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Good Practice Guide
- PUBLIC DRAFT 2 -

Integrated Qualification and Validation

A guide to effective qualification based on Customer - Supplier Partnership

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Table of Contents

Appendices

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Public Draft 02	1 Oct 2019	Second draft issued for public comments	Public Draft
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1 Introduction

1.1 History and Background

The purpose of this guide is to streamline Qualification and Validation (Q&V) by enabling a better cooperation and mutual understanding between customers and suppliers on projects related to pharmaceutical manufacturing systems, including equipment, facilities and utilities. The Q&V activities can be very time consuming, expensive and causing delay of new products to market, facility expansions etc.

It is about close involvement of suppliers in pharmaceutical projects in order to enable a more effective project execution by reducing multiple testing throughout the qualification activities and to enable a more streamlined approach to qualification and validation. However, it must be emphasized that the ultimate legal responsibility for qualified equipment and validated processes cannot be delegated but shall be retained by the pharmaceutical manufacturer.

US FDA's Process Validation Guide from 2011 and the European GMP Annex 15 on Qualification and Validation from 2015 are both based on the quality risk management principles in ICH Q9, the quality guideline from International Council of Harmonisation (ICH). Both FDA and EMA are open for more effective approaches to commissioning, qualification and validation that may involve strong customer-supplier cooperation. This guide is based on these regulations and does not create new legal obligations for suppliers nor for customers beyond the regulations.

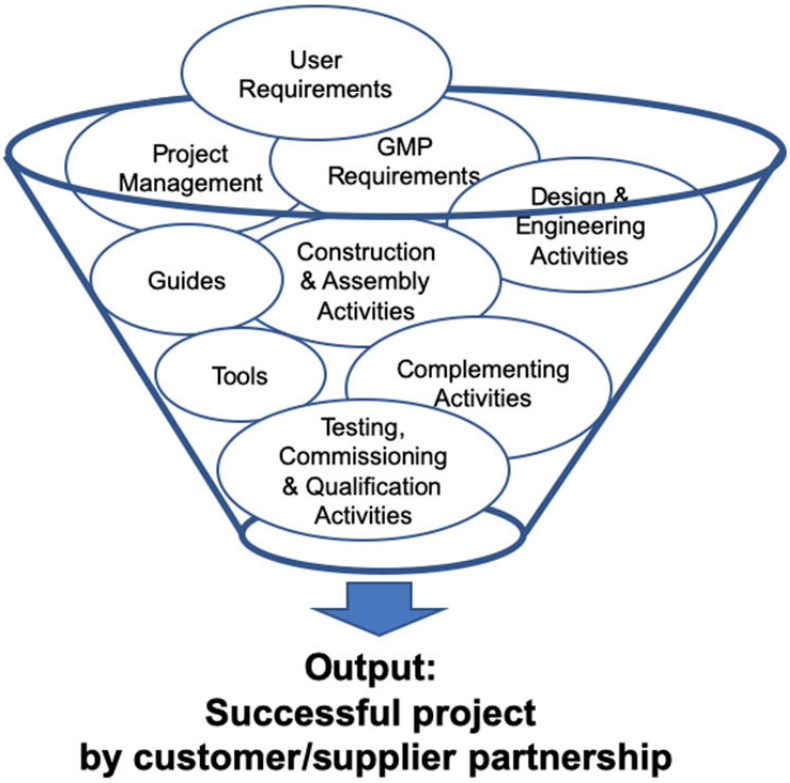
The principle is that Good Engineering Practice in design, construction, testing and documentation should establish the basic qualification documentation. During the cooperation between pharmaceutical customers and suppliers both win most if they share knowledge in an integrated approach using the supplier's understanding of their equipment and the customers of their products, requirements and regulatory context of their application.

Suppliers are often directly or indirectly covered by many of the GMP regulations. Pharmaceutical companies have their own quality systems, technical requirements and procedures and they often differ significantly between companies, thereby complicating the cooperation between 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 from the standard ASTM E2500 on Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment.

This guide uses the term "Integrated qualification and validation" for approaches that includes quality risk management, scientific product- and process understanding and close cooperation between customers and suppliers. It is based on an integrated 'science- and risk-based approach' as successful projects require good cooperation between the pharmaceutical customers and their suppliers throughout the project. It covers a number of activities and documents as illustrated below in figure 1 and supports enhanced flexibility of qualification activities compared to traditional qualification projects.

This guide uses the ASTM E2500 term “manufacturing system” for equipment, facilities and utilities related to pharmaceutical manufacturing based on the definition 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” (ASTM E2500-13).

Figure 1



The term “Supplier” is used throughout this guide as “A supplier is a person, company, or organisation that sells or supplies something such as goods or equipment to customers” (Collins Dictionary) and may include relevant subcontractors 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 qualification activities so it can be demonstrated that the equipment and systems are “fit for intended use”. This is part of the qualification package that enables fast and sufficient qualification and maintenance. Other benefits are:

- Increased understanding of the project, the process and the technical solutions involved
- Reduction of time and effort to achieve compliant systems
- Change and Configuration management during design and testing
- Less need for expensive and time-consuming re-testing
- Reduced risk of creeping escalations of requirements by using established tools and methods
- Better transparency of projects to ensure delivery on time, according to budget and the agreed quality standards
- Common language, terminology and documentation expectations

This guide is published by an authoring team (ECA 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 requirements to bring the industry forward - with mutual benefits for both parties. The guide will be updated based on feedback from its readers, users and regulators. Annex 13 includes a feedback form which should be used for both general and specific comments and suggestions for the next version of this guide.

2 Scope of this Guide

The guide is applicable to new manufacturing systems, including equipment, facilities and utilities and its principles may also be used for projects executed in existing facilities and systems such as upgrade or expansions.

It covers the project expectations and requirements for both the pharmaceutical customers and the suppliers of equipment, utilities, systems and solutions to the pharmaceutical industry as well as engineering and consulting suppliers in order to support mutual understanding and successful cooperation.

The main purpose of the qualification activities described in this guide is to demonstrate that a manufacturing system is fit for intended use and operates as intended throughout its whole operational life-cycle, described in EU GMP Annex 15 (2015) and in FDA's Process Validation guide (2011).

Sections in this guide about the Essential Joint Activities, Customer Activities and Supplier Activities are intended to facilitate good cooperation between customers and suppliers. The cooperation must be based on the fact that the legal responsibility for qualified equipment and validated processes belongs to the pharmaceutical customer and cannot be delegated.

The guide builds on existing guidelines, standards and company case studies in order to stimulate progress and best practice sharing to support better practices regarding commissioning, qualification and validation of pharmaceutical equipment, systems and facilities. It does not specifically cover computerised systems because this subject is well covered in the GAMP Guide (Good Automated Manufacturing Practices) family of guidelines from ISPE and others.

This version of the guide is an update from the previous public draft version 1 with the title "Good Practice Guide for Modern Qualification", released in September 2018. There are several changes to the previous version, including a new section 5.8 about the link to Process Validation (EU) and Process Performance Qualification (US), and this guide enhances its scope into Integrated Qualification and Validation, as reflected in the title of this version. The team behind the guide welcomes all feedback and encourage the readers to use the form in Appendix 13 for this.

3 Outline of the Approach

3.1 Introduction

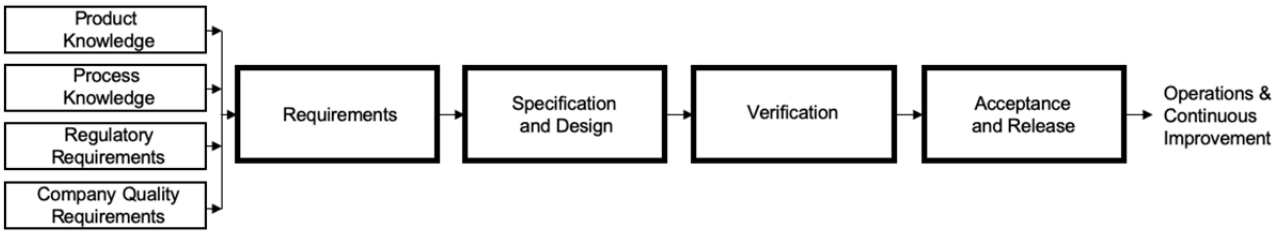
Pharmaceutical companies must comply with Good Manufacturing Practice regulations, including requirements concerning the manufacturing systems, including the processes, facility, equipment and utilities. Suppliers are directly or indirectly covered by many of these regulatory requirements. Moreover, all pharmaceutical companies have their own quality systems which often include technical requirements and procedures.

This guideline is based on a project model that avoids duplications of tests by customer and supplier using a cooperation model that enables

- An efficient cooperative project management process
- Avoidance of duplications of tests by assessing previously performed successful tests; re-use of supplier testing results provided acceptance criteria etc. are as previously agreed
- 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-critical deviations

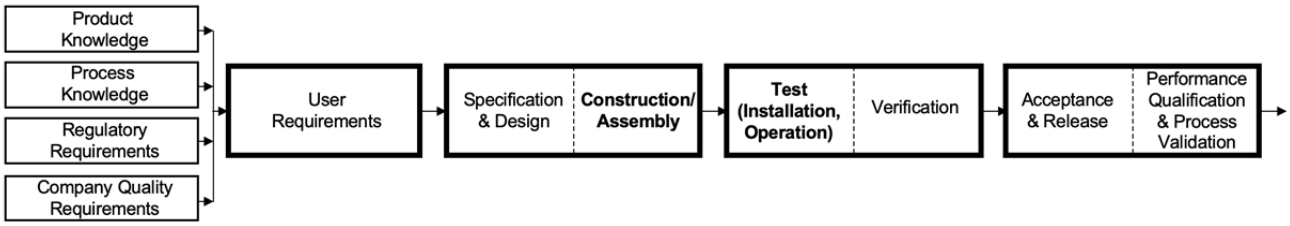
The overall project flow builds on the original ASTM E2500 project life cycle model, which is illustrated in figure 2.

Figure 2 ASTM E2500 project life cycle model



To clarify the cooperation between customers and suppliers the model has been enhanced to illustrate the supplier-related activities during the project execution, thus emphasizing the User Requirements, the assembly and construction activities following the specification and design and the test activities that precedes the verification activities as illustrated in Figure 3. These are typically conducted by suppliers and are important for the activity descriptions in the supplier section of the guide. The additions of typical supplier activities (construction/assembly and Installation/operation test) are emphasised in bold in the figure. The life cycle is enhanced to cover the Performance Qualification and Process Validation activities, as described below and in EU GMP and PIC/S GMP Annex 15 Qualification and Validation.

Figure 3 Enhanced ASTM E 2500 Model

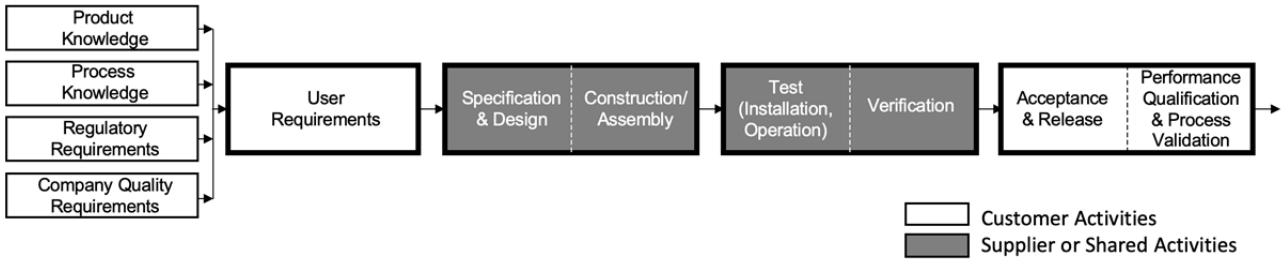


3.2 Cooperation between Customer and Supplier

The cooperation between the customer and supplier(s) of pharmaceutical manufacturing equipment, facilities and utilities can simplify qualification and validation activities significantly if done right. 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 leveraged by the pharmaceutical customer in order to demonstrate that the system is designed, built and tested in a way that ensures that it is “fit for 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 follow good testing and documentation practice. An example of a typical split of main responsibilities is illustrated in Figure 4.

Figure 4 Enhanced ASTM E 2500project life cycle model with customer/supplier focus areas



Suppliers to the pharmaceutical industry generally have a very deep understanding of their equipment and their use. However, even the best supplier needs to understand that customers might have different quality systems, different applications and different approaches to fulfil the GMP requirements. Projects should be based on mutual understanding of the expertise on both the customer and the supplier side.

