinking”

b) the pharmaceutical customer
   - knowing the processes and defines the critical aspects
   - listens to the suppliers, be open for widely used solutions and does not want to reinvent the wheel
   - does not force the supplier into not engineer to order (ETO) solutions (unless this is clearly communicated and mutually agreed)
   - has a focus on the mandatory requirements (GMP)

Categorisation can only be applied as critical aspects are identified. The process for categorization should be thoroughly described, e.g., in a SOP

7.2 Starting Point for Categorisation of Manufacturing Systems

A categorisation approach may start with a first decision, whether a manufacturing system needs to be subject to qualification or not. This may be done via a system impact assessment where non-direct-impact systems, which have no direct impact on process or product quality, will not need any qualification, but only commissioning activities. Direct impact systems need qualification and for this can undergo categorization.

7.3 Categorization of direct Impact Manufacturing Systems

7.3.1 Categorization for Qualification Activities

What is the purpose and expected benefit of categorisation of direct impact systems? The aim is to reduce the time and effort of related qualification activities. The EU GMP Guide Annex 15 is providing a mandatory frame of the qualification approach but has to be also based upon the individual GMP risk of each system and there is a huge variation among the variety of the used equipment and systems.

Within these Guide, we have defined the following describes 3 main categories of manufacturing systems with regards to their complexity:

A. *Standard* (Commercial off-the-shelf systems (COTS))

B. *Configured* (COTS with customer specific configuration of, e.g., sequence, setpoints, timers, etc.)

C. *Customised* (designed for the specific customer with specific requirements, that is not available commercially, due to a special application, technology innovation etc.)

The categorisation has an impact on the entire equipment life cycle and even though it seems in most cases obvious to which category a system belongs to, this should be analysed very carefully. Of course, other categorization models with a different number of categorization classes are possible.

For categories A and B, the customer may reduce some activities such as:

- The supplier assessment or audits may be reduced or a documented justification might be sufficient if the supplier is well-known to the industry and has manufactured the said chosen system for several years in higher numbers.
- Every qualification activity according to Annex 15 must be conducted, such as the DQ. In most cases, the DQ will be done after purchasing by a dedicated group and in accordance with the formal DQ approach. Category A and B system purchase requirements and commercial technical descriptions (or even catalogue information) might be sufficient to decide on the equipment's suitability for intended use. This should be documented in a simplified approach into the life cycle documentation. No dedicated additional DQ phase needs to be performed.
- The supplier provides technical documentation for that type of equipment (e.g., functional specification, conformity certificates, risk analysis etc.) and the related quality department of the pharmaceutical customer accepts the supplier standard as long as all GMP aspects are covered. No customization of design documents is necessary in terms of layout or preferred structure.
- Customer test activities including Factory Acceptance Test might be done by physical presence of the customer, hybrid or remotely.

Other simplifications can be done based on a case-by-case risk-based decision.

With regards to quality or qualification related activities at least the following activities should be done for any of the direct impact systems:

- Risk assessment, possibly supported by equipment-based supplier risk assessment
- Performance Qualification (PQ) to ensure that the manufacturing system as installed operates as intended in the integrated environment (see also section 5.7 Integration Testing)

All other qualification activities as per Annex 15 must be considered. For category A and B systems a risk-based rationale might allow for reduced verification for IQ or OQ. Properly documented supplier verification of non-customized features or functions might be considered as sufficient as proof for intended use.

In any case, decisions on reduced testing need to be justified, documented and should be part of the systems life cycle documentation.

For customised manufacturing systems (category C) where the reduced approach does not apply, the full approach of this guide should be applied.

For all categories, tests focusing on critical aspects always involve the customer's SMEs and Quality Function.

7.3.2 Additional Points to consider

A system categorisation approach is often useful but should be combined with an assessment of the criticality of the system, e.g., the technology complexity, the specific application criticality and the supplier capabilities. Here are some points to consider:

System criticality, considering:
- system complexity
- grade of automation
- grade of standardisation

Usage criticality, considering:
- impact on product quality and process
- ease of operation
- interaction with other systems
- knowledge and experience of the pharmaceutical manufacturer

Supplier criticality, considering:
- experience with pharmaceutical customers and GMP requirements, history, quality
- system experiences (number of systems produced)
- standardised manufacturing process

7.3.3 Examples for categorized Systems

The following table provides some examples for categorization including the proposed verification procedures. The table considers the system's complexity as well as the other critical attributes as outlined in section 7.3.2

Table 2 includes examples of the 3 categories:

Category	Name	Verification Approach	Typical example
A	*Standard* Non-complex system (few functions), low impact on process and product quality, long term supplier (Also called Commercial off-the shelf – *COTS*)	Typically verified by commissioning based on GEP, typically supervised or executed with the customer. Qualification (IQ/OQ) reduced to income checks and/or onsite as built checks. If the system includes Critical Aspects the testing typically involves the customer's quality function (PQ).	Refrigerator Mobile tanks Stand-alone transfer pump
B	*Configured* Low complexity, with essential influence on process and product quality, well known, long term supplier	Verified as A, but the systems have to undergo special verification for its specific configurations and finally has to pass Performance Qualification to ensure that it is fit for its intended use The PQ involves the customer's quality function.	Filter Unit Blender Stand-alone CIP System
C	*Customised* Complex with essential influence on process and product quality. Supplier is known but it is not a fully standardized system for him<	Typically verified by commissioning and qualification, supplemented by specific testing of customized components and functionalities, working closely together with the customer within several areas. The project involvement typically includes close cooperation and approval of the customer's quality function, not only on PQ.	Bioreactor WFI distribution systems Purification Column Integrated CIP system

Category A manufacturing systems are typically standard systems that are sold many times (COTS) and they are to be tested by well-known suppliers using GEP principles. Suppliers often provide a range of different products, systems and services, so it must be ensured that the selected equipment meets the specific customer requirements for the application. Nevertheless, such systems can become critical in the sense of the categorisation, when they are complex and are intended for use in a process with high influence on product quality. Also, in case the supplier is a new one, newly started a business, even a standard system may become critical and will be categorised as B or C.

For **Category B** manufacturing systems, customers and suppliers are encouraged to cooperate on the relevant qualification approach to reach a common understanding of the parts where GEP testing is sufficient and the parts where more in depth verification and documentation is needed. It is recommended to use supplier's standard solutions, when possible, to save time and minimize the risk. Also, it is recommended to use supplier's standard documents for design and verification activities

thus limiting the number of new documents to be developed. It is still the responsibility of the customer to review the supplier's standard documents and test procedures and approve the documents as applicable for the manufacturing system. The number of review and approval cycles for documents should be appropriate to risk and limited. It is recommended to focus on critical aspects.

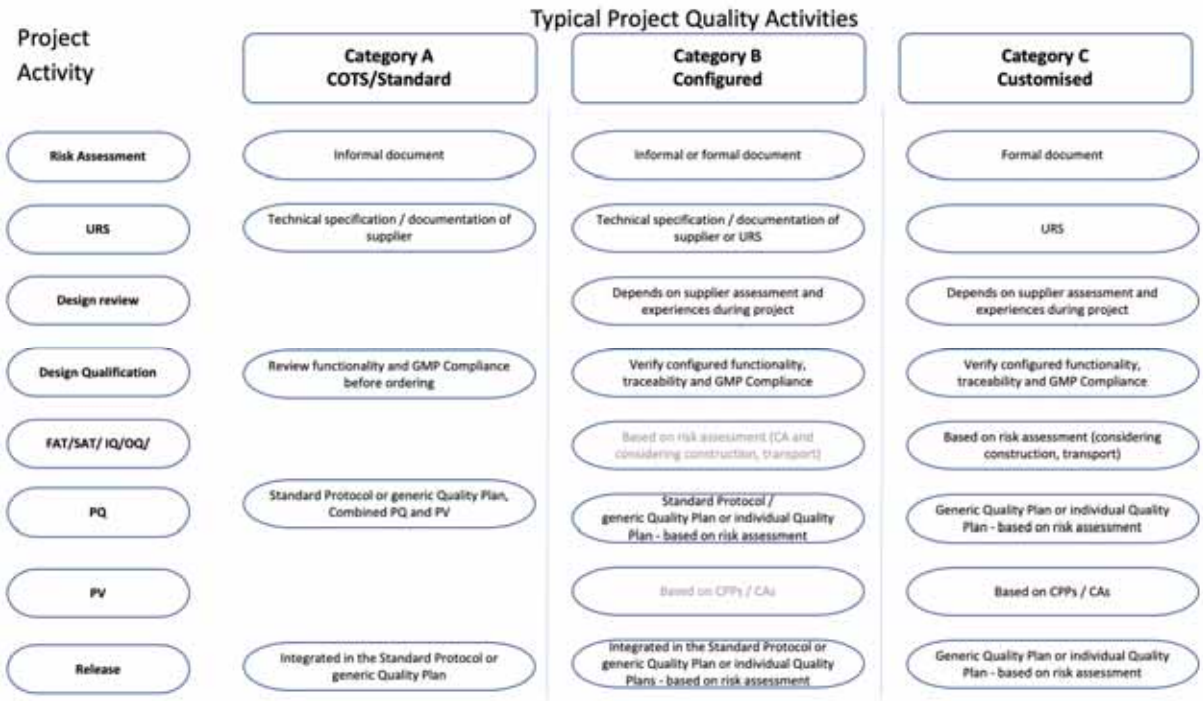
Category C is to be selected when the customer requirements cannot be fulfilled by a standard manufacturing system, equipment, or function. This category is also to be selected for standardized systems when the system is complex with a high influence on process and product quality or the interaction with other systems leads to a high influence on process and product quality. Critical Category (C) may also be the category selected when the system itself is standardized but there is doubt about the quality of the supplier and there is no other choice. Customised equipment is designed specifically to the customer needs, but if the same partners (pharmaceutical company and supplier) using similar design and functionality in follow up projects, the criticality maybe lower, and the systems may be transferred into category B.

7.3.4 Possible Life Cycle Approach for Defined Categories

Appendix 9 provides examples on how to do a risk-based categorisation keeping the system, usage, and supplier criticality in mind. It also provides examples on the resulting and qualification related activities.

Figure 8 illustrates the typical project quality activities that should be considered for the three main categories of manufacturing systems. Boxes with grey text indicate an activity that may be omitted depending on the project. The planning of activities should reflect the risk assessment for the manufacturing system and its application. The assessment, decision and planning in specific projects should be documented.

Figure 8 Typical project quality activities for the three main categories



Explanation: grey font indicates that extent of testing activities should be based on risk

The herein suggested approach is just one possibility of categorisation. The categories and the belonging life cycle activities might not fit for all pharmaceutical companies. The intention of this section is to provide guidance and suggestions, which must be adapted to the own needs. Anyway, categorisation provides a pathway to reduce qualification effort. This is beneficial for each project and each company.

8 Support by Use of Electronic Documentation

The use of Electronic Documentation (ED) offers benefits for a qualification/validation project when implemented upfront. The general expectations for Good Documentation Practice should be followed, as described in section 3.2 for both the pharmaceutical customer and the supplier. The pharmaceutical customer should manage the ED according to the requirements in EU GMP Annex 11 Computerised Systems so that technical solutions and technical documentation can be used in the pharmaceutical company's final qualification and validation documentation. The integrity of the qualification and validation data and documentation must be ensured by all participants independent on whether they are on paper or electronic. Basis for data integrity activities are reflected by ALCOA++ principles (*attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and traceable)*.

For data integrity aspects please refer to authority guidance, e.g., PIC/S PI-041 and FDA guidance Data Integrity and Compliance with Drug cGMP Questions and Answers Guidance for Industry.

These agreed preconditions should be described in the PQP or contract as described in sections 4 and 6.2. For further description, see EU GMP volume 4, Part 1, Chapter 4 Documentation.

For the life cycle of the documents the pharmaceutical customer has to decide how data storage and archiving should be done.

There are many advantages by following paperless qualification and validation execution by faster and more efficient workflow.

Standardization of processes, templates and documents is a key to success for electronic qualification and validation tools. Documented evidence should be available, that the system is suitable for intended use before implementing.

It may be useful to distinguish between two types for Electronic Documentation: The traditional approach, where handwritten qualification and validation documentation is scanned, or using an eDMS (electronic Documentation Management System)/VLMS (Validation Life Cycle Management System).

Traditional approach: Scanned, paper-based qualification/validation documentation
Customer and supplier need to agree on the format of *digitalized* qualification documentation. Since various systems and software packages are on the market, it is recommended to agree on "pdf/A" as the common file format. Customer and supplier may agree on additional formats (e.g., for drawings), but this is not the focus of this section.

During the scanning process it has to be ensured that the paper original and the scan have identical content, in particular that colors (e.g., spectra, plots) are maintained. The scanning and verification process should be described in an instruction, which should include the verification of the compliance of the electronic file with the paper original. This is recommended to be verified using

an electronic signature. After scanning, the document may be uploaded to an eDMS for subsequent processing (e.g., approval).

Advanced approach: Documents are being created, test executed and approved in electronic format
Software tools or comprehensive software solutions are available to facilitate the life cycle of qualification and validation information. If a software tool or solution is applied, it needs to be validated for its intended use.

Paperless qualification and validation documentation can be designed to be more efficient and effective in project execution and later-on managing the documented evidence for the system over its life cycle. If the engineering data base is connected to qualification and validation data base/software, there may be automatic linking to the correct design documents used as test- and reference documents.

It is preferable to use a validated VLMS of the customer as the repository for all types of documents created during the qualification and validation process.

This approach can range from single event digital documented evidence creation (e.g., video, pictures) closely linked to the qualification and validation documentation over Validation Life Cycle Management Systems for drafting, sharing, executing and approving of documents further on to systems for handling all qualification and validation activities.

When applying any kind of electronic documentation, the interface for data exchange (original data plus related meta data (e.g., audit trail, dates, …) between customer and supplier is key. Therefor all involved parties should discuss and agree upfront, how this should be implemented and maintained. If data are kept in the cloud (e.g., by a subordinated SaaS service provider) such CSP (Cloud Service Provider) must be audited in order to verify the GxP compliant handling of data and validation of the cloud application.

ED offers benefits when the following points are addressed:

- Transparency for involved parties (incl. easy navigation): A validated software tool (preferrable VLMS of the customer) might be useful to enable a good overview on stored documentation and status (such as in draft, under revision, for approval, under execution)
- Allow monitoring and oversight for ongoing testing activities
- Allow attaching and incorporation of files (e.g., pdf files, pictures, videos, trend curves) in test plans as documented evidence during test execution or reports using modern digital equipment (smart phones, tablets, laptops).
- Approach shall comply with data integrity requirements at the start and in the life cycle.

ED also offers quick and efficient interfacing. To facilitate this collaboration, it should be clearly outlined and agreed before implementation. This includes

- a listing of all documents that need to be handled or exchanged electronically
- data format
- name/file conventions, if applicable
- Change Management
- Deviation Management
- Upload and download procedures
- Approval of documents.

It must be agreed (e.g., via data flow map, quality agreement, Project Quality Plan) how data exchange is handled.

ED can also be applied in remote testing (see 6.8.4).

It is important to mention, that ED in a larger project offers full benefit only, if all suppliers are included. It might be appropriate to compromise on the scope for ED for the sake of 100 % completeness for defined items. The suitability of the supplier's Document Management system should be checked during supplier qualification, in case GMP relevant documents are created and stored for the customer.

9 Abbreviations

Abbreviation	Definition
ASTM	American Society of Testing and Materials
C&Q	Commissioning and Qualification
CA	Critical Aspects
CDE	Critical Design Element
CARA	Critical Aspects Risk Assessment
cGMP	Current Good Manufacturing Practice
CIP	Cleaning in Place
CMA	Critical Material Attribute
COTS	Commercial off-the-shelf (system)
CPP	Critical Process Parameter
CPV	Continued Process Verification (FDA Process Validation Guidance)
CPV	Continuous Process Verification (EU GMP Annex 15)
CQA	Critical Quality Attribute
CSV	Computerized System Validation
CTQ	Critical to Quality
DQ	Design Qualification
ED	Electronic Documentation
EHS	Environment, Health and Safety
EMA	European Medicines Agency
EU	European Union
FAT	Factory Acceptance Test
FDA	Food and Drug Administration (US)
FMEA	Failure Mode and Effects Analysis
FMECA	Failure Mode, Effects and Criticality Analysis
FS	Functional Specification
GAMP	Good Automated Manufacturing Practice
GDP	Good Documentation Practice
GEP	Good Engineering Practice
HMI	Human Machine Interface
ICH	International Council on Harmonisation
IQ	Installation Qualification
ISO	International Standardisation Organisation
N/A	Not applicable
NOR	Normal Operating Rage
OPL	Open Point List
OPV	Ongoing Process Verification (EU GMP Annex 15)
OQ	Operational Qualification
PAR	Proven Acceptable Range
PAT	Process Analytical Technology
P&ID	Piping & Instrumentation Diagram

Abbreviation	Definition
PFD	Process Flow Diagram
PPURS	Product and Process User Requirement Specifications
PPQ	Process Performance Qualification (FDA Process Validation Guidance)
PQ	Performance Qualification (EU GMP Annex 15)
PQ	Process Qualification (FDA Process Validation Guidance)
PQP	Project Quality Plan
PV	Process Validation
PVP	Project Verification Plan
Q	Quality
QAA	Quality Assurance Agreements
QA	Quality Assurance
QRA	Quality Risk Assessment
QRM	Quality Risk Management
QTPP	Quality Target Product Profile
RACI	Responsible, Authorise, Consult and Inform (Chart)
RFP	Request for Proposal
RTM	Requirement Traceability Matrix
RTR	Real Time Release
SARR	System Acceptance and Release Report
SAT	Site Acceptance Test
SDS	Software Design Specification
SIP	Sterilisation in Place
SME	Subject Matter Expert
SOP	Standard Operating Procedure
SW	Software
TM	Test Matrix
URS	User Requirement Specifications
USP	United States Pharmacopeia
VLMS	Validation Life Cycle Management System
VMP	Validation Master Plan
VTOP	Vendor Turn Over Package (aka Supplier Turn Over Package)

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Appendices

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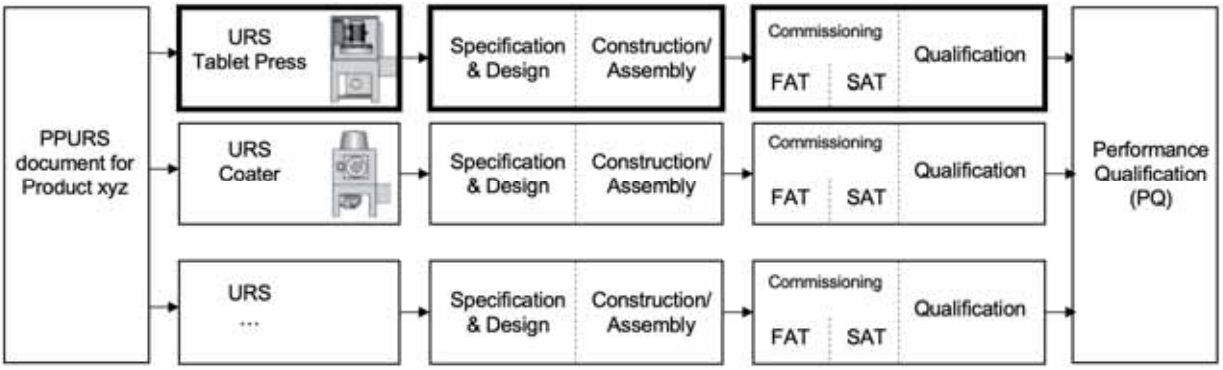
Appendix 1: Explanation of the Integrated Qualification Core Concept

Here is a brief explanation of the core concept of the ECA Q&V approach of this guide. The purpose is to integrate customer and supplier activities for effective and efficient qualification and validation of manufacturing systems. Basis for that approach is a common understanding of "Critical Aspects" and Quality Risk Management as well as the use of Good Engineering Practice. It can be applied to small or large projects containing other types of manufacturing systems in both new and existing facilities.

A tablet press has been selected as manufacturing system to explain this Integration Core Concept. As a starting point the pharmaceutical customer is performing an initial Quality Risk Assessment (QRA0) of the relevant tablet production process; he knows the Critical Quality Attributes (CQA) and the Critical Process Parameters (CPP). Besides he drafts a User Requirement Specification (URS).

Some companies use an overall document for the whole manufacturing process from formulation to final package, e.g., called a Product and Process User Requirements Specification (PPURS) to develop the URS for each equipment, as illustrated in figure 1.

Figure 1 Project scope overview of the manufacturing systems used for tablet production related to the PPURS



The tablet press machine feeds powder to pistons that compresses the tablet and the product and process development determines the relevant process parameters. In this example the customer's product and process development has identified the compression force of the tableting piston as a CPP.

The Quality Risk Assessments during this project is documented in a CARA Matrix (Critical Aspects Risk Assessment) which also includes the possible failure modes of the equipment that can affect the compression force. Each failure mode is listed in the table, as illustrated below (table 1) and includes:

- *cause of the failure mode* related to the compression (machine parts: die cavity, punches, cam truck and tablet adjuster),
- related measures to prevent the failure from affecting the product *(risk control),* and
- related measures to detect the failure *(risk detection).*

Appendix 1: Explanation of the Integrated Qualification Core Concept

Table 1 Link between CQA, CPP and Critical Aspect (CA) for a tablet product produced on tablet press

CQA	CPP	Quality risks / Failure mode	Critical Aspect (CA)		
			Cause of the quality risk / Failure mode	Risk control	Risk detection
Tablet hardness	Compression force (CPP)	Wrong compression forces	Failure of compression station, die cavity, punches, cam truck, tablet adjuster	Compression control (In process control)	Alarm Indicated and recorded on Control System

Table 2 shows an extract of the first CARA step (QRA1) for a tablet press example with only one CQA and one CPP, based on the data in Table 1. The example shows the failure mode of the critical aspects as well as the cause of the failure mode, the risk control and possible risk detection measures, for example the failure mode "Wrong compression force". The risk score scale for Severity, Probability and Detectability is described in more details in Appendix 4.

Table 2 Extract of QRA 1 for tablet press - Critical Aspects/CPPs Risk Assessment [CARA]

QRA1											
Process Step	Critical Aspects	Failure modes	Failure impact	*Severity Score S*	Failure causes	Risk Controls	*Probability score P*	Detection method	*Detectability score D*	*RPN (S x P x D)*	Comments
Tableting	Compression	Wrong comp.force	Broken tablets	*4*	Wrong set point	Setpoint check	*3*	Operator procedure	*5*	*60*	Add sensor? Add alarm?
...											

The CARA matrix is a useful tool for Design Qualification, where the URS and the design documents are discussed between customer and supplier and the conclusion for each Critical Aspect may be documented. The use of the CARA matrix is described in further details in appendix 4.

In this way the CARA matrix serves as an overview document which keeps track of all critical aspects during the life cycle of the project.

To summarize, the commissioning and qualification activities for the manufacturing systems, incl. the DQ, FAT, SAT etc., shall ensure that the design, installation and operation of the manufacturing systems are as intended, meets good engineering practice and relevant GMP requirements and the documentation of the commissioning and qualification activities meets good documentation practice, so they correctly describe the commissioning and qualification activities, with conclusions on that all requirements are met. The CARA documents these activities related to the critical aspects of the manufacturing systems. In many companies the quality organization is deeply involved in the qualification activities related to the critical aspects whereas other commissioning and activities may be delegated to relevant subject matter experts (e.g., process, automation etc.) with oversight from the quality organization but without detailed involvement, unless deviations or other concerns are found.

The "red thread" of the activities with the CARA matrix can be summarized as follows:

Appendix 1: Explanation of the Integrated Qualification Core Concept

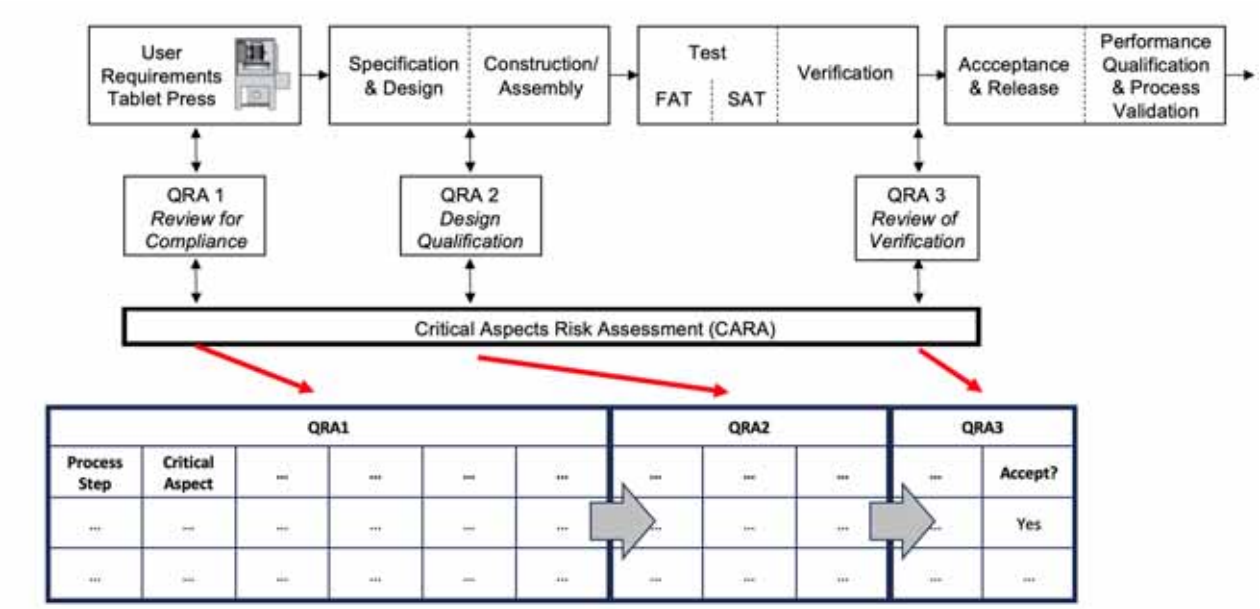
1. *User Requirements and quality risk assessment:*
   The URS for each manufacturing system is stating the requirements including both the Critical Aspects and other user requirements. The CARA typically summarizes only requirements related to the Critical Aspects.

2. *Requirement design review and design qualification:*
   During the project the supplier will deliver design documents (drawings, functional specifications etc.) and the design qualification (DQ) involving both customer and supplier ensures that all user requirements and respective design documents are discussed and accepted by both customer and supplier. The CARA is used to document the DQ activities for the critical aspects whereas all other requirements not related to critical aspects can be documented elsewhere.
   In some companies the quality function is only involved in discussions about the design of Critical Aspects (together with other subject matter experts) whereas other technical components and solutions are reviewed and accepted by subject matter experts only.

3. *Verification:*
   After design reviews and based on design specifications the verification activities should be outlined. It is recommended to clearly distinguish between commissioning activities and GMP related qualification activities. Both should be linked to the URS either by an RTM or CARA.

The relation of the life-cycle CARA matrix (QRA1, QRA2 and QRA3), URS and verification (Commissioning and Qualification) activities is illustrated in Figure 2.