An effective qualification project depends on a number of principles such as:

- **Customer-supplier partnership cooperation:** A good cooperation intent and team-spirit between the customer and supplier organisations should be based on clear contractual and commercial terms and may include mutual incentive elements in order to stimulate win-win solutions between customer and supplier. The coordination activities on both sides should start early and be continued throughout the project, including e.g. how to behave in a cleanroom during the installation process, how to operate in classified areas or how to ensure a clear transition from project into operations.
    - Special topics related to the products and the processes of the customer should be clarified early, so that important product attributes such as heat stability, light stability, humidity stability of the product etc. are discussed early in the project.
    - The risk assessments in this guide mainly focuses on Quality Risk Management but other risk aspects such as Health-, Safety and Environmental requirements should also be handled with risk management principles.
- **Cross-functional teamwork**: A good cross-functional cooperation on both the customer organisation and the supplier organisation, especially an effective cooperation between the technical side (engineering/manufacturing/process etc.) and the quality side within the customer's organisation. For example, the quality function may delegate responsibly to an internal engineering department or other areas of expertise within the company.
- **Subject Matter Experts (SMEs):** Specialists, who cover the most important areas of expertise such as product, process 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 cross-functional team and meet frequently at cross-functional project meetings for e.g. risk assessment, design review, qualification planning etc. The term is used based on the definition in the ASTM E2500 standard.
- **Good Engineering Practices** (GEP) consist 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. GEP underpins activities in day-to-day operations and planning of a pharmaceutical business. GEP documentation can be leveraged to support qualification and verification work. For a full description see ISPE Good Practice Guide on Good Engineering Practice (2008).
- **Good Documentation Practices:** Clearly understood and agreed practices should be used for both customer and supplier activities so that solutions and documentation can be used as part of the qualification package in the pharmaceutical company's final qualification documentation. Handwritten entries should be made in clear, legible, indelible way. This includes that 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. For a full description, see EU GMP volume 4, Part 1, Chapter 4 Documentation.

- **Company standards and guidelines:** Pharmaceutical companies often 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 guideline as a reference for mutual agreement on how to cooperate and document the project outcomes as part of the overall qualification package.

- **Single test approach:** The use of Good Engineering Practices, including Good Documentation Practices, is a prerequisite for achieving an overall qualification status where the quality activities and documentation require little or no repeat testing in order to demonstrate the "fitness for intended use" of the manufacturing system.

- **Life cycle approach: The pharmaceutical customer must control the critical aspects of their** manufacturing systems during the full life cycle of the product and 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 validated status etc. should be assessed. The life cycle may involve the supplier on issues such as spare parts, maintenance, service agreements etc.. The ICH guidance ICH Q12 on "Technical and Regulatory Considerations for Pharmaceutical Product Life Cycle Management" may have an influence when implemented in GMP regulations, e.g. in the EU, US and Japan.

In some cases, depending on the project, other special approaches may apply in order to support a cost effective approach to qualification and validation:

- **Worst Case Approach: Tests should be planned with worst-case scenarios in mind. Based on a risk** assessment a pragmatic approach to realistic worst-case situations should be used, considering both the severity, probability and detectability of the worst-case scenarios. Worst-case consideration on process parameters (e.g. highest temperature, biggest volume etc.) may be useful for cost-effective test planning

- **Fast Track Approach:** In fast-track projects where the project execution time plays an important role these elements are especially important. For example, the time to develop and agree on the user requirement specifications and the test methods and documentation are typically on the 'critical path' of a project so an early agreement on these may have significant impact on the whole project. Besides, a close cross-functional cooperation between production, engineering, quality etc. in the customer organisation is very important to ensure an effective project execution under fast-track conditions.

3.3 Risk Management in the Project

Pharmaceutical companies are expected to use risk-based approaches in their quality activities. The regulatory expectations have changed towards so-called "Science- and Risk-based principles" based on a scientific understanding of the pharmaceutical product and processes. 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 based on Quality Risk Management principles. Like the ASTM E2500 standard this is based on two primary principles of the guideline ICH Q9 Quality Risk Management (ICH, 2005):

- *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".* Besides Annex 15 states: *"A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes."*

This guide applies these principles and the concept of pharmaceutical quality risk management 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 before the project, preferably 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 as described in Section 5.2.

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

3.4 Project Cooperation Model

The project model in this guide starts with the initial user requirements and follows the project steps of specification & design, construction/assembly, testing and verification activities of a project. The specific requirements depend on individual project circumstances and should be adjusted to the project. The model includes risk assessments and especially a quality risk management (QRM) approach to the design and verification. Quality risk management gives important input concerning risk identification, analysis and mitigation, including optional re-design, in order to minimise the risk to an acceptable level. There should be a close linking between the design and verification activities on one side and risk assessments, design qualification and change management and all activities should follow Good Engineering Practice and Good Documentation Practice etc. so documentation of e.g. tests at supplier's premises are understandable and valid, even after transfer to the customer's site.

3.5 Roles and Responsibilities

The customer is responsible for the planning of the commissioning and qualification activities with support of the supplier. The roles and responsibilities should be clearly defined among the involved suppliers, engineering companies and other involved parties as part of a Project Quality Plan.

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. The pharmaceutical customer typically has an overall Validation Master Plan (VMP) or similar in which the qualification activities are defined. It typically describes the overall qualification and validation approach from a customer perspective.

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

Subject Matter Experts can take a lead role in the design, manufacturing, commissioning and qualification activities within their area of expertise and responsibility. Subject matter experts within similar areas of expertise on both the customer and supplier side typically are able to discuss testing methods, acceptance criteria, solutions etc. on a qualified level. This can ensure a more competent, cross-technical approach to solutions as well as to commissioning and qualification activities.

Generally, the customers SMEs have responsibility for the overall qualification & validation planning and execution whereas the suppliers SMEs have main focus on the detailed design, construction and testing activities to ensure that the system meets the user requirements and is tested to ensure correct installation and function as intended.

Examples of subject matter experts 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.
- Process SME: e.g. chemist, pharmacist, process engineer etc. involved in process aspects, including process knowhow, material selection, overall design, risk management etc.
- Technical SME or Equipment SME: e.g. mechanical, utility or HVAC engineer with special knowledge in technical utilities, cleanrooms, risk management etc.
- Automation SME: e.g. experts in the area of design, implementation, testing and documentation of automation- and IT systems, including network, data integrity, configuration management for computerized systems etc.
- Operation SME: e.g. manufacturing personnel with knowledge concerning the operation of the system or facility including sampling, writing of SOPs, training of operators etc.

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

4 Essential Joint Activities

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

- **User Requirement Specification (URS)**: The URS is the customers responsibility. It is further described in sections 5 and 6 as well as in Appendix 2. An agreed URS is the starting point for the supplier activities in order to ensure a successful project.

- **Risk Management:** Risk management and especially Quality Risk Management (QRM) activities including risk assessment and risk mitigation are important joint activities since risk elements should be identified, assessed and managed, including mitigated where possible. The customer is responsible for carrying out a quality risk assessment of the manufacturing processes and for assessing their impact on the finished pharmaceutical product, but several risk management activities and risk mitigations should be executed jointly, as described below. A number of quality risk management methods and tools are described in the ICH Q9 document on Quality Risk Management.

- **Project Quality Plan (PQP):** Customer and suppliers should agree on a common Project Quality Plan. Often customers and suppliers have more detailed plans for their quality activities, but the overall PQP should be a high-level document which is the agreed basis for the common quality activities of the project. They should be agreed between the customer and supplier(s) to ensure the mutual understanding of the quality activities, depending on the size and complexity of the project.

- **Project Management:** A successful project execution requires a close cooperation between customer and supplier as regards to project management activities, including activity planning and follow-up on both technical and quality-related topics. Both the customer and the supplier will be involved in project management activities (e.g. documentation, deviation and change management) and the cooperation between them is a core element for successful projects.

- **Design Review and Design Qualification (DQ)**: The Design Qualification should ensure and document how the requirements from the URS are met in the design and specifications as described in section 6.7. The customer is responsible for the design qualification and should involve the supplier in order to ensure implementation as agreed. There may be a number of design review meetings during a project depending on its scope and approach, but there should be a clear conclusion on that the design meets its intended use and related GMP requirements. The scope of the DQ may be captured in a Requirement Traceability Matrix (RTM) as described in appendix 6. The relevant test scopes may be documented in a Test Matrix (TM) and Critical Aspects Risk Assessment (CARA) as described in appendix 7 and 4.

- **Commissioning and Acceptance Testing (FAT and SAT):** The Factory Acceptance Test (FAT, executed in the supplier's factory before shipping to the customer), the Site Acceptance Test (SAT, executed at the customer's site after installation) and other commissioning activities should be clearly defined and agreed, including the documentation requirements, procedures and acceptance criteria.

This guide uses the terminology “Installation Testing” for the ‘static’ test of installation, piping, wiring etc. and “Operational Testing” for the ‘dynamic’ test of functions, controls, alarms etc. to emphasize that the associated documentation (test plans, test documentation, certificates, pictures etc.) may be used to demonstrate Installation Qualification (IQ) and Operational Qualification (OQ) activities within the pharmaceutical company.

Some companies use slightly different terminology, e.g. “Pre-functional Testing” for installation test and “Functional Testing” for operational test to clarify that they use the same approach on GMP-related and non-GMP-related manufacturing systems.

The test documentation may be fully or partly used by the customer to demonstrate Installation Qualification (IQ) and Operational Qualification (OQ) or the customer may decide to do additional activities and/or call them IQ, OQ or IOQ activities, depending on company preferences.

The EU GMP Annex 15 on Qualification and Validation is flexible on content and combination of IQ and OQ, OQ and PQ or PQ and Process Validation. The US FDA Process Validation Guide uses the term Process Performance Qualification (PPQ) similar to the EU GMP definition of Process Validation and is also flexible on the specific approach to qualification, without going into detailed requirements.

- **System Acceptance and Release:** The final System Acceptance and Release for subsequent process validation activities is an important step as it formally acknowledges that the manufacturing systems are “fit for intended use”. This may not involve the supplier, depending on the project approach.

  An important part of this is the availability of the supplier documentation as outlined in the original project scope agreement. It is sometimes called the Supplier Turnover Package or Vendor Turnover Package (VTOP) that is handed over from the supplier to the 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.

5 Customer Activities

5.1 Introduction

In a pharmaceutical customer organisation, a project is typically conducted according to a Validation Master Plan (VMP) which also covers the qualification and validation activities. Within this framework, a project starts with a set of customer activities related to the planning and concept of the manufacturing systems scope, before addressing one or more suppliers with a Request for Proposal document. A User Requirement Specification (URS) which states the essential elements of quality need to be built in at this stage and any process and GMP risks mitigated to an acceptable level. The URS should be agreed with the supplier and be a point of reference throughout the qualification and validation life cycle.

Both customers and suppliers benefit from an URS that is built upon a good understanding of the pharmaceutical product, processes and requirements associated with the project scope, possibly documented in a Product- and Process User Requirement Specification (PPURS). This guide assumes that the customer's initial requirements are defined in internal - probably confidential - documents and specifications regarding the product and process aspects. These may not be shared with suppliers but should provide useful basis for the quality risk management activities and the identification of Critical Aspects. Appendix 1 includes a template example of a PPURS.

The customer may supplement the product- and process information in the URS with various technical standards, GMP requirements and specification document outlining company technical requirement to the design if applicable

Before selecting and contracting the supplier there should be a thorough evaluation. Appendix 3 Supplier Evaluation shows an example of a supplier evaluation approach. Supplier audits, references etc. should be considered and documented depending on the supplier cooperation history, capabilities and the criticality and complexity of the project.

Once the supplier is identified the following activities should ideally be planned in joint workshops during which the original URS requirements are further developed with the supplier(s) in order to define a mutually understood set of project requirements that will become the agreed URS and the point of reference throughout the projects.

Depending on the scope of services agreed between the customer and the supplier the European GMP regulations regarding outsourced activities (EU GMP Volume 4, Part 1, Chapter 7 Outsourced Activities) may apply, including the expectation that the pharmaceutical quality system of the customer should include the control and review of any outsourced activities and that customer is ultimately responsible to ensure processes are in place to assure the control of outsourced activities, incorporating quality risk management principles.