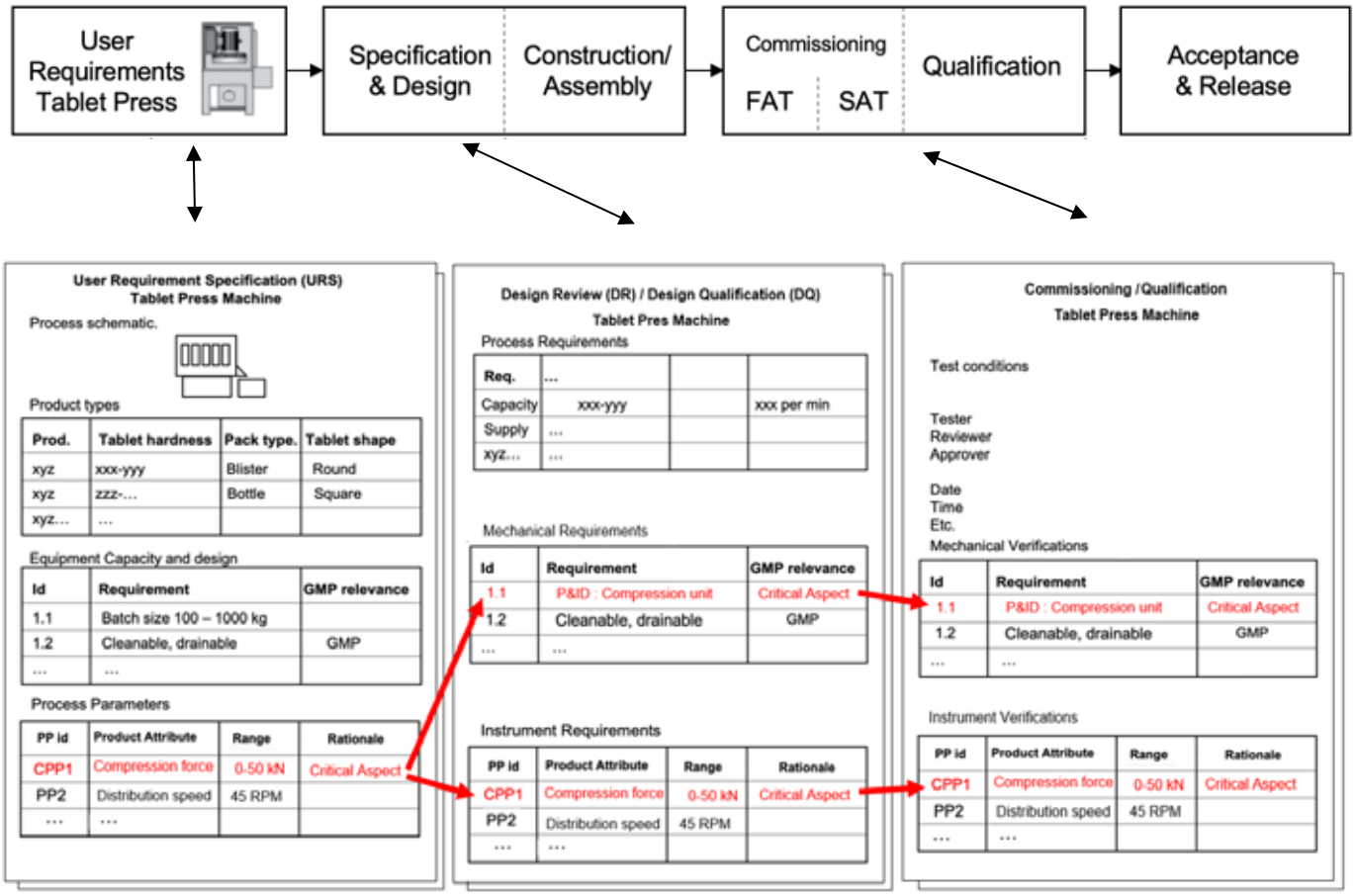
Figure 2 Critical Aspects Risk Assessment matrix, engineering, and verification activities for a tablet press



The Figure 3 illustrates how user requirements are carried over into subsequent documents. The red text is related to Critical Aspect requirements and black text to other requirements.

Appendix 1: Explanation of the Integrated Qualification Core Concept

Figure 3 Project document flow example of Critical Aspects requirements (in red) for a tablet press



When all manufacturing systems used for tablet production have been commissioned and qualified and relevant interim release reports are available for each system, the overall production system is subjected to an integrated Performance Qualification to confirm that all the manufacturing systems have been installed as specified, operate as required, and are fit for the intended use when operating together. In this case where the pharmaceutical company has a PPURS for the tablet product, the acceptance and release report documents that the manufacturing systems overall can produce the tablet product in accordance with the relevant PPURS.

Appendix 2: User Requirement Specification (URS) Template

The User Requirement Specification (URS) should reflect the pharmaceutical customer requirements for the manufacturing system in scope of the project. There may be an initial URS issued by the pharmaceutical customer and a final URS supported by and agreed with the supplier. An *agreed* URS is the starting point for the supplier activities in order to ensure a successful project. The URS is further described in sections 5 and 6 of this guide.

Typically input from the suppliers is important as they may have significant expertise within their scope of delivery, e.g. types of equipment and systems, and they may be able to provide useful URS examples or templates that may be used to provide useful input to the pharmaceutical company's user requirements.

The URS may include several documents describing the manufacturing system for a specific pharmaceutical application as well as more general, technical document. A clear, well-structured URS document may also be achieved an indication of where each URS requirements origins (e.g., quality related, GMP-related, HSE-related, business-related, Technical and others). For each requirement it may be stated whether this should be tested and documented or not. If relevant the reference for each requirement may be marked too.

The URS should be written in accordance with an initial Quality Risk Assessment that identifies the Critical Quality Attributes (CQA), Critical Process Parameters (CPP) which are input to Critical Aspects of the manufacturing system together with other requirements that are Critical to Quality (CTQ) of the pharmaceutical product, see section 5.4.

The following template example illustrates the structure and content of a URS from a project.
Suggested content is described in brackets < > and data entry examples are indicated as "xyz".

Appendix 2: User Requirement Specification (URS) Template Example

User Requirement Specification

Project name

Document number
Revision

Approval Table				
Signs for	Role	Name	Date	Signature
Finished Document	Author …	<name>	<date>	<signature>
…				

Table of Content

Appendix 2: User Requirement Specification (URS) Template Example

1.0 Objective

1.1 This document summarizes the User Requirement Specification (URS) of the project, equipment or system xyz

1.2 The URS is a summary of the company xyz requirements and description of their requirements for the single equipment or system

1.3 The xyz URS focuses in what is needed for a system and which requirements are set to the system. The xyz URS requirements are the basis for the further development of the system documentation and shall provide a list of design objectives and criteria for the testing of the system xyz

2.0 Scope

2.1 This document states the requirements for project xyz and for the system xyz which will be operational in facility xyz

Limitations: This document does not cover …

3.0 References/Related Documents

3.1 Reference documents

<This section summarizes reference documents for the URS, e.g. project scope, product and process specifications (or PPURS) etc.>

3.2 Related documents

<This section summarizes other documents related to the URS, e.g. technical requirement documents etc.>

4.0 Definitions

4.1 References documents

<This section summarizes the abbreviations and definitions used in the document>

5.0 Project Introduction

5.1 Project Description

<This section is a brief description of the goals and limits of the project, incl. location, systems and activities involved>

Appendix 2: User Requirement Specification (URS) Template Example

5.2 Process Description

<This section summarizes at a very high level the process associated with the project, equipment or system. This section should include inputs to the process, description of process steps, output from process. Required equipment automation systems, Building Management System and/or environmental management system. It is recommended to keep the description at a higher overall level. A flowchart may be used to complete this description. Add diagrams such as process diagrams, context diagrams or others useful illustrations>

5.3 System Description: <Context diagram of systems around this equipment>

<This section summarizes the systems involved in the project and its system boundaries to other manufacturing systems, including the main components, the operation and the location. This includes automation systems, Building Management Systems and utilities that are shared with other parts of the facility. Possibly supplemented with drawings or schematics that illustrates the scope of the project and its boundaries>

6.0 User Requirements

6.1 Process Requirements

< This section gives an overview of the process parameters for each process step including the operation range and tolerances of the general process parameters including quantities of materials, sequence of additions/operations, Critical Quality Attributes (CQA), Critical Process Parameters (CPP), other requirements Critical to the Quality (CTQ) of the product, Critical Aspects (CA), non-critical process parameters, heating/cooling rate as well as control, monitoring and alarm functions associated with each parameter. The URS may include general project reference documents, e.g. media list, approved list of materials, preferred components etc.>

6.1.1 Product Volume / Equipment Capacity

Requirement ID	Requirement	Type of requirement
xyz	The Filling System should be able to run continuously at xyz per hour (Minimum Effective Output)	Business-related
xyz	The Filling System shall be able to process various Product and Sizes as described in Section …	Critical Aspect
	…	

Appendix 2: User Requirement Specification (URS) Template Example

6.1.2 Process Parameters

Requirement ID	System Parameters	Controlled	Monitored	Alarmed	Operating Range (Min-Max)	Accuracy	Unit	Type of requirement
xyz	Line Speed	X	X	X				Business-related
xyz	Temperature		X	X				Critical Aspect
	…							

6.1.3 Process Constraints and Limitations

< Some steps in the process may limit the design, type, dimensions or arrangements of the systems or auxiliary equipment. Examples:

- Input conditions (number, pressure, temperature, etc.) of the incoming flows.
- Open and/or closed systems, risk of cross-contamination, from a facility viewpoint etc.>

Requirement ID	Requirement	Type of requirement
xyz	Potable Water is supplied at a minimal pressure of xyz bar	GMP-related
…	Ambient temperature is xyz °C	Operation related
	…	

6.1.4 Production Period

< What is to be produced in what period, e.g. 24 hours day, day shift, night shift…
What is the required availability of the product, the guaranteed throughput rate etc.>

Requirement ID	Requirement	Type of requirement
xyz	The xyz water production is a continuous process (24h/day)	Business-related
	…	

Appendix 2: User Requirement Specification (URS) Template Example

6.1.5 Other process requirements

< Other requirements for the manufacturing system>

Requirement ID	Requirement	Type of requirement
xyz	xyz	
	…	

6.2 Installation Requirements

6.2.1 Material Requirements

<Specify adequate construction materials, or to know compatibility / incompatibility for construction materials (including seals) for the system components>

Requirement ID	Requirement	Type of requirement
	All lubricants and fluid utilized on process equipment shall be identified and confirmed as Food Grade Quality	Critical Aspect
	…	

6.2.2 Construction Requirements

<Specify construction requirements such as gravity flow, slopes, no dead spaces, no dead legs (design according to the 6-D rule), heat tracing, etc. >

Requirement ID	Requirement	Type of requirement
xyz	Dead spaces shall be avoided at critical locations	GMP-related
	Process piping is installed according to standards of sanitary design	GMP-related
	…	

6.3 Operational Requirements

<The operational and functional requirements specify the way the equipment, the automation and the system should perform. The sequence and correlation between the process functions can be illustrated with a diagram. The process steps with acceptance criteria, actions in case of failure or exceeding of the limits, quantities, and frequency of a process are items can be added in this section if not in a separate functional specification>

Appendix 2: User Requirement Specification (URS) Template Example

6.3.1 Operation & Functional Requirement

<Special operational and functional requirements that applies>

Requirement ID	Requirement	Type of requirement
xyz	xyz	
	…	

6.3.2 Automation and Records (DCS, SCADA, PLC…)

<Special automation requirements, control system requirements etc. >

Requirement ID	Requirement	Type of requirement
xyz	Language: The SCADA/HMI Interface shall support the following languages: xyz and xyz. languages. All Graphic Labels and Operator messages shall be switchable between the languages	Operation-related
	…	

6.3.3 Building Management System

<similar to 6.3.2>

6.4 Other Requirements

6.4.1 Facility/Room Classification and Environmental Conditions Requirements

Requirement ID	Requirement	Type of requirement
xyz	All production suites shall meet class ISO <…> in operation	Critical Aspect
	Core production area shall meet class ISO <…> in operation	Critical Aspect
	…	

Appendix 2: User Requirement Specification (URS) Template Example

6.4.2 Cleaning/Sanitization/Sterilization Methods, Products and Limits/Visual Inspection Requirements

<Cleaning/sanitation/sterilization methods and their specific products and specifications may influence the design of systems (e.g. manual, automatic, CIP, combined cleaning) and the design of system components (e.g. required finishing.). The requirement for visual inspection of the equipment or components should also be mentioned>

Requirement ID	Requirement	Type of requirement
xyz	The production system and storage shall be drainable and chemically cleanable	Critical Aspect
	…	

6.4.3 Utility Requirements

Requirement ID	Requirement	Type of requirement
xyz	Compressed air coming in contact with product must be filtered (Type xyz filter)	Critical Aspect
	…	

6.4.4 Personnel/Material/Waste Movement Requirement

< Specific requirements related to the building layout and movement of personnel, materials, and waste are mentioned here >

Requirement ID	Requirement	Type of requirement
xyz	The building layout must include areas for receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection	GMP-related
	…	

Appendix 2: User Requirement Specification (URS) Template Example

6.4.5 Environmental, Health, and Safety (EHS) Requirements

< Specific requirements related to aspects of operational safety, industrial health and hygiene, and environmental discharges, permits, etc. are mentioned here. These can be grouped together or segregated into separate subjects>

Requirement ID	Requirement	Type of requirement
xyz	The noise level generated during operation of the <…> equipment shall not exceed <…> dBA.	Safety-related
	…	

6.4.6 Ergonomic (Accessibility, Maintainability) Requirements

< This section may include requirements such as: the space required around equipment for operability and maintenance, accessibility to the equipment and components for maintenance activities and normal operation, etc. >

Requirement ID	Requirement	Type of requirement
xyz	All components shall be located at an accessible place. A platform shall be provided around the <…> tank	
	…	

6.4.7 Maintenance Requirements

< specific requirements related to the preventive maintenance of processes and systems are mentioned in this section, e.g. information required to establish a preventive maintenance program, recommended spare parts requirement, etc. >

Requirement ID	Requirement	Type of requirement
xyz	All Lubricating Points must be Registered, Shown and clearly Labeled in an overall Plan. Inaccessible Lubricating Points must be made Accessible by installing Corresponding Lines without opening the Protective Doors. It must be guaranteed that no Lubricants entering the Production	
	…	

Appendix 2: User Requirement Specification (URS) Template Example

6.4.8 Training Requirements

< Specific training requirements of personnel for processes and systems are covered in this section >

Requirement ID	Requirement	Type of requirement
xyz	The training material must be delivered in paper and electronic version in advance <…>	
	…	

6.4.9 Documentation Requirements

< Specific documentation requirements for templates, document control etc. >

Requirement ID	Requirement	Type of requirement
xyz	All documents from Vendors shall follow these Requirements: - They shall be Approved and Provided with the latest Revision - Language for Document and Drawing shall be <…> - Units in Documents and Drawings shall be International Unit, such as m for Length, kg for Weight, m/s for Velocity and so on - All Documents must be provided in Hard Copy and Electronic in advance for Review - All Description shall be Microsoft Word Version, preferable Word version <…> or pdf.	
	…	

7.0 Appendices/Attachments

7.1 Drawings or diagrams, context diagrams, photos, other illustrations relevant for specifying the URS requirements.

8.0 Template for History of Change

< Should be required for all documents >

Version Number	Change Control Number	Section	Reason for Revision (Description of Change)	Remarks
xyz				
			…	

(End of template example)

Appendix 2: User Requirement Specification (URS) Template Example

About Product and Process User Requirement Specification (PPURS)

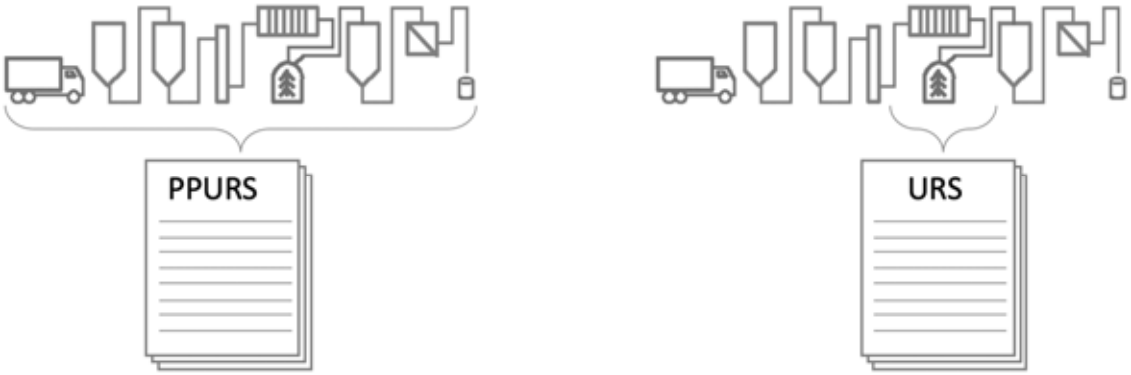
In some pharmaceutical companies the URS documents refers to a so-called "Product and Process User Requirement Specification" (PPURS) for the pharmaceutical product in scope for the project.

The PPURS document typically contains the specific process requirements for each process step and area of the facility, based on the so-called Control Strategy for the pharmaceutical product. Both the PPURS and the Control Strategy are internal and confidential document for the pharmaceutical company and includes process requirements and the initial Quality Risk Assessment for the product and processes. An example of PPURS content is shown at the end of this Appendix.

If a PPURS does not exist in a project an initial Quality Risk Assessment (QRA 0) should summarize the CQA, CPP and other CTQ requirements.

As illustrated in figure 6 the scope of the PPURS is typically the whole process whereas the scope of an URS is typically one manufacturing system within the overall process flow.

Figure 6 PPURS document for the overall process and URS documents for each of the manufacturing systems



Content example for a PPURS:

1. Objective
2. Scope
3. References/Related Documents
4. Definitions
5. Product and Process Description
   - 5.1. Product Description (main stages)
   - 5.2. Process Description (main process steps with input and output, required equipment)
6. Product and Process related User Requirements
   - 6.1. Product: Critical Quality Attributes (CQA)
   - 6.2. Process: Critical Process Parameters (CPP)
   - 6.3. Additional Requirements
7. Control Strategy
   - 7.1. Process Step 1 (including process operations, CPP and In-Process -Controls (IPC)
   - 7.2. Process Step 2, etc.
   - 7.3. …
8. Appendices/Attachment

Appendix 3: Supplier Evaluation

The supplier management may be organized as lifecycle management process of e.g. five stages of supplier evaluation: Selection, Qualification, Performance Evaluation, Development and Termination. They often involve both the sourcing (e.g. procurement) and the business organisation (e.g., production, quality, engineering etc.), typically as a cross-functional evaluation team. The depth and frequency of supplier evaluation depends on the importance and the risk of the system and should be based on a documented risk assessment.

Pharmaceutical customers typically have a questionnaire or similar tool for the evaluation, and it may include several focus areas such as Quality, Technical capability, EHS (Environmental, Health & Safety), Financial performance etc.

Questionnaires may be used instead of an audit for less critical equipment and systems. Questionnaires may also supplement audit(s) as a preliminary assessment (initial evaluation) to gather information relevant for the audit planning.

Depending on the order and magnitude of the delivery the following point should be considered in the supplier evaluation:

- Size of supplier, business track record and customer references, especially within the pharmaceutical industry
- Mutual history between the customer and supplier
- Technical capabilities,
- Assessment of the supplier's quality management system (QMS) and its implementation
- GMP capabilities and knowledge of regulatory requirements, including Good Engineering Practice (GEP)
- Project Management up to on-site installation of the system
- Process and procedures for design and construction, and inspection (for intermediate steps and finished goods
- Procedure(s) implemented for Change Management
- Procedures for management (incl. calibration) of measuring devices and their use
- Documentation management incl. version control, especially for design and test documentation
- Management of materials and related certificates
- Use of sub-suppliers, incl. track record and follow-up
- Use of software, including software development procedures and control
- Capabilities and capacity for planned verification activities (e.g. resources, procedures, documentation of results, …)

Appendix 4: CARA and Verification Planning Tools Templates

The Critical Aspects Risk Assessment (CARA) matrix is a useful tool to manage the critical aspects during design qualification and verification.

1. Critical Aspects Risk Assessment Matrix (CARA)

The Critical Aspects Risk Assessment matrix (CARA) is used for the risk management of Critical Aspects. There may be a CARA matrix for each manufacturing system.

The CARA matrix is made before Design Qualification to identify the critical aspects of the manufacturing system and their failure modes as well as agreed risk mitigations and verification activities for each critical aspect.

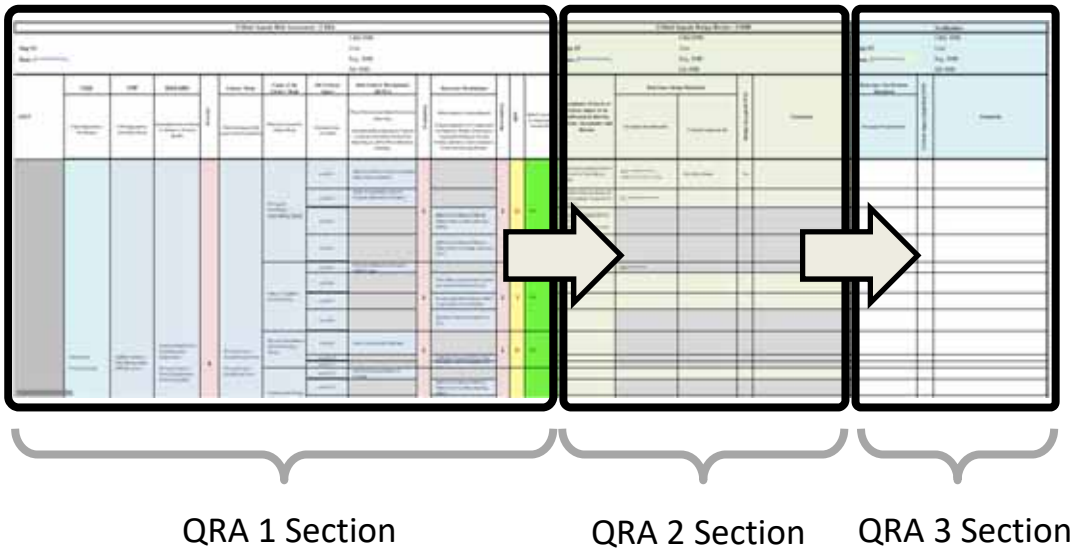
The CARA is based on the initial Quality Risk Assessment (QRA0), based on the Critical Quality Attributes of the product, the Critical Process Parameters (CPP) of the process and other aspects that are critical to product quality.

The CARA includes the following main sections (QRA 1-3) for the project life cycle:

- QRA 1 is used for identifying and assessing the Critical Aspects of the URS requirements and potential risk mitigations.
- QRA 2 is used for Design Qualification of the Critical Aspects as seen in the design documents.
- QRA 3 is used for planning the qualification activities for each Critical Aspect to ensure acceptance criteria are met and traceability is given.

The documentation of QRA 1-3 in the CARA matrix is illustrated in Figure 1.

Figure 1 CARA matrix steps



After the completing of a project, CARA matrix may be considered a life cycle living document and updated with the related URS in case of important changes.

The CARA matrix may also be useful during a regulatory inspection of the factory to explain the management of the Critical Aspects of the manufacturing system.

Appendix 4: CARA and Verification Planning Tools Templates

The following CARA example is based on a FMECA risk management tool (Failure Mode, Effects and Criticality Analysis) with Severity, Probability and Detectability of each failure mode. The risk of each Critical Aspect's failure mode is calculated as a Risk Priority Number (RPN) by multiplying S x P x D.

(Please note that Severity is linked to a product risk and can normally not be modified. Risk mitigations can decrease occurrence and increase detectability and may be changed by design or operating procedures to an acceptable residual risk)

The CARA example is based on the following company example of a risk score:

Severity (S)

Score	Description	Definition
10	Catastrophic	Product CQA affected and OOS
8	Critical	Product CQA affected but no OOS
3	Minimal	Cosmetic defect
1	Negligible	No defect

Probability (P)

Score	Description	Definition
10	High	Failure is almost inevitable
8	Moderate	Repeated failures
3	Low	Occasional failures
1	Negligible	Failure is unlikely

Detectability (D)

Score	Description	Definition
1	Almost certain	Existing controls will almost certainly detect a failure
3	High	High chance that existing controls will detect a failure
8	Low	Low chance for detection of a failure
10	Negligible	No possibility of detection of failure

The overall Risk Priority Number (RPN) is evaluated with following action levels:

RPN (S x P x D)	Action level
Intolerable (red)	Unacceptable if no risk reduction measures are feasible [Individual risk may be accepted on a case-by-case by proving that the risk/benefit ratio is favorable, once all reasonable reduction measures have been taken]
As low as possible (ALAP) (yellow)	Tolerable only if further reduction is not possible and benefits outweigh the residual risk
Broadly accepted (green)	Accepted. No further risk control measures needed

Appendix 4: CARA and Verification Planning Tools Templates

Table 1 QRA1 template

QRA1: Critical Aspects/CPPs Risk Assessment [CARA]																Specific CA/CPP Design Requirement [User Requirement Specification] (incl. Requirement number) URS ref. 22456789
Process Step / Process sub-step ID number	Process Step / Process sub-step	Critical Process Parameter (CPP) / Critical Aspect (CA)	Type [CPP or CA]	Failure [What can go wrong in the Process Step]	Hazard / Potential impact [Potential Harm to Patient or Product Quality]	CQA Tablet hardness	Severity (S)	Cause [What can Cause the Failure Mode]	ID number [based on Process Step/Sub-step ID number]	Risk Control [What Prevents the Failure from Occurring]	Probability (P)	Detection [What Detects the Failure]	Detectability (D)	RPN (S x P x D)	Comments	

Table 2 QRA 2 and QRA 3 templates

QRA#2: Critical Aspects/CPPs Design Verification [CADV]		QRA#3a: Critical Aspects/CPPs High level test strategy [CATS] (before protocols approval)	QRA#3b: Critical Aspects/CPPs Traceability matrix [CATM] (after tests execution)				
			Verification Reporting [Commissioning and Qualification until PQ]				
Reference to Design / Functional document [Document Name]* * Add document Number if available	Design Acceptance [YES, NO] and Comments [Including, if applicable, comments from supplier, alternative solution, deviation, etc.]	High-level Test strategy and high-level Acceptance Criteria	Document number and name	Test number and name	Archiving reference	Critical item Qualified [YES, NO, N/A] Justify in "Comments" if N/A	Comments

Appendix 4: CARA and Verification Planning Tools Templates

1. Requirement Traceability Matrix

Some companies use a Requirement Traceability Matrix (RTM) for each URS to demonstrate how the user requirements are addressed in the design documentation.

The RTM is useful for the Design Qualification and may be combined with the CARA into one combined matrix.

2. Design Qualification Report

CARA is used during Design Qualification to confirm, that critical aspects are sufficiently covered and risks are mitigated to an acceptable level.
The output of CARA step 2 is often captured in a Design Qualification report.

Design reviews for the requirements not linked to a critical aspect/CPP can be documented in a separate report containing the design discussions and agreements between customer and supplier for these requirements.

Appendix 5: Change Management and Deviation Management Template

The templates in this section can be used to facilitate Change Management (see section 6.4) and Deviation Management (see section 6.5). It is important, that the way, how these templates are used, is agreed and documented upfront (e.g. in the PQP).

The Change Management form is mainly intended to stipulate change proposals to approved documents in the area of scope (adding or deleting of verifications), acceptance criteria, procedures or test situations, if applicable. It similarly can be used to stipulate changes to agreed design ("engineering change request").

Non-conformities during inspection and verification can be captured either in the Deviation Form or the Punch List. It might be helpful to use the Deviation Form for tests related to critical attributes (CQA, CPP, CTQ) to allow orchestrated corrective action.