There must be a written contract between the customer and the supplier which clearly establishes the duties of each party. The customer is responsible for assessing the legality, 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 regarding data integrity. Also, the mutual understanding of terminology and definitions between supplier and customer is essential for project success, including impact of key regulatory terminology. The

customer should be clear which pathway should be followed (EU or FDA regulation or both) and prepare accordingly early in the project, preferably as part of a Project Quality Plan (PQP).

The customer activities in this guide should be conducted with a life-cycle perspective including the use of operational experience to challenge and update the previous risk assessments.

Many suppliers have been part of customers' qualification activities or at least Factory Acceptance Test (FAT), Site Acceptance Test (SAT) or other commissioning activities that their document standards fully meets pharmaceutical expectations e.g. quality documents, good documentation practice, change management and other requirements for documentation of qualification activities that demonstrates the "fit for intended use" of pharmaceutical suppliers.

The pharmaceutical customer must take responsibility especially for the agreed User Requirement Specification and Performance Qualification. Most other activities can be directed by guidelines, standards, supplier documentation and Good Engineering Practices.

5.2 Quality Risk Assessment and Critical Aspects

The Quality Risk Assessments are part of the quality risk management activities and should identify and manage risk associated with:

- product quality and process robustness
- general regulatory requirements
- specific GMP requirements
- other technical and operational aspects with potential impact on product quality

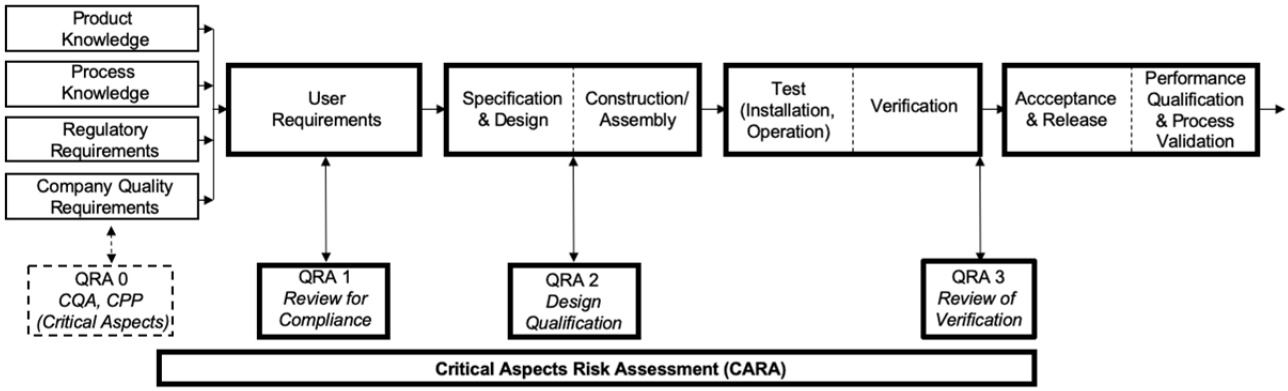
This guide uses the term Critical Aspects according to the ASTM E2500 definition as 'functions, features, abilities, and performance or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety. They should be identified and documented based on scientific product and process understanding" (ASTM E2500-13).

The communication between the customer and the supplier regarding identified risks and related activities are an important part of Quality Risk Management. The project approach of this guide builds on repeated risk management activities including quality risk assessments with associated risk mitigation activities that may be adapted by each company and to each project.

The related supplier activities are described in section 6 and include a number of activities during design, including the development of functional specifications that are an important part of the basis of the risk assessment activities. The relations between the URS and the design documents may be described in a Requirement Traceability Matrix as described in section 5.5. and illustrated in Appendix 6.

Figure 5 illustrates the associated quality risk management activities of the science- and risk-based qualification approach. The starting point is the quality risks associated with the pharmaceutical product and process, based on the development of the pharmaceutical product (QRA 0). Follow-up activities relates to the User Requirements (QRA 1), the Design Qualification (QRA 2) and the Verification (QRA 3). The risk management approach may be adapted according to the project needs.

Figure 5 Project life cycle model and Quality Risk Management Activities



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

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

The initial Quality Risk Assessment should be based on product and process knowledge and initial control strategy, GMP requirements and other critical requirements, including Critical Quality Attributes (CQAs) of the pharmaceutical product, Critical Process Parameters (CPPs) and possibly Critical Material Attributes (CMAs) of the involved process steps. Other critical requirements may be included. Some companies use an overall Product- and Process User Requirement Specification (PPURS) to capture the essence of the control strategy and the quality risk assessment from the company's product development activities, see Appendix 1.

The initial Quality Risk Assessment can be used as part of a System Risk Assessment for each manufacturing system in a specific project in order to identify and document which equipment affects CQAs of the product and the related CPPs and Critical Aspects.

Quality Risk Assessment 1 (QRA 1): URS Review for Compliance

The URS should be reviewed and possibly adjusted to ensure that risk mitigation and GMP compliance have been addressed sufficiently based on risk management principles.

Quality Risk Assessment 2 (QRA 2): Design Qualification

The design of the manufacturing systems should be reviewed by the customer and supplier with regard to a sufficient quality risk mitigation and GMP compliance, including formal acceptance of residual risk elements. 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

Quality Risk Assessment 3 (QRA 3): Test Review & Review of Verification Reports

After the completion of the testing activities, the test results of critical aspects are reviewed and documented in order to accept and release the system for performance qualification and/or process validation activities. If IQ and OQ are conducted as separate activities, they may also be concluded at this step (provided that they were successful or that outstanding issues have been concluded).

The above activities, the decisions taken, and the related documentation may be captured in a Critical Aspects Risk Assessment (CARA) matrix which contains identification and traceability of the critical aspects, their failure modes, the identified risk control mechanisms and the related activities of the project execution. The CARA matrix is a life cycle document that enables full traceability of the risk management of the Critical Aspects of the manufacturing system. The CARA matrix is described in Appendix 4.
Depending on the complexity and size of a project, CARA activities and related documents may become difficult to handle in which case more advanced risk management software support tools may be helpful.

The customer and the supplier should carry out reviews, risk assessment and change management together but the final responsibility for review, acceptance and documentation lies with the pharmaceutical customer company. In case of outsourced activities these tasks must be clearly defined.

Changes concerning the scope, technical questions, time etc. should result in a review and might lead to an update of the risk assessment. The review and test activities should be agreed upon and described with a clear mutual understanding of roles and responsibilities between customer and supplier.

Pharmaceutical customers have different organisational structures and the roles of departments such as production, engineering, quality etc. depends on the company. This guide assumes that projects are conducted in close cooperation between internal organisations, e.g. production, engineering, quality etc. The cooperation internally, including the cooperation on quality-related issues regarding testing and qualification is important in order to ensure an effective project execution. This internal cooperation is also important to ensure a successful cooperation with supplier(s).

Reflecting the aspects of the manufacturing system and the process the quality risk assessment should ensure, that the Critical Quality Attributes (CQAs) of the product (and Critical Material Attributes (CMAs) of raw materials and intermediates) and critical process parameters (CPPs) of the pharmaceutical manufacturing process are identified. These attributes and parameters have a potential impact on quality and compliance and therefore have a potential impact on the patient. The overall concept is illustrated in Appendix 11 Integrated Qualification and Validation (The “Red Thread”).

The identification and management of Critical Aspects of manufacturing systems is based on the ASTM E2500 standard guide and the EU GMP Annex 15 on Qualification and Validation. Some industry guidelines have added additional notions to the concept of Critical Aspects.

The ISPE Baseline Guide on Commissioning and Qualification edition 2 (2019) has added the notion of “Critical Design Elements” (CDEs) which are “design functions and features that are necessary to consistently manufacture products with the desired quality attributes. Examples of automation design functions include alarms and data management. Identified and documented based on technical understanding of the product CQAs, process CPPs, and the equipment design/automation. CDEs are verified through C&Q” (ISPE C&Q, 2019).

The PDA Technical Report 54-5: “Quality Risk Management for the Design, Qualification, and Operation of Manufacturing Systems”, PDA 2017 has added the notion of “Critical Aspects Design Elements” (CADEs) as “the design elements that directly impacts the Critical Aspect and detection controls, and design elements that have the ability to discover or determine the existence/presence or fact of a hazard. These design-based risk controls constitute CADEs”.

Such additional notions may be useful for qualification projects, depending on the specific project, pharmaceutical customer, suppliers etc. and the use of them may be decided as part of the planning of the Quality Risk Management approach of the specific project.

5.3 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 elimination (or mitigation) of GMP-related risks to an acceptable level.

The URS should be based on the intended use of the equipment and ideally a starting point can be a Product and Process User Requirement Specification (PPURS) outlines the critical aspects of the URS as well as the GMP requirements. A PPURS typically covers one product throughout the whole facility or section of the facility, whereas a URS is typically developed for each main equipment, utility or system and is described in Appendix 2.

The URS should be a point of reference throughout the project life cycle and is especially important for the final Performance Qualification in order to demonstrate that the user requirements can be met, and that the manufacturing systems are fit for intended use. It should be written in the way that the requirements can be tested. Initially the customer's URS is often like a 'wish-list' of what the customer desires, including both 'need to have' and 'nice to have' items. To reach a final URS it has to be precise and explicit on what has to be accomplished ('must have') and it has to be agreed between customer and supplier. The URS may refer to a Project Quality Plan (PQP) or outline activities, documentation to be delivered and roles and responsibilities.

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. It should be written and approved by the pharmaceutical company so it can be used as a point of reference during the project execution (including qualification activities) as long as the equipment, system or facility is used for commercial manufacturing. Appendix 2 contains a template example for a URS.

5.4 Supplier Assessment

The supplier selection should include an assessment of the supplier's ability to deliver the expected technical scope of supply, documentation, testing and procedures for Good Engineering Practice. This selection should be part of the Quality Risk Management.

This assessment should include but is not limited to the supplier's capabilities for provision of expected technical documents, design documentation, test plans, testing protocols, test execution, deviation management, change management. These may be part in the supplier's quality management system. Therefore, the supplier evaluation is an important part of the 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 customer should involve relevant subject matter experts in the supplier evaluation, depending on the scope of the equipment, system or service. 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. After the selection of the supplier there should be a quality agreement for the project, typically in the Project Quality Plan (PQP).

The supplier evaluation should be based on a risk assessment resulting in the evaluation of the supplier's capabilities including the supplier's ability to deliver the expected documentation, tests and other Good Engineering Practice including fulfilment of relevant industry standards.

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 leveraged into final qualification
- Expected level of oversight and participation that the customer or 3rd parties should perform
- Expected level of additional testing and documentation to be performed by the customer or 3rd parties

These conclusions should be reflected in the Project Quality Plan.

An description of a supplier assessment is described in appendix 3.

5.5 Requirement Traceability Matrix

The Requirement Traceability Matrix is based on the URS requirements, and links to the engineering design documents (e.g. PID, Data Sheets, Component List, Functional Specification) to verify that the URS have been met in design. It is used for the verification that requirements in the URS have been met in the design. It typically includes supplier information and is used in workshops and meetings to track compliance with requirements and meeting acceptance criteria as well as to evaluate and improve the design.

Appendix 6 contains a template example of a Requirement Traceability Matrix (RTM).

5.6 Test Matrix

The Test Matrix is one of the useful tools for commissioning and qualification activities. It is a planning and follow up tool for installation and operational testing. It may include acceptance criteria and allows tracking of activities and their documentation. Proper completion of testing and related documentation including signing off can be verified. The starting point of a Test Matrix is during or immediately after Design Qualification.

The Test Matrix should be used by both the customer and the supplier, but the document is normally owned by the customer and follows the project until all acceptance tests are completed. Appendix 7 contains a template example of a Test Matrix (TM).

5.7 Verification

Verification should demonstrate that the manufacturing systems are fit for their intended use. All tests should have been successfully conducted and documented according to Good Documentation Practice, change management and deviation management.

A so-called “punch list”, “open items list” or Open Point List (OPL) may be used to capture deviations and non-conformities. Appendix 8 includes template examples for deviations, changes and punch list for inspiration. Both supplier and customer should agree on how to solve these open issues. See also section 6.5 on deviation management.

Some GMP regulations use the term Installation Qualification (IQ) for the formal inspection or verification by the customer’s quality function that the design and build of the manufacturing system is fit for intended use and Operational Qualification (OQ) for the formal inspection or verification by the customer’s quality function that the manufacturing system operates as intended and is fit for its intended use.