Appendix 5: Change Management and Deviation Management Template Examples

Change Request Form

Title:	
Change # ID:	
Project Name:	
System reference:	
Activity:	

Observation (actual situation):
Should be (planned situation)
Proposed action (proposed change)
Risk from the change (to previous tests/qualifications or to product quality)
Risk Mitigation (suggested actions to minimise or eliminate the risk)

Author: Name: Function:	Signature:	Date:
Reviewer: Name: Responsible User:	Signature:	Date:
Approved: Name: Quality Responsible	Signature:	Date:

Appendix 5: Change Management and Deviation Management Template Examples

Deviation Registration Form

Deviation No.:	Project Activity:	Date/ initials creator:
Test:		
Deviation:		
Responsible for solving:	Name/ department:	☐ Critical ☐ Uncritical
Deadline for solution:	Date:	
Planned and agreed measures:		
Results:		
Deviation solved/closed ☐ Yes ☐ No	Name/ department/ date	Signature:
Approved	Name/ department/ date	Signature:
Approved	Name/ department/ date	Signature:

Appendix 5: Change Management and Deviation Management Template Examples

Punch List

Project ID:		Project Name:	
Customer:		System ID:	

Open issues							Closed issue	
Punch ID	Test ID	Description	Date	Corrective action	Responsible	Critical? (Y/N)	Reference	Responsible
Remarks							Closeout (date, sign)	

Appendix 6: Project Quality Plan (PQP) Template

A Project Quality Plan should be the basis for the cooperation between customer and supplier and regulate important aspects during the project. All verification activities, responsibilities and applicable procedures should be covered.

The following template example is based on a project where it was used as the joint Project Quality Plan (PQP) between customer and supplier throughout the project. This PQP example does not distinguish between the terms Installation Qualification vs. Installation Verification and Operation Verification vs Operational Qualification since the use of these terms depends on the pharmaceutical customer company's terminology.

Test activities are outlined in clause 5 and the scope of them should be described as agreed in the contract. It is up to the author if they are grouped, put in logical order, or follow a timeline.

Project Management activities may be added or outlined in depth as agreed in the contract.

The use of appendices is highly recommended, since the documents out of standard applications can be attached without reformatting.

A Project Quality Plan should be the basis for the cooperation between customer and supplier and regulate important aspects during the project. All verification activities, responsibilities and applicable procedures should be covered.

Appendix 6: Project Quality Plan (PQP) Template Example

Project Quality Plan

Project name xyz

Document number
Revision

Customer	xyz
Project ID	…
Project Name	
Site	
Unit/Equipment	

Project Quality Plan approval by <Supplier>				
Signs for	Name Title	Department Company	Date	Signature
Created by	Name xyz	Qualification Dept <supplier)	…	
Reviewed by		Project Manager <supplier>		
Approved by	…	Qualification Project Manager <supplier>		

Project Quality Plan approval by <customer>				
Signs for	Name Title	Department Company	Date	Signature
Approved by	Name xyz	…	…	
Approved by				
Approved by				

Appendix 6: Project Quality Plan (PQP) Template Example

Change log

Revision	Date	Responsible	Change description
xyz	dd-mmm-yyyy		Removal of xyz Adding of xyz
…			

Table of Content

1. References

No.	Reference title
[1]	Confirmation of order xyz date dd-mmm-yyyy
[2]	EC machinery directive 2006/42/EC
[3]	<supplier> Quality Management System
[4]	SOP-AG-06.012e: Qualification deviation procedure
[5]	SOP-AG-24.005e: Procedure for change control
[6]	SOP-AG-23.006e: Hand-written documentation for qualification

Appendix 6: Project Quality Plan (PQP) Template Example

No.	Reference title
[7]	Department handbook: Electro design and software development
[8]	GAMP Guide for Validation of Automated Systems in Pharmaceutical Manufacture 5
[9]	US 21 CFR Parts 11 & 210 & 211
[10]	EU GMP Annex 1 "Manufacture of Sterile Medicinal Products"
…	

2. Introduction

This document forms the plan for the <supplier> (in the following named <supplier>) qualification and validation related activities for development, manufacturing and testing of the manufacturing system xyz for customer xyz (in the following named <customer>) in project xyz…

The line will be manufactured at <supplier> facility in xyz and installed at <customer> in site xyz.

This plan has been produced according to reference [1] with reference to [9] by the <supplier> Qualification and Validation Department on behalf of <customer>. The document is part of the overall <customer> qualification activities for project xyz.

3. Scope

This document consists of

- a qualification plan section with qualification and validation related activities in combination with
- a project plan section, which includes details about the <supplier> project team, the deliverable documentation, and the planning activities with milestones. Time schedule changes will not lead to an update of the PQP. Further plans are issued by the project manager.

According to the agreed scope of supply (see reference [1 Confirmation of order]), the qualification and validation activities defined in this plan include a planning phase, a specification & design phase, and a testing phase.

4. Overview

The xyz line consists of the following types of machines:

<List all the machines, types and machine numbers of the line>

- Machine xyz type xyz
- Machine …

Appendix 6: Project Quality Plan (PQP) Template Example

The design of these machines complies with reference [2] EC Machine Directive. <supplier> is working with an internal quality assurance system that has been ISO 9001 certified/recertified (certificate is included in appendix 1). The ISO 9001 system with reference [3] forms the basis for all quality assurance activities of planning, development, design, manufacturing, assembly and testing for the <supplier> supply. Special GMP/cGMP requirements (references [10], [11]) requirements are taken into consideration and reflected in this plan.

The internal activities of <supplier> (producing internal specifications, reviews for the electrical and pneumatic drawings and the detailed machine layout reflecting the purchase order) and the definition of <supplier> internal work orders are not subject to customer approval.

The computer software development will be done according to the <supplier> internal development process [8], based on reference [9] GAMP.

5. Qualification Plan Section

5.1 Qualification and Validation Management

5.1.1 Good Documentation Practices

All documents from <supplier> related to qualification and validation documentation (project quality plan, qualification reports, specifications, test protocols and handwritten test results [6]) which includes also documentation version control, will be produced according to <supplier> internal SOPs

5.1.2 Deficiency and Deviation

Non-conformities, which will be found during qualification & validation testing, will be reported according to <supplier> SOP (see [4]) and classified as “Deficiencies” or “Deviations”. Installation-related non-conformities are labelled “Deficiencies” whereas operational non-conformities are labelled “Deviations”.

<Supplier> will make a proposal for the solution of a deviation in the <supplier> deviation sheet. If <customer> does not approve within 5 working days, <supplier> will continue with the qualification activities by using the proposed solution to finish the work in the given time schedule. In case that the approval cannot be given after these 5 days by <customer>, any additional testing needs to be ordered separately.

5.1.3 Changes during the Project Change Control

Changes during the qualification and validation testing shall be treated according to <supplier> QMS and SOP [5]. In the change control form the change has to be evaluated, whether a re-qualification will be necessary or not.

Appendix 6: Project Quality Plan (PQP) Template Example

5.1.4 Personnel

The execution of the qualification and validation tests will be done only by trained and instructed personnel.

5.1.5 Standard Operating Procedures

The qualification and validation tests will be executed by <supplier> according to supplier QMS.
The SOPs used are specified in the activity list (see Appendix 2).

5.2 Planning Phase

The planning activities are executed as follows:

Activity	Responsibility Supplier	Responsibility Customer
Produce Project Quality Plan	<supplier> Qualification Dept.	
Review Project Quality Plan	<supplier>	<customer> Quality Dept.
Approve Project Quality Plan	<supplier>	<customer> Quality Dept.

The planning of other supplier-internal activities and the definition of <supplier> internal work orders are based on the DIN EN ISO 9001 system and / or < supplier > internal procedures and not subject to customer approval.

5.3 Design Phase

5.3.1 Mock-up Meeting

The machines will be modelled with customized equipment in a wooden model.
Based on this wood model, an ergonomics study and process simulation will be carried out to define physical design and work positions. It should be noted that the mock-up meeting is not part of the qualification, but how the design review meeting serves to determine the design and is thus assigned to the engineering phase.

Activity	Responsibility Supplier	Responsibility Customer
Execution Mock-up	<supplier> Engineering Dept.	<customer>Technical Dept.
Produce Mock-up summary	<supplier>	…
Approve Mock-up summary	<supplier>	<customer>

Appendix 6: Project Quality Plan (PQP) Template Example

5.3.2 Design Qualification

The Design Qualification (DQ) will be exercised during a DQ workshop at <supplier> site. The suppliers design documents will be reviewed against the customer URS. A Design Qualification summary will be issued after the meeting, documenting the design documents used, the personnel involved, the decision-making process used, the open points and the result of the workshop.

Activity	Responsibility Supplier	Responsibility Customer
Execute DQ workshop	<supplier> Dept. (Engineering, Qualification dept...)	<customer>
Produce DQ summary	<supplier> Qualification Dept.	…
Approve DQ summary	<supplier> Qualification Dept.	<customer>

5.3.3 Requirement Traceability Matrix (RTM)

After issuing the Functional Specification, a draft version of a Requirement Traceability Matrix (RTM) will be written for each machine, showing the conformity of the specified functionality with the confirmation of order and the specification of <customer>.

After OQ testing these documents will be issued as final version.

5.4 Risk Analysis

After issuing the process flow diagrams, a draft version of a risk analysis (RA) will be written for each machine and will be sent to <customer>. Subsequently there will be a workshop with <customer> at <supplier> site. According to the critical points, necessary installation tests (IQ), functional tests (OQ), and integration tests will be identified.

5.5 Testing Phase

5.5.1 General

All single machines, their parts, and the complete line as well as the software will be part of a detailed test program during manufacturing and assembly at Supplier xyz's site, and after commissioning at <customer> site.

The test program includes the following

- <Supplier> Internal Testing for the complete line at <supplier> site consisting of:
  - Safety verification of mechanical items
  - Safety verification of electrical items

- Installation verification of documentation
- Installation verification of mechanical items
- Installation verification of electrical items
- Operational verification of mechanical items
- Operational verification of electrical items

- Internal hard- & software testing
- Disaster Recovery Testing at < supplier > site
- Customer Specific Factory Acceptance Test (CFAT): Testing of machine performance according to requirements (focus: technical & commercial) at supplier's site.
- Alarm and Function Testing for PLC & PC systems
- Commissioning Phase
- Customer Specific Site Acceptance Test (CSAT): Testing of machine performance according to requirements (focus: technical & commercial) at customer's site
- Calibration at <customer>
- Operational Verification (or OQ) at <customer>:
    - Alarm and Function Testing (controls testing): part of the GMP compliant Operational Verification (or OQ) of the line with focus on software functions of the line. Scope of testing will be based on the risk analysis results for the GMP critical functions only
    - Operational Verification Testing of the line with focus on the unit functions of the line
      at <customer>

5.5.2 Disaster Recovery Tests (DR)

Prior to the Factory Acceptance Test, the Disaster Recovery Tests (DR) will be executed.
The DR is the verification of the description on how the machine and line functions need to be recovered after terminal hardware failure has occurred.

Activity	**Responsibility Supplier**	**Responsibility Customer**
Produce DR plan	<supplier> Qualification Dept.	
Approve DR plan	<supplier> Qualification Dept.	…
Perform DR	<supplier> Qualification Dept.	
Document DR	<supplier> Qualification Dept.	
Approve DR results	<supplier> Qualification Dept.	<customer>

Appendix 6: Project Quality Plan (PQP) Template Example

5.5.3 Customer Specific Factory Acceptance Test (CFAT)

Prior to commissioning the <supplier> machines will be tested during Factory Acceptance Test (FAT) at <supplier> premises.

The final FAT-activities will be agreed and fixed with <customer>. The tests will be executed according to <supplier> SOPs.

The FAT plan must be approved prior to testing cf. the time schedule in Appendix 4. The test results will be documented and handed over to <customer> for approval at the end of FAT. After FAT the line will be delivered to < customer>.

The FAT activities are executed as follows:

Activity	**Responsibility Supplier**	**Responsibility Customer**
Produce FAT plan	<supplier> Qualification Dept.	
Review FAT plan		<customer>
Approve FAT plan	…	<customer>
Execute and document FAT		
Approve FAT results		<customer>

5.5.4 Commissioning Phase

During the commissioning phase at <customer>, the complete line will be assembled and connected to the site services (electricity, pressured air, etc.). At the installed machines informal start-up tests will be done to show that they are installed correctly and work properly.

5.5.5 Customer Specific Site Acceptance Test (CSAT)

The final Site Acceptance Test (SAT) activities will be agreed and fixed with <customer>. The tests will be executed according to <supplier> SOPs.
The SAT plan must be approved prior to testing (cf. the time schedule in Appendix 4). The test results will be documented and handed over to <customer> for approval at the end of SAT.

Appendix 6: Project Quality Plan (PQP) Template Example

The SAT activities are executed as follows:

Activity	Responsibility Supplier	Responsibility Customer
Produce SAT plan	<supplier> Qualification Dept.	
Review SAT plan	<supplier> Qualification Dept.	<customer>
Approve SAT plan	<supplier>	
Perform SAT	<supplier>	
Document SAT	<supplier>	<customer>
Approve SAT results	<supplier> Qualification Dept.	<customer>

5.5.6 Installation Verification (Installation Qualification, IQ)

The Installation Verification will be executed at the completely installed line according to < supplier > SOPs at < customer >. The activities with the corresponding <supplier> SOPs are listed in Appendix 2. The Installation Verification plan must be approved prior to testing cf. the time schedule in Appendix 4. The test results will be documented and handed over to <customer> for approval.

Activity	Responsibility Supplier	Responsibility Customer
Produce IQ plan	<supplier> Qualification Dept.	
Review IQ plan	<supplier> Qualification Dept.	<customer>
Approve IQ plan	<supplier> Qualification Dept.	<customer>
Perform IQ testing	<supplier> Qualification Dept.	
Produce IQ Report		
Approve IQ report	<supplier> Qualification Dept.	<customer>

Appendix 6: Project Quality Plan (PQP) Template Example

5.5.7 Calibration

After commissioning of the machines and prior to Operational Verification (OQ) all process critical sensors and measuring loops will be calibrated according to <supplier> SOP for the different equipment.

The calibration results will be documented and handed over to <customer> for approval

Activity	**Responsibility Supplier**	**Responsibility Customer**
Produce Calibration plan	<supplier> Qualification Dept.	
Review Calibration plan	<supplier> Qualification Dept.	<customer>
Approve Calibration plan	<supplier> Qualification Dept.	<customer>
Perform calibration	<supplier> Qualification Dept.	
Document calibration	<supplier> Qualification Dept.	
Produce calibration report	<supplier> Qualification Dept.	
Approve calibration report	<supplier> Qualification Dept.	<customer>

Appendix 6: Project Quality Plan (PQP) Template Example

5.5.8 Operational Verification Phase (OQ)

5.5.8.1 Alarm and Function Testing for PLC & PC Systems (AFT)

The Alarm and Function Testing for PLC & PC systems shows that all alarms of the machine and important system functions work properly with the correct machine/system reaction. The tests package is comprised of all of the alarms of the control system and includes also a set of standard checks of single system / machine functions.

It will be executed at the completely installed line according to <supplier> SOPs at <supplier> site. The test results will be documented and handed over to the < customer > for approval.

Activity	**Responsibility Supplier**	**Responsibility Customer**
Produce AFT plan	<supplier> Qualification Dept.	
Review AFT plan	<supplier> Qualification Dept.	
Approve AFT plan	<supplier> Qualification Dept.	
Perform AFT testing	<supplier> Qualification Dept.	
Produce AFT Report	<supplier> Qualification Dept.	
Approve AFT report	<supplier> Qualification Dept.	<customer>

Appendix 6: Project Quality Plan (PQP) Template Example

5.5.8.2 Operational Qualification (OQ)

The Operational Verification (OQ) will be executed according to <supplier> SOPs at the completely installed line at <customer> The OQ activities with the corresponding <supplier> SOPs are listed in Appendix 2.

The IQ testing and calibration must be finished, except the customer agrees to another proceeding. The OQ plan must be approved prior to testing. The test results will be documented and handed over to <customer> for approval.

Activity	Responsibility Supplier	Responsibility Customer
Produce OQ plan	<supplier> Qualification Dept.	
Review OQ plan	<supplier> Qualification Dept.	
Approve OQ plan	<supplier> Qualification Dept.	<customer>
Perform OQ testing	<supplier> Qualification Dept.	
Produce OQ Report	<supplier> Qualification Dept.	
Approve OQ report	<supplier> Qualification Dept.	<customer>

5.6 Requirement Traceability Matrix (RTM)

After issuing the Functional Specification, a draft version of a Requirement Traceability Matrix (RTM) will be written for each machine, showing the conformity of the specified functionality of the confirmation to order and the specification of <customer>.

After OQ testing these documents will be issued as final version.

5.7 Training

As part of the <supplier> supply staff training will be supplied at <customer> site. After the training will be completed, all participants will receive a training certificate.

Appendix 6: Project Quality Plan (PQP) Template Example

6 Project Plan Section

6.1 Project Organisation

The following personnel form the project team:

Responsibility	Name	Department
Project Manager	Name xyz	PM Dept
Project Manager Qualification	…	Qualification Dept.
Mechanical design		
Electrical design		
Software PLC		
Software HMI		
…		
Documentation		
Assembly		

As a standard <supplier> sub-contractor for the software application, < sub-supplier 1> will also be involved in this project. <Sub-supplier 1>, located in < sub-supplier 1 site >, has a formal quality management system and is audited periodically by < supplier >.

6.2 Scope of Documentation

The documentation to be delivered according to the order confirmation (ref. [1]) is listed in Appendix 3.

6.3 Project Activities

The project activities will be listed in a time schedule (see Appendix 4), issued by the <supplier> project manager. This schedule will be produced using project software xyz (Gantt Chart) and updated following the project progress. It will include

- Project milestones
- Timelines

Appendix 6: Project Quality Plan (PQP) Template Example

7 Glossary.

Abbreviation	Definition
CFAT	Customer Specific Factory Acceptance Test
CSAT	Customer Specific Site Acceptance Test
…	…

8 Appendices.

Appendix	Content
Appendix 1	ISO 90001 Certificate (2 pages)
Appendix 2	IQ/OQ/AFT - Activity Listing (xy pages)
Appendix 3	Deliverable Documentation (xy pages)
Appendix 4	Project Time Schedule (xy page)

Appendix 7: Qualification Documentation Template

The following section contains one test example from Operational Verification (or OQ) from a project where the testing is done by the supplier with approval by the customer.

In general, the test sheets contain the following sections:

- **Title of test**
  This should be unique and unambiguous and allow tracing back to TM (and Qualification Plans, if used)

- **Test number**
  This is typically a consecutive numbering within a defined activity (e.g. within a FAT)

- **Test run no.**
  In case that multiple runs are foreseen, a numbering (or any other ID) should be used to identify them

- **Test objective**
  Short description on what is intended with the test (might be solely mentioned in the template or taken from a previously issued document (e.g. Test Matrix or Qualification Plan))

- **Test prerequisites**
  Lists items or conditions that need to be available to allow a successful execution of the test

- **Test procedure**
  Description on how to perform the test. This can either be done in the template or a reference to a SOP can be given
  It should be noted, that the procedure should be written (and verified upfront) to allow a knowledgeable (SME) and trained person to achieve equal results when repeating the test

- **Acceptance criteria**
  Precise and unambiguously with respect to scope and test procedure; if multiple acceptance criteria are part of the test, they should undergo an individual assessment

- **Test result(s)**
  Foreseen to capture the test results (handwriting or prints of electronically captured data, that belongs to the test); requires multiple lines, if several acceptance criteria are in scope of the test

- **Comments section**
  Open space that can be used to record things that happened during the test execution; if not used it needs to be crossed out (oblique stroke)

- **Final test assessment**
  This is for the assessment for the performed test and related tests and includes a review that the procedures has been followed, compliance to Good Documentation practice, and meeting the acceptance criteria

Appendix 7: Qualification Documentation Template Example

- **Test result raw data**
  The test sheet should also have a defined area for recording of test results, this could be a blank sheet (also for attaching print outs) or better predefined to guide the tester on what to record and how

In addition, all test documentation contains the following

- Customer
- Page numbering (page x of y)
- Doc ID

Notes:
Coloured boxes on the test example sheets are for explanation and reference only. They are not in the real project example documentation.
The example is dual language English/German. It is from a German supplier and the project language is English.

Appendix 7: Qualification Documentation Template Example

Test Plan

<customer>	Test of xyz			Page xyz of xyz
Test Procedure	SOP xyz		Test number	
Test identification	(mark with X or N/A)		Test [ ]	Retest [ ]
Test Objective	xyz			
Test Prerequisites	Machine Type	xyz		
	Machine no	xyz		
	Test location	(e.g. factory or customer site location)		
	Format	xyz		
	Number of items tested	xyz		
Test Results				Yes/No
Acceptance Criteria	xyz			
Comments				
	Yes/no		Date	Initials
Results comply			xyz	xyz
Results approved			xyz	xyz
Comments				

Appendix 7: Qualification Documentation Template Example

< customer >	Check of counting process / *Überprüfung des Zählprozesses*		Page / *Seite* 1 / 2
Test procedure / *Testdurchführung*	SOP-AG-07.008e/d	Test number / *Testnummer*	OQ 3

Test identification / *Test Kennzeichnung*	Mark with [X] or [n.a.] / *Kennzeichnung mit [X] oder [n.a.]*	Test	X	Retest	n.a.
Test objective / *Testziel*	This test checks the reliability and accuracy of the object counter in production mode.				
Test prerequisites / *Testvoraussetzungen*	Machine type / *Maschinentyp*: < manufacturing system >				
	Machine no / *Maschinen Nr.*: < manufacturing system ID >				
	Test location / *Testort*: < customer site >				
	Format / *Format*: 2R				
	Number of containers to be tested / *Anzahl der zu testenden Behältnisse*: 300 ≥ n ≥ 200				

Test results / *Testergebnisse*		Yes – No / *Ja - Nein*
Acceptance criteria / *Akzeptanzkriterien*	Max. fault of counting: < 1/n	
Comments / *Kommentare*	Acceptance criteria are met 08. Jan. 2020 dl. Attachment 1: Batch report 08. Jan. 2020 dl.	

	Yes / No *Ja /Nein*	Date / *Datum*	Initials / *Kurzzeichen*
Results comply / *Ergebnisse entsprechen*	Yes	08. Jan. 2020	dl.
Results approved / *Ergebnisse genehmigt*		08. Jan 2020	

Appendix 7: Qualification Documentation Template Example

< customer >	Check of counting process / *Überprüfung des Zählprozesses*		Page / *Seite* 1 / 1
Test procedure / *Testdurchführung*	SOP-AG-07.008e/d	Test number / *Testnummer*	OQ 3

Test results / *Testergebnisse*

Name of counter / *Name des Zählers:* Good objects

		Test 1	Date / Initials	Test 2	Date / Initials	Test 3	Date / Initials
Counter reading / *Zählerstand*	Start / *Start*	0	08. Jan. 2020 cl.	0	08. Jan. 2020 cl.	0	08. Jan. 2020 cl.
	End / *Ende*	216	08. Jan. 2020 cl.	216	08. Jan. 2020 cl.	216	08. Jan. 2020 cl.
Difference / *Differenz*		216	08. Jan. 2020 cl.	216	08. Jan. 2020 cl.	216	08. Jan. 2020 cl.
Number of containers / *Anzahl der Behältnisse*	Person 1	216	08. Jan. 2020 cl.	216	08. Jan. 2020 cl.	216	08. Jan. 2020 cl.
	Person 2	216	08. Jan. 2020 Ba	216	08. Jan. 2020 Ba	216	08. Jan. 2020 Ba
Results of persons 1 and 2 fulfill acceptance criteria / *Ergebnisse Person 1 und 2 erfüllen Akzeptanzkriterium:* Yes/ja / No/nein		Yes		Yes		Yes	

Comments / *Kommentare*

Counter was reset before each test cl. 08. Jan 2020

08. Jan. 2020 cl.

		Date / *Datum*	Initials / *Kurzzeichen*
Comments by / *Kommentare von*		08. Jan. 2020	cl.

Appendix 7: Qualification Documentation Template Example

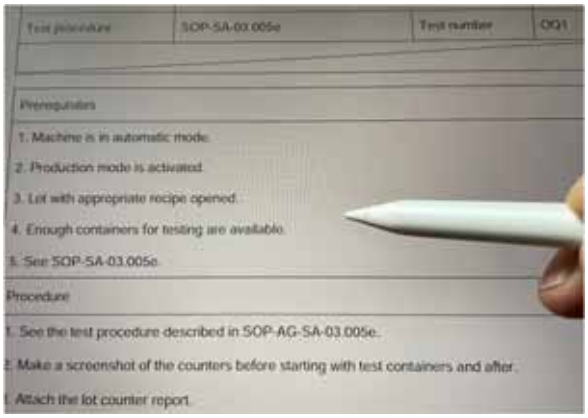
Electronic documentation of test and qualification activities may be executed similar to paper-based execution of tests, but on a digital media, e.g., a tablet computer. Some companies have started to use the electronic documentation more integrated with images, recordings and other types of documentation that supports the test documentation. For example, the use of electronic tablets enables attachment of images of an inspection or video of a test run.

The qualification activities can be streamlined significantly with such tools and the following example is from a project where an iPad-based application using Adobe Acrobat as the software tool was used to plan, execute and document the testing of a machine for pharmaceutical application, both during Factory Acceptance Test (FAT) and Site Acceptance Test (SAT).

There are many benefits of using digital electronic test descriptions and documentation and the following examples serves as inspiration from projects that used these tools. The examples are performed with a simple Adobe Acrobat based tool that has been used by both, pharmaceutical customers and suppliers. Requirements related to data integrity and regulations may apply, depending on the specific application.

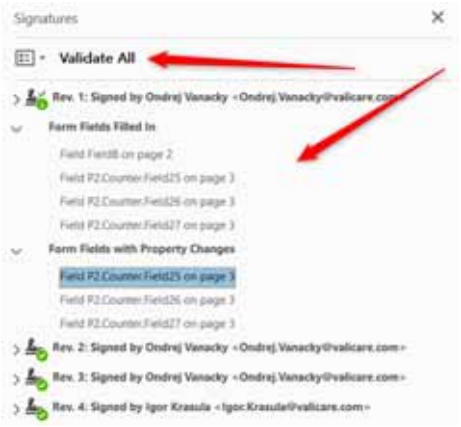
Appendix 6 Product Quality Plan (PQP) includes an example of a project test plan with paper-based test results and here is an example of the same test using an electronic recording method. Although the two formats look comparable, the electronic version enables a number of automatic recordings on e.g., the date, time, user ID etc. as desired. None of this is possible with traditional paper-based test and qualification activities.

Appendix 7: Qualification Documentation Template Example

Paper-based test execution	Electronic test execution
	

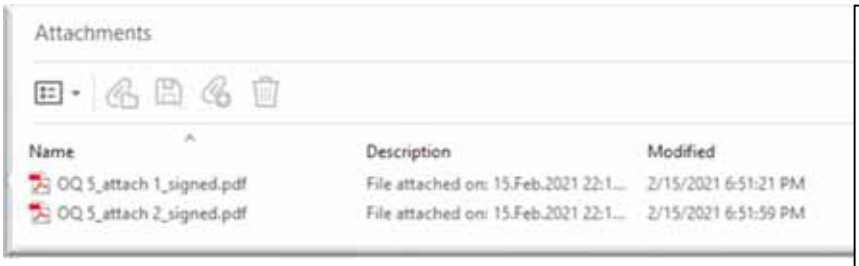
Appendix 7: Qualification Documentation Template Example

During test execution the digital document can be expanded for the specific test details, acceptance criteria, signatures etc. as illustrated below:



Validation function for actions performed within electronic qualification record pairs actions with their executor.
This feature is intended to check if actions/records were created in the correct order and signed by the correct personnel.

During the execution, digital images and other recordings may be added as follows:



Attaching of raw data (e.g. pictures, audio, video files or recordings of various measuring devices) in their original format to the electronic record is another advantage that leads to increased transparency and efficacy during qualification execution.