5.8 Performance Testing

Performance testing is typically an integration test which is carried out at the finally installed and tested systems together with their associated utilities and other support systems. It should be done using production materials or qualified substitutes such as simulated product in order to demonstrate that the equipment, system or utility is fit for the intended use with equivalent behaviour under normal operating conditions. It may be performed by the supplier and customer in collaboration, or by the customer alone. This is typically driven by the type of technology and scope being supplier. The intent for this should clearly be specified in the contract and the PQP.

This testing should include that all manufacturing systems can operate in accordance with the process requirements in all anticipated operating ranges and challenge the equipment or system functions while under performance conditions comparable to future routine production, including interventions, stoppage, and start-up. The performance test should cover the intended operating ranges of the process unless previous testing or documented evidence obtained during pharmaceutical product development activities justify other ranges. It should include the full range of the specified functions during production or related features such as cleanability test, test of temperature distribution during sterilisation in Place (SIP), filling performance and many others, if not previously tested..

It should be verified that operating ranges can be maintained over the routine production time and in-process controls and sampling should be done to establish their frequencies for future production

The Performance Testing activities are a regulatory expectation and should serve as basis for subsequent Process Performance Qualification (US) or Process Validation (EU) activities. Some pharmaceutical companies consider the successful performance testing of each single equipment an “interim release” before the overall, integrated system incl. utilities are released by the subsequent System Acceptance & Release as described below.

5.9 System Acceptance & Release

The System Acceptance and Release is the formal acceptance of all the previous design, review, inspection and test activities by the quality function. It should refer to the Project Quality Plan and other related documents, e.g. Test Matrix, CARA, and should include a clear conclusion on whether the manufacturing system is fit for its intended use, as specified in the User Requirement Specification.

5.10 Performance Qualification and Process Validation

5.10.1 Introduction

The requirements of Performance Qualification and Process Validation should ensure a process capable to deliver the specified product quality over the whole life cycle of product commercialization.

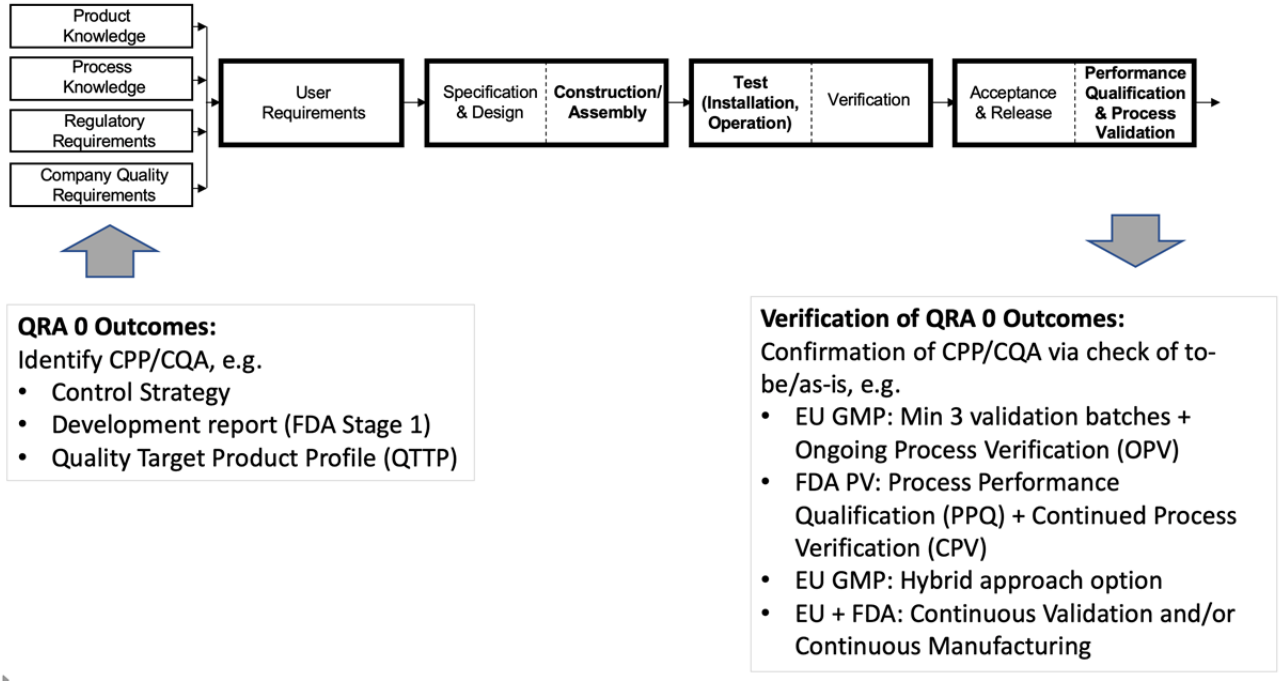
The purpose of the **Performance Qualification** (PQ) is to ensure that the finally installed and tested manufacturing systems functions together, including associated utilities etc. and are fit for the intended use, before the process validation activities starts. The purpose of the **Process Validation** (PV – or in FDA terminology Process Performance Qualification, PPQ) is to establish documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

The PQ should demonstrate that the overall manufacturing system, including all relevant subsystems, operates in accordance with the process requirements in all anticipated operating ranges and challenge the equipment or system functions while under performance conditions comparable to future routine production, including interventions, stoppage, and start-up. The PQ activities may be using production materials or qualified substitutes such as simulated product with equivalent behaviour under normal operating conditions.

It should be verified that operating ranges can be maintained over the routine production time and in-process controls and sampling should be done to establish their frequencies for future production. The Performance qualification activities may overlap with process validation activities to perform the Process Performance Qualification (US) or Process Validation (EU) activities.

In practice the key interfaces between qualification and validation are at the beginning and the end of the qualification flow assuming that no GMP relevant changes during the qualification process trigger changes of CPPs and CQAs as illustrated in Figure 6.

Figure 6 Input and output from integrated Qualification and Validation



5.10.2 Process Validation

The approaches to EU GMP Process Validation and US FDA Process Performance Qualification are comparable, although described quite differently in the EU GMP Annex 15 Qualification and Validation (2015) and FDA's Guidance on General Principles of Process Validation (2011).

FDA's Process Validation Guides describes three stages of Process Validation:

- Stage 1 Process Design: The R&D and tech transfer activities in the pharmaceutical company to develop the commercial manufacturing process so it is suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes. This includes identification and specification of CPPs and CQAs as well as the acceptable ranges as key elements of the Control Strategy for the pharmaceutical product's manufacturing process.

- Stage 2 Process Qualification: The evaluation of the implemented process in the final facility with the relevant manufacturing systems to demonstrate that it can be used for the commercial manufacture of the pharmaceutical product. FDA distinguish between a 'technical' element (1) design of the facility and qualification of the equipment and utilities and a process evaluation element (2) process performance qualification (PPQ). It must be done as the commercial production and must be successfully completed before commercial distribution of the pharmaceutical product.

  (1) is similar to the EU GMP Annex 15 requirements for *Qualification*, although FDA does not specify detailed qualification elements like e.g. DQ, IQ, OQ etc.

  (2) is similar to what EU specifies as *Process Validation* to show that the processes are robust and ensures consistent product quality before any product is released to the market.

- Stage 3 Continued Process Verification: An ongoing activity after the successful completion of Stage 2 to ensure that the process remains in a state of control (the validated state) during commercial manufacture system. It must be continued as long as the pharmaceutical product is being produced and distributed commercially. It should be based on the collection and evaluation of information and data about the performance of the process including undesired process variability and should be evaluated regularly. This is similar to the EU GMP Annex 15 requirements of *Ongoing Process Verification.*

As described, there are many similarities in the approach of FDA and EU GMP Annex 15 although small differences in specific requirements, for example that EU GMP Annex 15 mentions minimum 3 batches for process validation whereas FDA requires sufficient of data for a meaningful evaluation.

The overall key expectation is to confirm based on the (statistical) evaluation of adequate sets of data that the process is sustainably under control and provides effectively and reproducibly the specified product quality on an ongoing and continual basis i.e. in a permanent state of control.

The process validation activities require close engagement of the customer's Quality Function as well as other subject matter experts with product and process knowledge and relevant technical knowledge e.g. development, process support, statistical support, engineering etc. For some equipment the process validation planning and execution may involve advanced manufacturing equipment that includes process models such as continuous manufacturing equipment, PAT-based manufacturing systems etc. should involve the supplier's knowledge as part of the basis for the process validation planning.

After successful evaluation of all data as specified in the Validation Protocol and after availability of adequate stability data the batches can be released to commercial distribution.

5.10.3 Continued or Ongoing Process Verification (CPV or OPV)

When both Qualification and Process Validation activities are successfully completed the pharmaceutical company should have (or establish) a program to continue to demonstrate that the process remains capable as mentioned above in FDA Stage 3 as continued process verification or in EU as ongoing process verification. This can be done on a continuous basis for example via establishment of Statistical Process Control Charts, PAT technologies (including Real-time Release (RTR) technologies) or via periodic statistical data evaluation (Process Capability, Trend Analysis etc.) and reporting, e.g. via periodic reporting to management or integration into the Annual Product Review (APR) or Product Quality Review (PQR) within the pharmaceutical company.

Key to prove successful validation is the successful evaluation of an adequate amount of data to demonstrate that CPPs and CQAs are permanently under control. As usually more data and easier accessible data should be available for CPPs than for CQAs, the URS specification should define GMP compliant and calibrated device to ensure access to data for validation and CPV.

Example: A CQA of a typical blistering process is the tightness of the blister. This CQA is influenced by 3 Sealing CPPs: Time, Temperature and Pressure. In the phase of QRA 0 these CPPs and the CQA should be identified and GMP compliant devices should be established at the blistering line that allow easy and automatized continual access to data regarding the process stability and performance.

The initial Process Validation data can be used as basis for the Ongoing Process Verification acceptance criteria (e.g. by Statistical Control Chart SPC) or for periodic activities, e.g. re-calculation of the capability indices, trend evaluation. The approach to calculate process capabilities can be used in the qualification arena as well, e.g. to calculate machine capabilities.

6 Supplier Activities

6.1 Introduction

Generally, suppliers should be expected to make significant effort in comprehensive testing of their products and solutions to demonstrate that they deliver good quality equipment or systems. If this testing is matching agreed acceptance criteria and the documentation is according to the agreed requirements then the pharmaceutical customers can use the outcome of these supplier activities to demonstrate that the manufacturing system is designed, built and tested and that it is "fit for intended use".

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 re-testing the same attributes in various stages of acceptance tests. The aim of a 'single-test qualification' approach is to leverage testing conducted throughout the complete project.

6.2 Agreed User Requirement Specification (URS)

A User Requirement Specification from the customer should be a description of what the manufacturing system is supposed to be capable of doing, as described in Section 5. As such the URS is normally written by the customer in its first version, and then sent to the supplier as part of a Request for Proposal (RFP) or Tender Requirement Specification (TRS). It may contain several supporting documents for example on technical requirements that are general and not specific to the project in scope such as global company standards. Appendix 2 includes a template example of a User Requirement Specification.

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 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 further development of the URS.

After the supplier has been selected a final revision of the URS should be prepared in cooperation between the customer and supplier. The final revision of the URS should be agreed by both the supplier and customer to establish the basis for the project scope of supply and services and it is recommended to form part of the contract for the project. The URS may be supplemented by Technical Requirement Specifications and other documents.

6.3 Project Quality Plan (PQP)

In early phases a Project Quality Plan (PQP) should be issued and shared between supplier and customer. It should reflect the contract details, such as scope of supply, services, timelines and documents. There should be a mutual agreement on the realization of the URS requirements.

It should include an overview of the scope, project organisation, reference to suppliers quality system (if applicable), document list and distribution, approval matrix, design reviews, sub-contractor management, procedures related to construction e.g. welding, software development standards, receiving inspections, construction inspections, overview of testing activities, change control, deviation management, storage and shipping, etc. See appendix 9 for a PQP example.

There should be a mutual agreement on the realization of the specified quality requirements (e.g. in the URS) covering an overview of all quality relevant design aspects, material management, certificate

management, document management and relevant test activities. It should cover responsibilities and applicable procedures and it may serve as basis for customer specific systems as well as for standard equipment and systems. It should include reference to relevant principles, procedures, standards and applicable guidelines.