The addition of files also enables a 'hybrid' approach where some of the documentation is paper based. In this example the documents are stored in an electronic document management system that keeps track on the progress, the records and the approvals associated with the test and qualification activities.

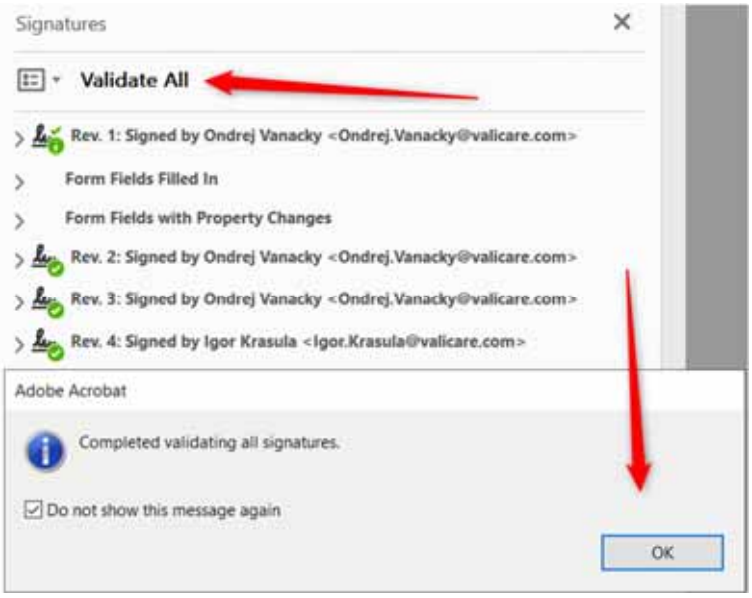
Appendix 7: Qualification Documentation Template Example

The electronic completion and signatures of a set of test activities is illustrated below:

Use of commenting/release functions eases the user traceability, readability of records and together with the e-signature provides requested level of reliability in terms of who its author/reviewer is.

The figure shows current practice, when attaching paper attachments with the arrow pointing to an electronic solution - the predefined electronic stamp equipped with the e-signature.

The electronic tools can be enhanced with several more options as illustrated below:



Function for signature validation to determine the authenticity of the signature's digital ID certificate status and document integrity.
A valid document gives you assurance, that content was not manipulated after being signed.

Appendix 8: Remote Testing of GMP Manufacturing Systems

Introduction to Remote Testing

For interaction between customer and supplier in the engineering phase and for testing activities, the physical presence at the supplier's plant or the customer's site may require significant resources on travel and time for the involved teams on both customer and supplier side.

Therefore, based on a trustful relationship between customer and supplier, it can make sense for activities to be carried out remotely rather than in person, at least for part of the teams. The remote activities can be combined with IT tools like video link, teleconference etc. so that only some of the customer representatives are present, and others are only connected. There are many different tools commercially available and the exact approach must be discussed and clarified in advance by all parties involved. If at least one person is not participating in an onsite joint activity and must be hosted remotely to the rest of the party, this condition is called "*hybrid situation*". Hybrid situations are more difficult than remote situations because all requirements to a joint communication and common understanding need to be considered.

During the coronavirus pandemic several remote activities were the only way out of the traveling restrictions. Since then, the use of remote activities such as supplier audit, Design Qualification workshop, factory acceptance tests (FAT), site acceptance tests (SAT), IQ tests, OQ tests and many others, can be planned case to case as a supplement to physical presence and the exact approach should be decided from a risk-based perspective.
Legally there are no formal requirements on physical presence, but inspectors expect detailed planning and documentation of remote activities. This is unlike formal regulatory inspections (e.g., GMP inspections by regulatory authorities or audit of suppliers of pharmaceutical product ingredients) where physical presence is the regulatory necessity.

The purpose of this chapter is to list advantages, disadvantages and prerequisites, to raise the acceptance of organizing remote and hybrid remote activities in a project. It is the goal to enable remote activities -if properly prepared, executed and documented – to be fully accepted by all parties.

Checklist for planning Remote or Hybrid Remote Testing

As stated in the introduction, there are many forms of remote or hybrid remote activities. The following "points to consider" have been collected to help customers and suppliers finding the most suitable way to perform successful remote or hybrid *testing* activities. These points can be used as inspiration for other remote or hybrid activities.

Before Remote Testing

Before starting the activity, the following points should be considered:

- Definition of a clear program including planning, duration, way of interaction during the remote testing execution
- Discuss which tests can be performed in advance and which results can already be derived from this testing
- Who will participate (assembly engineers, software engineers, mechanical engineers, etc. need to be available during the remote test duration); time difference between customer and supplier

location must also be considered

- Scope of the remote testing; 100% remote, partly remote or partly in physical presence
- Which documented evidence is needed
- Define IT-platform and IT exchange and communication tools
- Training or presentation of the technical infrastructure and telecommunication devices
- At least one pre-test is recommended prior remote follow-up for testing of all technique, connections, etc. (avoid hick-ups when start of remote testing execution)
- Level of interaction between supplier and customer– ranging from customer only getting test results and documentation presented by supplier up to fully witnessed tests by customer via video feed
- In case of video-feed, clarification of how many cameras, in which positions, and for which tests should be used
- Confirmation if according to local supplier country regulations staff executing the tests must sign a declaration accepting that they are being video recorded (General Data Protection Regulation),
- For each test at least one acceptance criterion (according to agreed testing protocol) needs to be defined
- Discussion and agreement on how to show and view the actual execution results

- Discussion and agreement how documentation should be reviewed
  - Which documents (incl. technical documentation, certificates & specifications) should be reviewed and in which format and maturity level?
  - Whether to send all documents by scan to the client before or during remote testing or whether to use an agreed electronic way of reviewing (see chapter electronical documentation in this guideline)
  - how are supplier internal testing results documented and in which way will these be part of the testing
  - How often should (intermediate) test result forwarded to the customer
  - How to handle test results approval, when supplier or customer representatives are witnessing the test especially when contemporaneous signature is expected
  - Discuss and agree between customer and supplier how raw data generated during remote testing is treated.
- Discussion how to clarify content questions during test execution (normally conversations on the sidelines)
- Clarification of possible language issues upfront
- Having an alternative plan in hand in case of technical difficulties
- Clarification in advance how to handle deviations and changes during test execution
- Discuss and agree on the staff that is performing the tests, personnel of the customer following and reviewing the performance as well as experts jumping in, in case of deviations or questions
- A system should be discussed and agreed on for indicating items having passed the test and for listing deviations
- Management of deviations should be described and approved by customer before the testing starts.
- Prepare the story book for each single day
  In case video-feed throughout testing has not been chosen or is not possible, consider in the beginning of day 1 to execute a virtual “tour” of the equipment even if no actual testing is done during this event.
- It should be discussed between customer and suppliers how tests should be executed to make leveraging possible (e.g. from FAT to IQ) regarding possible limitation due to remote testing

Starting and Progress of Remote Testing

- Fill in the story book for each day
- The testing should start with a common web conference where the agenda for the day(s) is presented, players are introduced, and timelines are discussed. Dependent on the agreed process this may be a daily agenda item.
- Use of supplier’s protocol approved by customer (early integration of the customer into the process is very helpful).
- Make customer familiar with the manufacturing system(s) and all the details - live demonstration of the running system(s).
- Run remote testing by teleconference using webcam if agreed.
- Review tests executed by supplier (protocol can be executed by supplier before the remote testing

and then a spot check – for which the methodology must be defined in advance - should be done by customer during remote testing). Alternatively, execute all tests directly during remote testing).

- Review of test documentation at the end of each day in a daily wrap up meeting.
- Consider live feed giving customer team access to HMI child monitor – i.e. all HMI communication directly visible to customer.
- All generated test proofs must be attached to the protocol by the supplier.
- Raw data generated during remote testing must be scanned and sent to the customer. The original paper or raw data should be sent, the latest, at the same time of manufacturing system delivery.
- Alternatively, an agreed way of electronic testing could be used to avoid paper and accelerate the advantages of remote testing (see also Chapter electronic documentation of the Guide)
- Microphones should be muted. Only the speaker should be unmuted otherwise there will be too many side noises. Noise cancelling would be desirable maybe using headphones.
- Check the possibility to use reality devices (bodycam, integrated webcam and glasses).

End of Remote Testing

- Questions & Answers session with the customer.
- Approval by the customer of all registered deviations and changes detected during remote testing.
- Executive summary report reviewed and approved/signed by customer.
- Authorization (or not) by customer for manufacturing system(s) shipment to customer’s facility.

Appendix 9: Categorisation of Manufacturing Systems: Template

As described in Section 7 some pharmaceutical companies use a categorisation of manufacturing systems not only to standardise the qualification approach for certain system types but also to reduce the qualification efforts in case of simple and/or less quality critical systems. There are several possibilities on how to do the categorisation and definition of the work scope. In this appendix, one method is shown, but other methods, like a matrix approach or a decision tree approach can be applied too. This is based on the individual needs and preferences. The example is based on the three categories as introduced in section 7:

A. *Standard* (Commercial off-the-shelf systems (COTS))
B. *Configured* (COTS with specific configuration of, e.g., sequence, setpoints, timers, etc.)
C. *Customised* (designed for the specific customer with specific requirements, that is not available commercially, due to a special application, technology innovation etc.)

On top of these three categories the dimensions related to the intended use of the system and knowledge on the supplier should be considered, e.g., as described in the example below.

For a tabular approach, the three aspects of "system criticality", "Intended use criticality", and "supplier related criticality" are assessed in combination as typically done in the qualitative risk assessments. Each of three aspects are first classified as "High", "Middle" or "Low"-critical dependent on the following aspects:

- System criticality, considering:
  - system complexity (e.g. customised systems)
  - grade of automation (e.g. configured systems)
  - grade of standardisation (e.g. standardised systems)
- Intended use criticality, considering:
  - impact on product and process
  - ease of operation
  - interaction with other systems
  - knowledge and experience of the pharmaceutical manufacturer
- Supplier related criticality, considering:
  - experience, history, quality
  - system experiences (numbers produced)
  - standardised manufacturing process

Each single item is classified individually for the system using the terms "low", "medium" or "high" for assessing the overall criticality. The level of effort, formality, and documentation should be commensurate with the level of risk.

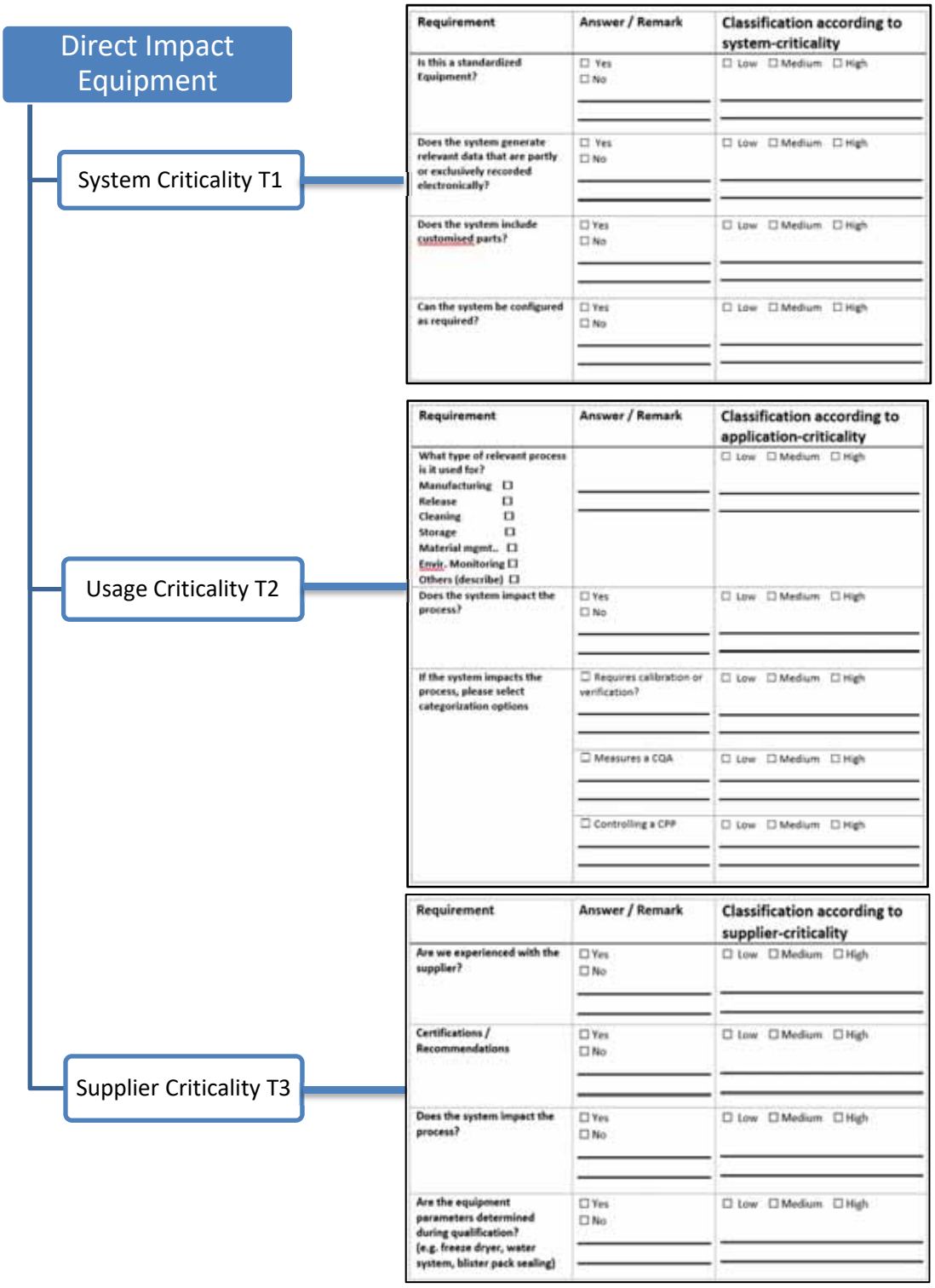
Additionally, it is possible to categorise each manufacturing system into a superordinate system group like A, B and C. It leads to a superordinate and harmonized categorisation within the company, as manufacturing systems of the same intended use and supplier will be handled similar.