The customer may consider the supplier's Project Quality Plan as a part of the overall Validation Master Plan (VMP), covering the supplier's part of the qualification activities. Therefore, the document might also cover the scope of the customer's qualification project and the used techniques with reference to documents (e.g. agreed URS, CARA, risk analysis process and others).

A PQP is important for an effective and efficient qualification and project. It should include at least:

- Identification and definition of critical aspects in the project
- Application of relevant quality activities (e.g. change control, deviation management, design reviews)
- Approval procedures
- Roles and responsibilities
- Details concerning execution of acceptance test (e.g. linking FAT, SAT and other tests and/or IQ, OQ)

Appendix 9 includes a template example of a Project Quality Plan from a supplier's perspective. It outlines the activities that the supplier will perform and the workflow between customer and supplier regarding review, approvals, change management, documentation and other project-related activities to be agreed.

For the specific testing activities as outlined in the Project Quality Plan Appendix 10 includes a template example of a supplier's Testing Activity Plan based on a project example. This can be used as part of the PQP to agree on the supplier's engineering, FAT, SAT and other qualification activities and documentation and the example lists a number of examples of specific tests to be performed.

Related to review, design and test there will be changes during the project execution and the handling of changes as well as deviations should be agreed and documented in the PQP. Especially change control related to Critical Aspects and other GMP related requirements should be specified and will typically require involvement of the customer's quality function.

6.4 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 in order to reflect agreed changes. Changes should be documented so they can be tracked, and they should be linked to quality risk management.

Normally the suppliers have an internal change management process, based on their internal 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' (OPL) (or 'open items list') as exemplified in Appendix 8.

The supplier is also expected to have a form for configuration management which at a suitable level ensures that all parts of the design is aligned as it develops and that subsequent changes are cascaded to all relevant elements of design.

It may be useful to distinguish between the engineering change management and GMP-related change management. For GMP related changes it can be necessary to involve the customer's quality function. Appendix 8 includes an example of Project Change Management.

6.5 Deviation Management

The management of deviations and non-conformities should be addressed in the PQP and should not only focus on documenting deviations and non-conformities but also on the correction of errors, including mistakes and misunderstandings from specifications and design. Besides, it should cover agreed deviations from agreed procedures and methods. Mistakes and errors should preferably be corrected during the review, inspection and test activities. They should be documented and managed as agreed between customer and supplier as part of the deviation management.

Appendix 8 includes an example regarding Change Management and Deviation Management.

The deviation management approach of the supplier and customer should be evaluated and agreed, specifically related to severity of events, reporting points and approvals needed. Differences should discussed and managed, for example may deviations related to critical aspects require involvement of the customer's quality function whereas others may be recorded and managed with a punch-list according to Good Engineering Practices.

Typically, all non-conformities should have been corrected, re-tested and signed off before performance test starts.

6.6 Design and Engineering Activities

During the design and engineering activities, a number of design documents are prepared on the basis of the URS and discussed among customer, engineering company and supplier. This creation of the design drawings, specifications, component lists and other design documents is the 'heart' of the design activities.

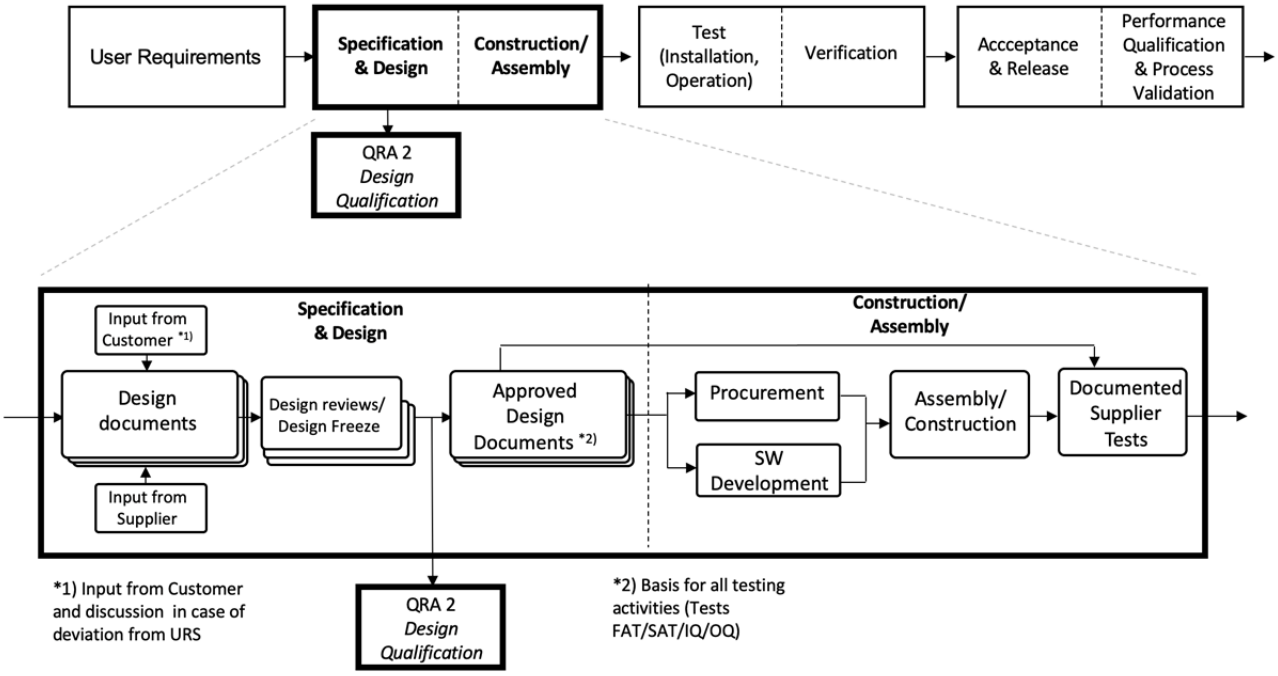
The cooperation between supplier and customer during the design phase can be described as a combination of *engineering* activities (where initial functional specifications, P&IDs etc. are developed by the supplier) and the *design qualification* activity (where the initial engineering documents are reviewed by the customer).

Design reviews and agreement of the design is very important for both supplier and customer since it is the basis for consecutive activities such as detail design, procurement, assembly software development etc. It is described in section 6.7.

Larger engineering projects typically follow three stages of design: Conceptual design, Basic design and Detailed design. **Concept Design** is a very general summary of the 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. These should be combined with the quality risk management approach

and the qualification plan according to the same project life cycle approach as described above, but with a specification of the deliverables and activities specified in the Project Quality Plan (PQP).
In the cooperation between the customer and supplier the supplier typically has a number of activities that does not involve the customer, but the joint activities and decision points should be described in the PQP. Figure 7 illustrates a cooperation example where the activities of Specification & Design and Construction/ Assembly are described in further details from a supplier perspective.

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 necessities of GMP have been taken into account and there is a common understanding between customer, supplier and engineering company, the design is “frozen”. This frozen design basis implies that design documents are approved and released for design, procurement, manufacturing etc. with the signature of all parties. Individual design documents may have their own individual design freeze. The term “design freeze” describes 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*”.

Due to the timeline of a project it is often not possible to wait until all design documents are finished and have one single design freeze for the complete scope of supply. If the design does not meet the agreed URS it should be revisited, and revised. After approval of the design, changes need to be subjected to change management as typically specified in the PQP.

There are many types of design documents, e.g. Functional Specification(s) and Software Design Specifications, Technical Design Documents, P&IDs, Component Specifications etc. The Functional Specification is one among many examples of documents that a supplier will develop during the design & engineering phase where 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 case there are changes necessary Change Management has to be followed.
These documents 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 customer and supplier and documented in the PQP.
It is typically useful to use suppliers' standard design documents, test documents etc. in order to best leverage the supplier's capabilities.

6.7 Design Review and Design Qualification (DQ)

The technical and compliance reviews of the design and engineering documents during the design process are an important element in the design process and especially for the customer's involvement in the Design Qualification activity that is described in Section 5. Design Review and review meetings should be planned into the design process, both the internal reviews in the supplier's organisation and design meetings that involve customers to assure correct requirements and solutions, involving both quality-related aspects, technical aspects, EHS aspects etc.

The supplier should clarify at the beginning of the project and define in the PQP, which key documents can and should be used also for review of GMP aspects. In addition, agreement can be made for how to document those reviews. In doing so, those reviewed documents can be used directly by the customer as raw data for the design qualification, which will save time and effort.

The Design Qualification may be a separate activity or the documented outcome from a number of design review meetings and activities. It should compare the agreed URS and outlined design to make sure that all specified requirements are met. It may be documented by Design Qualification report, depending on the agreed PQP.

6.8 Activities during Assembly/Construction

Depending on the equipment, the customer's knowledge concerning the supplier and the supplier's capabilities, a 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 activities during assembly/construction to ensure that the design is realized with the right level of quality, and that this is especially important when using sub-suppliers for significant parts of the work. The customer may also like to perform supervision in key stages or for specific elements like welding, material selection, calibration etc.

6.9 Qualification Testing

6.9.1 Introduction

Most suppliers have developed or can agree to adapt specifications, drawings, material management procedures, testing and inspections in acceptable formats and methods, that pharmaceutical customers are able to leverage the supplier documentation as part of their qualification activities. The purpose for testing is to identify errors and correct them in early phases. 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.

Before test and qualification, the supplier may conduct internal tests, and these may include areas that the customer has not specified in the test matrix. The relevant supplier tests can be used as part of the qualification documentation provided, they are done according to Good Engineering Practice and Good Documentation Practice, change management, deviation management etc. as described above.

6.9.2 Installation Testing

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 includes 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 part of equipment and systems that are not disassembled for transportation to the customer's site. Normally some elements of the installation test must be performed during the Site Acceptance Test (SAT) after the equipment or system has been installed in the customer's facility. Thus, the installation tests are typically a part of both FAT or SAT.

Installation testing may also be called static testing, pre-functional testing or similar terms. The documented tests may be used as part of Installation Qualification (IQ), as mentioned in some GMP regulations, e.g. EU GMP Annex 15 on Qualification and Validation.

6.9.3 Operational Testing

Operational testing is focusing on operational aspects and is intended to demonstrate that equipment or system 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 equipment and systems that are not disassembled for transportation to the customer's site. For parts of equipment that has been disassembled for transportation and re-assembled at the customer´s site the integration tests should be (re-)executed during SAT.

Many aspects of the operational test must be performed during the Site Acceptance Test (SAT) after the equipment or system has been installed in the customer's facility and connected to the customer's utility systems. Thus, the functional tests may be a part of both FAT and SAT and should be documented in e.g. the Test Matrix (Appendix 7) and/or the Project Quality Plan (Appendix 9).

The documented tests may be used as part of Operational Qualification (OQ), as mentioned in some GMP regulations, e.g. EU GMP Annex 15 on Qualification and Validation, expecting a formal approval by the customer's quality function of at least the operational test of Critical Aspects of the manufacturing system.

6.9.4 Performance Testing

Depending on the project and customer requirements there may be performance testing activities of the overall, integrated system, before the performance qualification (PQ). The performance testing and the PQ may also be combined , but the performance testing under production-like conditions cannot replace the customer's PQ which is based on the intended use of the equipment or system with its installed utilities, connected systems, operators etc. as described in Section 5.8.

The customer will perform an evaluation of the testing performed, to conclude if the test and documentation may be used directly or will need to be supplemented. Evaluation may be based on criteria like the following:

- Requirement tested and acceptance criteria met.
- Tester is trained in accordance with PQP
- Documentation is legible as per GDP
- The test is documented and presented as appropriate.
- Punch-list items raised as necessary: Y/N
- All relevant Punch-list items closed.
- Relevant changes implemented and documented in baseline.
- System dismantling and shipping did not affect the validity of the test.
- For dynamic/operational tests only: Are instruments calibrated and documented.

7 Qualification Activities for Equipment Categories

7.1 Introduction

When planning and executing a qualification project, it may be useful to distinguish between some main categories of manufacturing systems. The main categories may be used to determine the general level of details and testing rigor linked to the risk of the application of the equipment. The following categories of manufacturing equipment are inspired by US Pharmacopeia for analytical instruments (USP) chapter 1058.

The categories are based on:

- the general quality risk impact (GMP critical aspects),
- product- and process critical aspects,
- technical complexity (degree of standardization of the manufacturing system),
- complexity of the process,
- the use for which they are intended (e.g. contact to product),
- the possible link to an automated system,
- supplier capabilities (GEP & project management maturity).

7.2 Equipment Categorisation Fundamentals

The categories are based on practical experience in pharmaceutical projects and should be used carefully in combination with other risk management activities. The classification of an equipment should be based on documented risk assessments and rationales, based on both supplier assessments (e.g. audits) and specific project guidelines for each company or application. The assessment of critical aspects and the decision regarding allocation of the category to each manufacturing system (Equipment/ function) should be documented. The assessment should include reflection on the complexity of the equipment and related manufacturing process. Other assessment subjects may be added for specific purposes and there must be some reflection based on the actual application of the system.

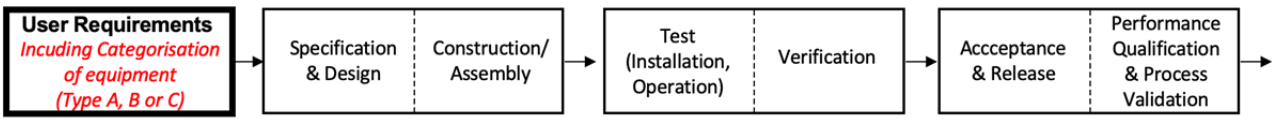
For the categorisation it is important to understand the concept in which *Critical Aspects* are the parts of a specific manufacturing system (e.g. equipment) that impacts Critical Quality Attribute and Critical Process Parameters as outlined in section 5.2. A supplier of a manufacturing system that contains Critical Aspects will need this information from the customer. If general (not product- and process related) GMP requirements applies to the equipment, for example the prevention of cross-contamination or ensuring sterilization processes, suppliers typically have experience in how to test and verify these from other customers with similar applications.

The categories do not relate to software but to the overall manufacturing systems, which may also contain computer systems and software, for which this guide refers to the GAMP 5 guide (Good Automated Manufacturing Practices) Appendix M4 “Categories of software and hardware”.

7.3 Process of categorisation

Figure 8 illustrates the chronological position of equipment categorisation within the engineering activities during design phase. The categorisation preferably should be performed during the creation of the URS. Latest, the categorisation has to be defined during engineering activities in the design phase. The final design document (e.g. technical specification for a buffer vessel) has to include the correct category.

Figure 8 Equipment Categorisation in the project life cycle



7.4 Three Categories of Manufacturing Systems

Table 01 describes the three types of categories for manufacturing systems in detail. The categorisation is determined individually for each manufacturing systems. Determining the most appropriate category is important for saving time and for more cost-efficient qualification decisions. The specific selection of category should be based on the specific application of each manufacturing system.

Equipment categorisation may be performed during the Initial Risk Assessment (QRA 0) as part of the system risk assessment of the manufacturing systems (see section 5.2) or related to the creation of the URS (see section 5.3). It should be revisited during Design Qualification (see section 6.7).

Table 01: Category, name, description, and typical examples for the three types of equipment categories

Category	Name		Qualification Activities	Typical example
A	Standard off-the-shelf equipment with no specific GMP requirements		Typically qualified by commissioning based on GEP. Can be done by supplier with documentation review and approval by customer SMEs.	- black steam generator - HVAC for rooms with no cleanroom requirements
B	Standard off-the-shelf equipment with specific GMP requirements that contains no or few Critical Aspects with direct impact on product quality		Typically qualified by commissioning based on GEP, typically supervised or executed with customer SME's. Critical Aspects test typically involves the customer Quality Function.	- Clean steam generator - WFI still
C	Customized equipment with product specific requirements critical to quality (ie. contains Critical Aspects)	C1: Configured standard equipment	Typically qualified as commissioning and qualification together with customer SMEs. Critical Aspects test involving the customer's Quality Function	- Filling machine, configured according to customer requirements
		C2: Customized equipment	C2: Typically qualified as commissioning, sometimes supplemented by specific testing of customized components and functionalities, working closely together with customer SME's. Critical Aspects test involving customer Quality Function.	- Bioreactor, designed according to customer requirements

7.5 Practical Hints for Categorisation

Category A equipment can be tested by supplier 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.

For Category B equipment, customers and suppliers are encouraged to cooperate on the relevant qualification approach. It is recommended to use technically mature supplier standard solutions when possible, in order to save time for discussion

Category C equipment is typically relevant when the customer requirements cannot be fulfilled by a standard manufacturing system, equipment or function. Category C1 Configurable standard equipment may use mature supplier standard documents for design and test/qualification, thus limiting the number of new documents to be developed for interconnections, overall functions etc. Category C2 Customized equipment is typically designed specifically to the customer, although some design and functionality may be used by the supplier based on previous, similar projects, if handled carefully to ensure that changes are controlled and reflected in the design, test and qualification documents

8 Abbreviations

ASTM	American Society of Testing and Materials
C&Q	Commissioning and Qualification
CA	Critical Aspects
CADE	Critical Aspects Design Element
CDE	Critical Design Element
CARA	Critical Aspects Risk Assessment
CCP	Critical Control Point
cGMP	Current Good Manufacturing Practice
CIP	Cleaning in Place
CMA	Critical Material Attribute
CPP	Critical Process Parameter
CPV	Continued Process Verification
CQA	Critical Quality Attribute
CSV	Computerized System Validation
DQ	Design Qualification
EHS	Environment, Health and Safety
EU	European Union
FAT	Factory Acceptance Test
FDA	Food and Drug Administration (US)
FMEA	Failure Mode and Effects Analysis
FS	Functional Specification
GAMP	Good Automated Manufacturing Practice
GDP	Good Documentation Practice
GEP	Good Engineering Practice

ICH	International Council on Harmonisation
IQ	Installation Qualification
ISO	International Standardisation Organisation
N/A	Not applicable
NOR	Normal Operating Rage
OPL	Open Point List
OQ	Operational Qualification
PAR	Proven Acceptable Range
PAT	Process Analytical Technology
P&ID	Piping & Instrumentation Diagram
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
QA	Quality Assurance
QRA	Quality Risk Assessment
QRM	Quality Risk Management
QTPP	Quality Target Product Profile
RFP	Request for Proposal
RTM	Requirement Traceability Matrix
RTR	Real Time Release

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
VMP	Validation Master Plan
VTOP	Vendor Turn Over Package (aka Supplier Turn Over Package)

9 References

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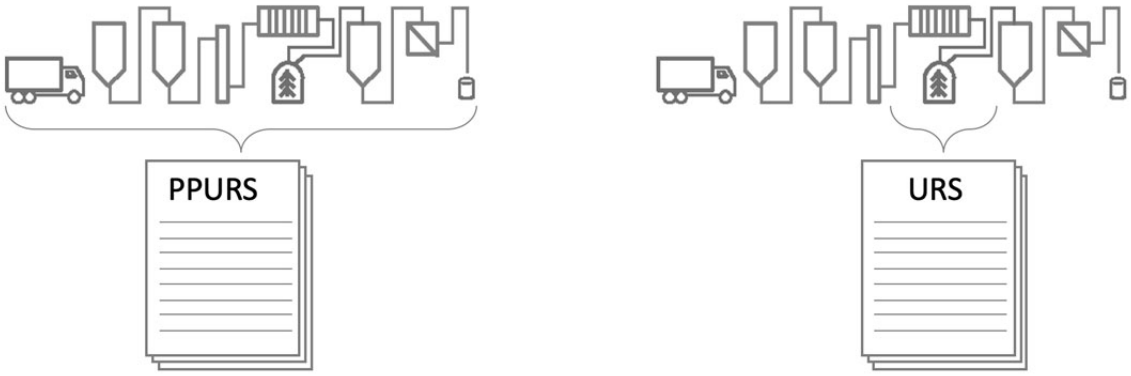
Appendices

Table of Content

Appendix 1: Customer: Product and Process User Requirement Specification (PPURS)

The PPURS is a useful tool, especially for mid-sized and large project and for projects covering a whole manufacturing facility. It contains roughly all information necessary to produce the product, preferably based on the Control Strategy of the product from which the URS requirements regarding product-, process- and quality risk management information can be extracted and some pharmaceutical companies it includes the initial Quality Risk Assessment (QRA 0) of a project. It is an internal customer document with high confidentiality classification and is used as input to the URS, Quality Risk Assessments and other project activities and documents.

A typical PPURS contains an overview of the Critical Quality Attributes (CQA), Critical Process Parameters (CPP) and Critical Material Attributes (CMA) as well as other key data, specifications and tolerance intervals that outlines the involved product manufacturing steps. Preferably it should also contain an overall risk assessment that facilitates the identification of Critical Aspects for the process equipment.



The following template for a PPURS is from a project example from which also is the basis for the URS template is taken. It contains the same headlines and sections as the URS template. The PPURS must be adapted to a specific project.

(The text in brackets < > is used as a placeholder for text and guidance for the user of the template)

Appendix 1: Customer: Product and Process User Requirement Specification (PPURS)

Product and Process User Requirement Specification (PPURS)

Product name

Document number
Revision

Approval Table				
Signs for	Role	Name	Date	Signature
Drawing up Finished Document	Author …	<name>	<date>	<signature>
Approval Correctness and completeness	Customer owner or user	…		
Correctness and completeness	Customer project manager	…		

Table of Content

Appendix 1: Customer: Product and Process User Requirement Specification (PPURS)

1. Objective

1.1 This document summarizes the Product and Process User Requirement Specification (PPURS) of the product <…>

1.2 This document contains manufacturing formula, manufacturing and packaging requirements that must not be divulged. This document is for internal use only

1.3 The Product and Process User Requirements is a summary of the product(s) and processes quality requirements and is used to define the equipment or systems fitness for use. It serves as the project repository document for the collection, evaluation, and confirmation of this information.

1.4 The PPURS serves as the input to subsequent project risk assessment activities, design objectives, control strategy, and acceptance criteria for testing and verification of the manufacturing system

2.0 Scope

2.1 This document constitutes the PPURS of the following product <…> for the project <…> which will be operational in facility <…>

2.2 Limitations: This document does not cover … <activities that are excluded for the scope of the project>

2.3 …

3.0 References/Related documents

3.1 References:
3.1.1 <relevant reference documents>
3.1.2 …

4.0 Definitions

The following abbreviations may be used in this document. Generally well-known acronyms are not given, e.g. GMP, SOP, FDA.

API: Active Pharmaceutical Ingredient
CPP: Critical Process Parameter
CQA: Critical Quality Attribute
CTD: Common Technical Document
DMF: Drug/Device Master File
IPC: In-process Control
NOR: Normal Operating Range
PAR: Proven Acceptable Range
PPURS: Product and Process User Requirement Specification
…

Appendix 1: Customer: Product and Process User Requirement Specification (PPURS)

5.0 Product and Process Description

5.1 Product Description

The product <…> is <This section describes the product(s) associated with the project, equipment or system. including

- type of active ingredient strength and what is used for
- destined market,
- type of pharmaceutical product,
- weight, color embossing, etc.
- type of pack,
- manufacturing formula
- any other pertinent information>

…

< The word “product” has here a general meaning and can mean a drug product, drug substance, medical device, an ingredient such as water, a utility if this utility is produced in the system, materials, data, etc.>

5.2 Process Description

This section summarizes the process including the following process steps, utilities etc.

< Regulatory documents such as the Common Technical Document (CTD) or the Drug/Device Master File (DMF) should be reviewed to ensure alignment of the process description>

5.2.1 Main process stages diagram <Process flow diagram>
5.2.2 The input into the process
5.2.3 The process steps
5.2.4 The output from the process
5.2.5 Required equipment: major equipment that is involved in the process
…

6.0 Product and Process User Requirements

<This section gives an overview product- and process information for the specific product, typically based on the Control Strategy or similar documents from the process development, pilot plant, tech transfer or similar functions in the pharmaceutical company. It includes the quality risk assessments of the product, based on the development information>

6.1 Process Requirements
6.1.1 Product: Critical Quality Attributes (CQA)

Appendix 1: Customer: Product and Process User Requirement Specification (PPURS)

<To be able to build systems that deliver products with the required quality attributes, the "product"- critical quality attributes (CQA) have to be known. Product characteristics such as cleanliness, impurities, metal concentration, moisture percentage, dissolution time, uniformity, toxicity, packaging, drug safety information for the associated materials and other product characteristics are mentioned here.