After qualification and release of a system the categorisation could also be used for the periodic evaluation of qualification status and if necessary, the determination of the frequency for requalification

e.g., category C = each year, category B = every 2 – 3 years, category A = every 5 years, for practical requalification the same extent of OQ / PQ could be used. The approach could also be used ongoing if changes are initiated impacting the intended use or causing modifications (life cycle approach).

The example shown in figure xx gives a deep insight into the attribute-specific criticalities and can be used to get a better overview of the criticality of a specific system and what kind of qualification activities must be performed. Also, you can justify your decision and use the detailed format to generate specific test plans covering those parts that are relevant for the intended use.

Appendix 9: Categorisation of Manufacturing Systems: Examples



Requirement	Answer / Remark	Classification according to system-criticality
Is this a standardized Equipment?	☐ Yes ☐ No	☐ Low ☐ Medium ☐ High
Does the system generate relevant data that are partly or exclusively recorded electronically?	☐ Yes ☐ No	☐ Low ☐ Medium ☐ High
Does the system include customised parts?	☐ Yes ☐ No	☐ Low ☐ Medium ☐ High
Can the system be configured as required?	☐ Yes ☐ No	☐ Low ☐ Medium ☐ High

Requirement	Answer / Remark	Classification according to application-criticality
What type of relevant process is it used for? Manufacturing ☐ Release ☐ Cleaning ☐ Storage ☐ Material mgmt.. ☐ Envir. Monitoring ☐ Others (describe) ☐		☐ Low ☐ Medium ☐ High
Does the system impact the process?	☐ Yes ☐ No	☐ Low ☐ Medium ☐ High
If the system impacts the process, please select categorization options	☐ Requires calibration or verification?	☐ Low ☐ Medium ☐ High
	☐ Measures a CQA	☐ Low ☐ Medium ☐ High
	☐ Controlling a CPP	☐ Low ☐ Medium ☐ High

Requirement	Answer / Remark	Classification according to supplier-criticality
Are we experienced with the supplier?	☐ Yes ☐ No	☐ Low ☐ Medium ☐ High
Certifications / Recommendations	☐ Yes ☐ No	☐ Low ☐ Medium ☐ High
Does the system impact the process?	☐ Yes ☐ No	☐ Low ☐ Medium ☐ High
Are the equipment parameters determined during qualification? (e.g. freeze dryer, water system, blister pack sealing)	☐ Yes ☐ No	☐ Low ☐ Medium ☐ High

Appendix 9: Categorisation of Manufacturing Systems: Examples

In addition to the system criticality, this example considers the criticality associated with intended use and supplier as well. Every company must decide whether these items will be taken into consideration or not. They can have an impact on a project, e.g. after several projects with the same (known and experienced) supplier, the risk decreases.

The final average evaluation may be done in a simple list, like shown below:

System Risk (T1)	***Usage Risk (T2)***	***Supplier (T3)***	***Total Risk***	***Result***
Cat A (low)	*Simple (low)*	*Well known (low)*	*Low*	*Use standard test template xxx for qualification*
Cat B (medium)	*With Cal. (middle)*	*Famous and certified, but not known here (middle)*	*Middle*	*Use standard test template for standard system parts. Develop a system specific protocol for configured options*
Cat C (high)	*CPPs (high)*	*Unknown (high)*	*High*	*System specific test protocol*

Appendix 10: Pharmaceutical Customer and Supplier Contract Checklist

This appendix is to cover the quality related aspects of a contract, which is normally done in writing before a project starts. Details and extent of a contract between pharmaceutical customer and supplier should be adapted to the complexity and the scope of supply. Duplications or repetitions within the contract or with other related documents should be avoided. When the contract has the status of a Quality Assurance Agreement (QAA), commercial aspects - such as prices, payment terms, delivery times, etc. – should whenever possible not be covered in the same document.

Regarding details and extent of the contract, following could be a first basic rule, when using the categorization system as proposed in chapter 4.2 of the main guide:

The contract details and extent for the supply of equipment category A (not-critical, typically highly standardized COTS systems, no critical process function) shall be minimal. In such a case, studying the contract documents should not cause more effort than studying the purchase documents or brochures.

The contract details and extent for the supply of equipment category B (low criticality, typically configured COTS systems with some influence on processes and product quality) shall be adapted to the specific risks and the ultimate impact of this manufacturing system to patient safety.

The contract details and extent for the supply of equipment category C (critical systems, customized and designed for the specific customer with specific requirements, having considerable influence on processes and products) has to be specific and detailed enough to mitigate or minimize the risks on processes and products and has to consider all relevant additional services in relation with the supply. Risks must be considered in connection with the ultimate impact of this manufacturing system to patient safety.

The contract details and extent for the supply of equipment category A, B or C depends very much on whether the services related to the supply are to be performed on site within the GMP-production environment or not. If such services on site are included, the contract has to consider this in all details – following a risk-based approach and keeping the impact of this service to patient safety in mind.

It is strongly recommended that before contract implementation the pharmaceutical manufacturer–- performs process, product and project related risk analysis respectively from which the level of supervision including life cycle activities are derived, forming the basis for the later contracts with the suppliers. This includes but is not limited to the definition, which GMP-tests and documents should be prepared by the supplier, where and when the customer will witness tests or will review test-protocols and many more. This can also be an advantage for the pharmaceutical manufacturer, as unnecessary repetition of tests can be avoided (“single-test-approach”).

Appendix 10: Pharmaceutical Customer and Supplier Contract Checklist

The following list shows contract contents which - depending on the result of the risk analysis - should be part of the contract and which considers not only the one-time delivery but also the life-cycle related services as far as appropriate:

(1) Responsibilities and demarcation of tasks, to ensure:
  1.1. that effective process is available for maintaining and calibrating critical equipment
  1.2. Appropriate reviewing and approving of validation protocols and reports, if agreed as part of the scope of services
  1.3. Deviation and escalation management is in place and followed
  1.4. Delimitation of responsibilities/ tasks/ functions for all individual activities

(2) Equipment deliverables and scope of services, also considering in the life cycle of the system

(3) Timelines and frequencies especially for life-cycle deliverables and activities

(4) Scope of documentation of the supplier's QMS

(5) The obligation to permit supplier audits

(6) Requirements & documentation on subcontracting and subcontractor's QMS (for critical parts, if applicable)

(7) Information exchange management

(8) Languages, versioning, general review and approval process of all kinds of documents

(9) General work conditions

(10) Provision of materials, devices, work facilities

(11) Environmental, Health and Safety aspects

(12) Contact information

(13) Organization charts

(14) Training requirements

(15) List with definition of terms and abbreviations used in common documents

(16) Confidentiality obligations, performance and guarantee values

(17) Raw data handling practices including recording and storage

(18) Regulations in force and marketing authorization details as far as relevant

In general, suppliers shall be aware of the principles and guidelines of good manufacturing practice as far as applicable and should support inspections carried out by the competent authorities as far as needed; arrangements for audits should be agreed upon if applicable, including permission to audit outsourced activities, performed by the Contract Acceptor and his mutually agreed subcontractors.

Appendix 11: Electronic Documentation (ED)

Aspects to be considered when implementing electronic documentation (ED)

Legal	**Legal stakeholder requirements** to be heeded.	1. GMP & Good Documentation Practice 2. Legal requirements 3. Local (e.g., company or country specific)
Supplier-Customer Interfaces	**Various feasibility aspects** between supplier and customer to be considered.	4. Understanding & willingness 5. Adaptability 6. Customer-Supplier management (e.g., audits)
	User management to be defined for processes and flows, systems, etc.	7. User groups definition/agreement/assignment 8. User rights definition/agreement/ assignment
	Interfaces between customer and supplier to be checked for feasibility and agreed.	9. Email correspondence 10. Online cloud solutions 11. External drives 12. Using same system (VLMS/eDMS)
	Possible Data types intended for exchange to be checked for feasibility and agreed.	13. Raw Data (e.g., video, pictures, device logs) 14. Documents: Scans/Originals 15. Using same system (VLMS/eDMS)
Workflows	**Workflows based on the intended use & circumstances** to be checked for feasibility and agreed.	16. Uni- / multi-directional 17. Conditional 18. Registered/Monitored
	Review & approval, to be checked for feasibility and agreed.	19. Electronic signatures 20. Standard/built in application 21. Qualified/ validated 22. Commercially available third-party applications
	Protection of approved content and possible correction of previously entered content to be thought through.	23. Editing protection when signed 24. Signature revocation/invalidation function or other means of entry correction 25. Data Integrity and ALCOA++ principles
System Lifecycle	**Capacity & robustness** of the system to be considered for intended use.	26. Capacity of handling 27. Processes & various qualification/validation steps 28. Stability 29. Accessibility
	Scalability & modularity of the system to be considered to fit for purpose.	30. Modularity 31. Downsize scope for smaller projects (e.g., complex line vs. laboratory equipment)
	Use of computerized systems with all its aspects to be considered if feasible for all involved parties. (even sub-suppliers)	32. Hardware (Laptops, tablets, smart phones) 33. Software (availability, compatibility, protection)
	Advanced automatic functions with intuitive tools and operations might be considered to ease and improve content creation.	34. Interactive forms 35. Use of templates 36. Pre-defined content 37. Execution of tests in the system 38. Data Management
	Archiving requirements of the created records, logs, flows, etc. must be considered.	39. Physical /Digital /Dual 40. Definition of retention period 41. Automatic Deletion after retention period
	Backup of archived but also “in use” data to be considered.	42. Data Back-up Routine
Qualification / Validation	**Qualification & Validation** of relevant aspects for GMP industry to be considered.	43. System needs to be validated (eDMS/VLMS) 44. Data Integrity and ALCOA++ requirements should be tested prior use 45. Personnel training, equipment, IT infrastructure should be also qualified/validated
	Management of qualification & validation activities with all its constraints to be considered within the whole project management lifecycle.	46. Project Management Lifecycle: 47. Initiating/ planning/ executing/ monitoring controlling/ closing 48. Project Management constraints: 49. cost/ time/ scope/ quality/ resources/ risk

Appendix 12: Technical Glossary

Term	Explanation
Calibration	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 (EU GMP)
Commissioning	A well-planned, documented and managed engineering approach to the start-up and turnover of facilities, systems, utilities and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations. (ISPE C&Q Baseline Guide version 2)
Critical Aspects (CA)	Functions, features, abilities and performances or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety (ASTM E2500-20)
Critical Design Elements (CDE)	Design functions or features of an engineered system that are necessary to consistently manufacture products with the desired quality attributes. Examples of automation design functions include alarms and data management. Examples of engineering design features include components, instruments, and materials of construction. CDEs are identified and documented based on technical understanding of the product CQAs, process CPPs and equipment design/automation. CDEs are verified through C&Q (ISPE C&Q Baseline Guide version 2)
Critical Process Parameter (CPP)	A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (ICH Q8)
Critical Quality Attribute (CQA)	A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product. (ICH Q8)
Design Qualification (DQ)	The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose (EU GMP Annex 15)
Design Review(s)	Planned and systematic reviews of specifications, design, and design development and continuous improvement changes performed as appropriate throughout the life cycle of the manufacturing system. Design reviews evaluate deliverables against standards and requirements, identify problems, and propose required corrective actions (ASTM E2500-20)
Factory Acceptance Test (FAT)	An Acceptance Test in the Supplier's factory, usually involving the Customer (IEEE).
Functional Specification or Functional Design Specification (FDS)	A document that specifies the functions that a system or component must perform (often part of a requirements specification) (ISO/IEC/IEEE 24765-2010)

Term	Explanation
Good Engineering Practice (GEP)	Engineering and technical activities that ensure that a company manufactures products of the required quality as expected (e.g., by the relevant regulatory authorities). Good engineering practices are to ensure that the development and/or manufacturing effort consistently generates deliverables that support the requirements for qualification or validation (Wikipedia)
Human Machine Interface	Mostly touch screens or any other kind of monitor connected to a control system or computer to provide the needed information to the user
Installation Qualification (IQ)	The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations (EU GMP Annex 15)
Manufacturing System(s)	Elements of pharmaceutical and biopharmaceutical manufacturing capability, including manufacturing systems, facility equipment, process equipment, supporting utilities, associated process monitoring and control systems, and automation systems, that have the potential to affect product quality and patient safety (ASTM E2500)
Operational Qualification (OQ)	The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges (EU GMP Annex 15)
Performance Qualification (PQ)	The documented verification that systems and equipment can perform effectively and reproducibly based on the approved process method and product specification (EU GMP Annex 15)
Process Qualification (PQ)	Confirming that the manufacturing process as designed is capable of reproducible commercial manufacturing (FDA Process Validation Guidance)
Process Performance Qualification (PPQ)	The process performance qualification (PPQ) is the second element of Stage 2, process qualification. The PPQ combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches. A successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected (FDA Process Validation Guidance)
Qualification	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 (EU GMP, ICH Q7)
SAT	An Acceptance Test at the Customer's site, usually involving the Customer (IEEE)
Subject Matter Expert (SME)	Individuals with specific expertise in a particular area or field (for example, quality unit, engineering, automation, development, operations and so forth) (ASTM E2500)
Supplier	Organisation that provides a product or a service (ISO 9001:15)
Quality Risk Management	A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle (ICH Q9)

Term	Explanation
Subject Matter Expert(s) (SME)	Individuals with specific expertise and responsibility in a particular area or field (for example, quality unit, engineering, automation, development, operations, and so forth) (ASTM E2500)
User requirement specification (URS)	The set of owner, user and engineering requirements necessary and sufficient to create a feasible design meeting the intended purpose of the system (EU GMP Annex 15)
Validation	Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (EU GMP)
Verification	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 (ASTM E2500)