The product specification of the CQA is listed here. Also, the filed range or regulatory range is listed if established (e.g. the upper and / or lower limits for the attribute values filed in regulatory documents.). Regulatory documents such as the Common Technical Document (CTD) or the Drug/Device Master File (DMF) should be reviewed to ensure alignment of product specifications and process ranges.>

Drug product CQA's have been identified in accordance with the documents <…>. The rationale of the critical quality attributes of the product is described in the table

The Severity Levels are defined as follows:

- Catastrophic: definition…
- Significant: definition…
- Marginal: definition…
- Minimal: definition…

CQA ID	Drug Product Quality Attribute	Severity Level of potential harm	Rationale for criticality (i.e. potential patient impact)
CQA 1	<…>	E. g. Significant	<…>
…			

Final Drug Product CQA's have been identified according to specifications and Regulatory File.

6.1.2 Process: Critical Process Parameters (CPP)

< to perform the different process steps of a product it is important to know the normal operation range and if known proven acceptable range (values) and tolerances of the critical process-parameters. These critical process parameters are obtained from various scientific sources (e.g. product development reports, laboratory reports, pilot studies, technology transfer reports, etc.).>

In each Process Operations a list of CPP's has been identified for each CQA based on the knowledge of the systems used. Other Process Parameters are also listed being identified as parameters that may have an influence on CQA but with minimal risk of hazard. This impact, even if minimal, will be evaluated during the following phases of Risk Assessment and Design Review of the systems involved in the Process Operations.

Appendix 1: Customer: Product and Process User Requirement Specification (PPURS)

Where available from other implementation of the same processes, Proven Acceptable Range (PAR) and Normal Operating Range (NOR) are provided for listed CPP's and PP's. These ranges are provided for reference only and will be confirmed or adjusted after the execution of the Performance Qualification step involving all the steps of the process and performed with API.

Process Operation	Process Action	CQA	PPURS ID	Process Parameter	Impact	NOR	PAR	Remarks
<…>	<…>							
…	<…>							
	…							

6.1.3 Additional requirements

The following list defines all the other requirements to be fulfilled to guarantee Final Drug Product Quality

PPURS ID	CQA	Source of requirement	Requirement
<…>	<…>		
…			

7.0 Control Strategy

The process described above needs to be controlled during its evolution to assure that a proper product quality is consistently achieved. In the following table it's described for each Process Operation the CCP and the associated IPC's

Process Operation	CCP	Materials	IPC
<…>	<…>	<…>	<…>
…			

8.0 Appendices/Attachments

8.1 Document…

8.1.1 …

8.1.2 …

Appendix 1: Customer: Product and Process User Requirement Specification (PPURS)

9.0 History of Change

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

Appendix 2: Customer: User Requirement Specification (URS)

The requirements concerning manufacturing systems should be defined in a User Requirement Specification (URS). It is a regulatory expectation that essential elements of quality requirements related to the pharmaceutical product and the manufacturing process are covered as well as requirements related to the elimination (or mitigation) of GMP-related risks to an acceptable level.

A URS should be based on Product and Process specific requirements, relevant GMP requirements, other regulatory requirements (e.g. EHS requirements, technical standards, etc.) and company specific requirements. The URS should be written in unambiguous and precise terms, stating for example what functions the pharmaceutical customer expects, what the operating conditions will be and what regulatory requirements and what documentation requirements should be fulfilled. Requirements should preferably be clear, specific and testable.

It can be useful to distinguish between the initial URS from the customer and the final, agreed URS (in agreement with the supplier), which is the contractual basis for the cooperation. In some pharmaceutical companies the URS has a life cycle beyond a specific project as a living reference document

Although the URS is a customer owned document the input from the supplier is important. Many suppliers have significant expertise within certain types of equipment and systems and some of them 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 or even an URS template or examples that can be used to specific the customer user requirements.

For certain types of standard equipment most of the design and functionality may be just the standard but often customers have certain special requirements from either local company standards and guidelines or due to their special application of the equipment, derived from the product and process requirements.

It is useful to distinguish between the URS requirements that relates to the pharma product quality and other requirements, where

- URS requirements related to pharma quality should mainly focus on the aspects of equipment, system or facility that relates to the risk assessment. Especially the Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs) and related Critical Aspects (CAs), i.e. the high-level pharmaceutical product requirements in a project lifecycle

- Other requirements such as (business) performance-related requirements, HSE related requirements, technical requirement and standards.

Appendix 2: Customer: User Requirement Specification (URS)

Some pharmaceutical companies prefer to separate it into two separate sections of the URS document or as two separate documents of which one is for the specific manufacturing system for a specific pharmaceutical application whereas the other is a 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 or not.

For effective project management may be useful to clearly identify some types of URS requirement, especially for critical requirements related to (potential) critical aspects of the equipment. If such grouping is used it should be kept clear and simple such as e.g.

- Critical (Product Quality related requirements, related to CQAs, CPPs etc.)
- GMP (related to specific GMP requirements for cleaning, sterilization etc.)
- HSE (related to health, safety or environmental requirements etc.)
- Business (related to operating efficiency, company standards etc.

For larger facility projects it has proven useful with a high-level URS, sometimes called a PPURS (Product- and Process User Requirement Specification) which contains the specific process requirements for each process step and area of the facility and equipment (the essence of the „control strategy“ for the pharmaceutical product) including the output of the quality risk assessments for Critical Quality Attributes, Critical Process Parameters and thus the input to Critical Aspects of the overall facility. This is very helpful for developing the URS for the specific manufacturing systems for the facility. See Appendix 1.

It is important to agree the handling of the URS during the project phases, including for examples:

- From when is the URS used as basis for the communication between customer and supplier?
- Who is responsible for the document and who should deliver what parts of it?
- How should the document be kept up to date with the progress of the design and development?
- How is the traceability from the design to the URS documented?
- How can specific requirements be verified in the final outcome?
- Who should verify that the requirements are fulfilled?

A URS may contain parts that require mutual understanding and insight into technical subject matters. It is important that detailed knowledge as well as mutual trust is built into the document as early as possible and at least before the document is approved and signed by the pharmaceutical company and the supplier.

There should be a documented change control in which all agreed requirements (including technical) are tracked from the signed document during the whole project until its end. This change document can also be used to ensure traceability of documents and tests done by the supplier.

Appendix 2: Customer: User Requirement Specification (URS)

The change management of the URS and other documents to ensure that it is updated and implemented is a significant task, especially on large or complex projects that requires high discipline. The updates should include agreements in meetings, workshops, emails and other agreements to ensure that it is kept in control and valid during the whole life cycle until the project ends. If not, there is significant risk for misunderstanding that may be difficult to correct or requires additional works and possible delays of the project.

User Requirement Specification

Project name

Document number
Revision

Approval Table				
Signs for	Role	Name	Date	Signature
Drawing up Finished Document	Author …	<name>	<date>	<signature>
Approval Correctness and completeness	Customer owner or user	…		
Correctness and completeness	Customer project manager	…		

Table of Content

Appendix 2: Customer: User Requirement Specification (URS)

1.0 Objective

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

1.2 The URS is a summary of the company <…> 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

1.4…

2.0 Scope

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

2.2 Limitations: This document does not cover … <activities that are excluded for the scope of the project, e.g. labeling, warehouse process, logistics…>

2.3…

3.0 References/Related documents

3.1 References:

3.1.1 <relevant reference documents>
3.1.2 …

3.2 Related documents

3.2.1 The requirements listed in this document include all the Critical Aspects/Critical Process Parameters/other items identified in the following documents

- Critical Aspect Risk Assessment Report for <…> (CARA)
- Process description with Product- and Process User Requirements for <…>
- …

3.3 Project Verification Plan

3.4 Change Control Procedure

3.5…

Appendix 2: Customer: User Requirement Specification (URS)

4.0 Definitions

The following abbreviations may be used in this document. Generally well-known acronyms are not given, e.g. GMP, SOP, FDA.

BMS: Building Management System
CIP: Clean in Place
EHS: Environment, Health and Safety
PID: Piping and Instrumentation Diagram
…

5.0 Project Introduction

5.1 Project Description

The project <…> is about <brief description of the goals and limits of the project, incl. location, systems and activities involved>
…

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>
…

Appendix 2: Customer: User Requirement Specification (URS)

6.0User 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), Critical Aspects (CA), non-critical process parameters, heating/cooling rate as well as control, monitoring and alarm functions associated with each parameter. Also special requirements for parameter settings etc.

General process parameters include all non-critical process aspects of the project and include parameters concerning general process operability, general process safety, environmental aspects, etc. Critical and other quality process parameters (CPP) for the product and the process>

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
<…>	The Filling System should be able to run continuously at <…> per hour (Minimum Effective Output)	
…	The Filling System shall be able to process various Product and Sizes as described in Section …	Critical Aspect
	…	
	The Filling System shall be able to process Material x (+ specification) Material y (+ specification)	Critical Aspect
	Batch Volume: <…> to <…>	
	…	

6.1.2 Process Parameters

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

Appendix 2: Customer: User Requirement Specification (URS)

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, quantities, etc.) of the incoming flows.
- Open and/or closed systems, possibility of cross-contamination, compartmentalization from a facility viewpoint.
- Ambient conditions for the process or operation of the system: interior/exterior erection, dirty–dusty/clean environment, ambient temperature, % relative humidity, air classification, pressure/flow patterns, etc.>

Requirement ID	Requirement	Type of requirement
<…>	City Water (xyz) is supplied at a minimal pressure of <…> bar	
…	Ambient temperature is <…> °C	
	…	

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
<…>	The <…> water production is a continuous process (24h/day)	
	…	

6.1.5 Other process requirements

< …>:

Requirement ID	Requirement	Type of requirement
<…>	<…>	
	…	

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
<…>	Piping materials in contact with city water or softened water shall be adapted for the application. The material shall be in accordance with <…>)	Critical Aspect
	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
<…>	Dead spaces shall be avoided at critical locations	
	Process piping is installed according to standards of sanitary design	
	…	

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: Customer: User Requirement Specification (URS)

<Examples:
Software:

- Requirements for the software: Application, Application Operating System, Third Party/Off-the Shelf, and Operating System; programming language or design method.

Automation:

- Modes of operation, e.g. start-up, shutdown, normal, manual override.
- Main sequences developed in relation to the process parameters.
- Important interlocks between sequences and equipment, components from the process viewpoint.
- Control range and accuracy of the systems in relation to the required process ranges and accuracy.
- Alarm sequences
- Recipe controls

…>

6.3.1 Operation & Functional Requirement

<Special operational and functional requirements that applies>

Requirement ID	Requirement	Type of requirement
<…>	<…>	Critical Aspect
	<…>	
	…	

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

<Special automation requirements, control system requirements etc >

Requirement ID	Requirement	Type of requirement
<…>	Language: The SCADA/HMI Interface shall support <…> and <…> Languages. All Graphic Labels and Operator messages shall be switchable from <…> to <…>	
	Unit Control System: The Unit Control System shall support Maintenance mode which will allow Control of all Devices from the HMI	
	Data Management requirements according to <…>	
	…	

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
<…>	All production suites shall meet class ISO <…> in operation	Critical Aspect
	Core production area shall meet class ISO <…> in operation	Critical Aspect
	…	

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. dismantling of system components to guarantee good cleaning, required finishing.). The requirement for visual inspection of the equipment or components should also be mentioned>

Requirement ID	Requirement	Type of requirement
<…>	The production system and storage shall be drainable and chemically cleanable	Critical Aspect
	Stationary CIP systems to be located at appropriate location to serve as a common CIP system for cleaning stationary process equipment and associated process piping	Critical Aspect
	…	

6.4.3 Utility Requirements

Requirement ID	Requirement	Type of requirement
<…>	Compressed air coming in contact with product must be filtered (Type <…> filter)	Critical Aspect
	Compressed air must be oil free in accordance with <…>	
	…	

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
<…>	The building layout must include areas for receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection	
	Laboratory areas should be separated from production areas.	
	…	

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
<…>	Discharge streams containing API or solvent must be treated before going to the environment, except the emergency vent lines	
	The noise level generated during operation of the <…> equipment shall not exceed <…> dBA .	
	…	

6.4.6 Ergonomic (Accessibility, Maintainability) Requirements

< Specific : in this section one can 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
<…>	All components shall be located at an accessible place. A platform shall be provided around the <…> tank	
	Light level in accordance with <…> standards	
	…	

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
<…>	The design documents shall include the requirements for preventive maintenance	
	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	
	…	

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
<…>	The design documents shall include the requirements for training and reflected in a training plan	
	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
<…>	The Vendor shall supply Template/Report for Design Review, Change Control, …l	
	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.	
	…	

Appendix 2: Customer: User Requirement Specification (URS)

7.0 Appendices/Attachments

7.1 Drawings or diagrams:

7.1.1 Context diagrams

7.1.2 …

7.2 Other illustrations relevant for specifying the URS requirements

7.2.1 Photos

7.2.2 …

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
<…>				
			…	

Appendix 3: Customer: Supplier Evaluation

Pharmaceutical customers are responsible for their selection and management of their suppliers and typically this is part of a broader supplier management approach that also may include Contract Research Organisations (CRO), Contract Manufacturing Organisations (CMO), Laboratories etc. 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. They may supplement an audit as a preliminary assessment (initial evaluation) to gather information relevant for the audit planning.

Depending on the scope of the supplier's delivery the supplier evaluation should involve one or more supplier audits, related to the scope of the delivery and the mutual history between the customer and supplier. It typically follows an approach like:

1. Preparation of audit, involving all participants and stakeholders

2. Audit, including start-up meeting, audit meetings and closure meeting

3. Audit Analysis and follow-up, including decision on supplier evaluation conclusion.
   The supplier evaluation varies but at least should include at least the following areas:

   - Assessment of the supplier's quality management system (QMS) and its implementation
   - Technical capabilities, history, size of supplier and customer references, especially within the pharmaceutical industry
   - GMP capabilities and knowledge of regulatory requirements, including Good Engineering Practice (GEP)
   - Documentation management, especially design, certification and test documentation
   - Use of sub-suppliers, incl. track record and follow-up
   - Use of software, including software development procedures and control
   - For manufacturing suppliers (e.g. equipment suppliers): Material control, manufacturing process controls, certificate management, calibration management etc.
   - Training

Appendix 3: Customer: Supplier Evaluation

An audit should be concluded by an audit report with a conclusion on if the supplier is evaluated to be acceptable for the relevant services or equipment in scope. There may be specific corrective actions, including changes to the supplier's quality system, including methods of documenting changes, test results etc. Also the report may conclude that the supplier cannot be used for the relevant scope, so that other actions must be taken.

After the audit there may be surveillance audits depending on the specific system and the ongoing relation between the customer and supplier organisation.

Appendix 4: Customer: Critical Aspects Risk Assessment matrix (CARA)

The Critical Aspects Risk Assessment table (CARA) is used for the risk management of Critical Aspects from the URS requirements throughout the project life cycle, starting with the risk assessment and associated failure modes for the critical aspects and ending with the verification of the design and implementation of the critical aspects of the manufacturing systems.

The first version of the CARA may be generated during the Design Qualification (DQ) as described in Appendix 5 or prior in the project.

The template example is based on a project where an initial risk assessment (QRA 0) has identified the Critical Quality Attributes (QRA) of the products and the Critical Process Parameters (CPP) of the process so that the Critical Aspects can be identified. The initial risk assessment may be documented in a Product- and Process User Requirement Specification (PPURS) (see Annex 1) or in a Control Strategy document for the specific pharmaceutical product. It is based on input from the pharmaceutical company's product- and process development experts, tech transfer experts and similar expertise.

The overall template document and its use during the project life cycle is illustrated in Table 1 (over two pages) and described in the following paragraphs.

Appendix 4: Customer: Critical Aspects Risk Assessment matrix (CARA)

Table 1

Step #1: Critical Aspects Risk Assessment [CARA]													
	CQA	CPP	HAZARD	**Severity (S)**	Failure Mode	Cause of the Failure Mode	ID# Critical Aspect	Risk Control Mechanisms (RCM's)	**Probability (P)**	Detection Mechanisms	**Detectability (D)**	**Risk Priority Number (RPN) (S x P x D)**	
	CQA Impacted by the Hazard	**CPP** Impacted by the Failure Mode	Potential Source of Harm to Patient or Product Quality		How the Hazard will occur in the Process Step	What can Cause the Failure Mode	ID# of the Critical Aspect	What Prevents the Failure Mode from Occurring (Procedural/Documentation Feature to prevent the Failure Mode from Occurring ex., SOP, PM, Calibration, Training)		What Detects a Failure/Hazard (Visual Inspection of Components via Operator while in production, analytical testing, in-process checks, alarms or other Indication from a monitoring device)			

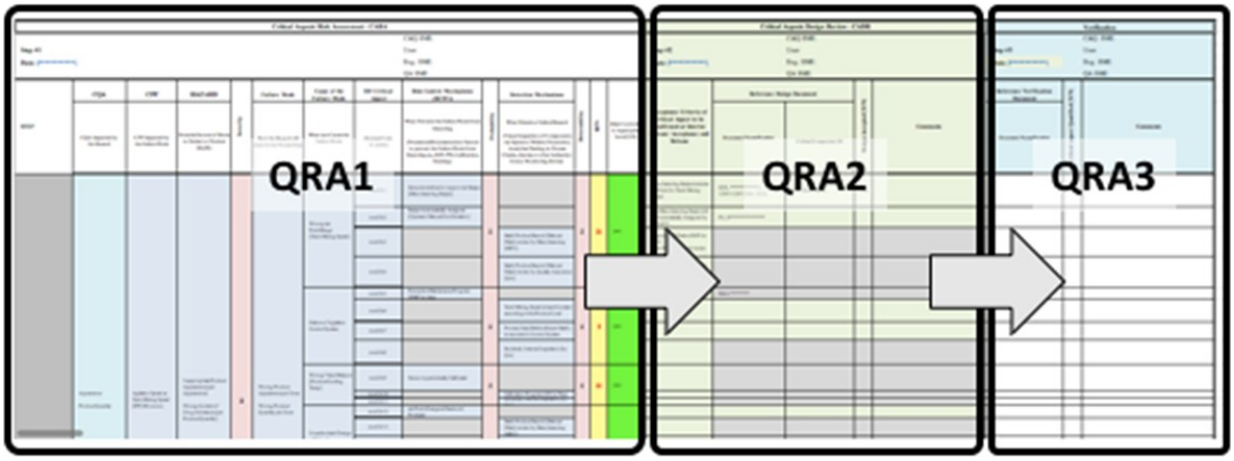
Appendix 4: Customer: Critical Aspects Risk Assessment matrix (CARA)

Step #2: Critical Aspects Design Review [CADR]					Step #3: Verification		
Acceptance Criteria of Critical Aspect to be Confirmed at Interim Release/ Acceptance and Release	Reference Design Document		**[Yes, No, N/A]** Design Accepted [Yes, No, N/A]	Comments	Reference Verification Document	**[Y/N]** Critical Aspect Qualified [Y/N]	Comments
	Document Name/Number	Critical Component ID			Document Name/Number		

Appendix 4: Customer: Critical Aspects Risk Assessment matrix (CARA)

During the project the Quality Risk Assessment 1, 2 and 3 may be documented as illustrated in figure 1

Figure 1



The first part of the CARA is filled out prior to or during the Design Qualification, based on the QRA 0 the main process steps that contains Critical Aspects (i.e. affecting CQAs and CPPs) based on the initial quality risk assessment (QRA 0). This includes a severity (S) ranking of each CA.

The risk assessment scale for Severity, Probability and Detectability in this project example is defined as follows:

Severity

Score	Description	Definition
10	Catastrophic	…
8	Critical	
5	Marginal	
3	Minimal	
1	Negligible	

Probability

Score	Description	Definition
10	Very High	Failure is almost inevitable
8	High	Repeated failures
6	Moderate	Occasional failures
3	Low	Relatively few failures
2	Very Low	Only isolated failures
1	Remote	Failure is unlikely

Appendix 4: Customer: Critical Aspects Risk Assessment matrix (CARA)

Detectability

Score	Description	Definition
1	Almost certain	Existing controls will almost certainly detect a failure
2	Very high	Very high chance for detection, e.g. by on-line, at-line instrumentation
4	High	High chance that existing controls will detect a failure
5	Moderately high	Moderately high chance of detection, would allow corrective actions to be taken
6	Low	Low chance for detection of a failure, but would be evident to a subject matter expert
7	Very low	Very low chance for detection of a failure but would be detected when data is being reviewed
8	Remote	Remote chance for detection of failure without further analysis and/or testing
9	Very remote	Very remote chance for detection of failure
10	Almost impossible	Almost impossible chance for detection of failure. Would not be detected by data review or testing

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

RPN	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

This first part of the matrix table headings are used as follows:

- Process Step identification: ID and name for each process step
- Critical Quality Attribute (CQA) of the product that are affected in the process step
- Critical Process Parameter (CPP) of the process step that affects CQAs in this process step
- Hazard that may occur to the product in this process step
- Severity ranking (S) of a hazard in this process step (according to a defined severity scale)
- Failure mode identifying the possible failure modes that can cause the hazard
- Case of failure mode describing the cause of each failure mode
- Critical Aspects identification number for reference purpose

Appendix 4: Customer: Critical Aspects Risk Assessment matrix (CARA)

- Risk Control Mechanisms to prevent or control the failure mode
- Probability ranking of each failure mode (according to a defined probability scale)
- Detection mechanisms by which the failure mode can be detected
- Detectability (D) of each failure mode (according to a defined detectability scale)
- Risk Priority Number (RPN) calculated as R*P*D
- Risk Control Assessment to decide whether the residual risk is acceptable or additional measures are required

The second part of the CARA is used for QRA 2, mainly the Design Qualification (with associated actions to mitigate risk by design changes etc.) ad described in Figure 4. It has the following headings:

- Acceptance criteria for each critical aspect to be confirmed during verification and assessed at the System Acceptance and Release
- Reference design documents (ref. number and name) for documents used for the Design Qualification
- Design Accepted? (Yes, No, N/A)
- Comments
- Reference Verification Document
- Critical aspect qualified? (Yes, No, N/A)
- Comments

Appendix 5: Customer: Design Review and Design Qualification (DQ)

Design Qualification (DQ) activities and documentation is a regulatory expectation in EU GMP Annex 15 Qualification and Validation and many other regulatory documents. The Design Qualification (DQ) should demonstrate and document how the requirements from the User Requirement Specification (URS) are met. Design Qualification is a responsibility of the customer but requires input from the supplier, possibly at joint meetings.

For risk-based qualification projects the Design Qualification related to the Critical Aspects and other GMP-related requirements typically involves the pharmaceutical customer's quality function, whereas other URS requirements may not. Useful tools for Design Qualification, including Critical Aspects Risk Assessment (CARA), Requirement Traceability Matrix (RTM) and Test Matrix (TM) are described in Appendix 4, 6 and 7.

Suppliers typically have internal design review activities as part of their quality management system, as required in the ISO9001 standard for Quality Management Systems. They are is typically organized as a number of design review meetings during a project depending of the scope, complexity and approach of the project with follow-up on agreed actions and may involve customer participation.

Design Review activities and documentation may be leveraged for the Design Qualification documentation as described in section 6.7.

The following template is based on a project example where the initial risk assessment is documented in a Critical Aspect Risk Assessment matrix (CARA) as part of the DQ activity. The CARA is used to document the risk assessment, the DQ actions related to the Critical Aspects and the subsequent qualification activities as described in Appendix 4.

Appendix 5: Customer: Design Review and Design Qualification (DQ)

Design Qualification Report

Project name

Document number
Revision

Approval Table				
Signs for	Role	Name	Date	Signature
Report writing Finished Document	Author …	<name>	<date>	<signature>
Approval Correctness and completeness	Customer owner or user	…		
Approval Correctness and completeness	Engineering SME	…		
Approval Correctness and completeness	Qualification SME			
…				
Approval Correctness and completeness	Quality Function Responsible			

Table of Content

Appendix 5: Customer: Design Review and Design Qualification (DQ)

1.0 Purpose

1.1 Design review consists of a review of relevant aspects of the proposed design to ensure compliance with the URS

1.2 Design qualification is part of design review, it shows the documented evidence that the proposed design of equipment/system complies with the critical requirements from URS coming from Critical Aspect Risk Assessment (CARA).

1.3 This document provides the result of the CARA and the Design Qualification for the equipment <…> for project <…> located at <…>.

1.4 The Design Qualification is based on identification risks to the product quality that may be present in the manufacturing equipment are identified and assessed as well as other GMP requirements and Good Engineering Practices (GEP).

1.5 This document provides the output of the Critical Aspects Risk Assessment and Design Qualification, a summary of critical aspects for in-scope process equipment and the conclusion.

1.6 This document also includes the results of the Critical Aspects Design Qualification which confirms that all critical aspects as defined in the Critical Aspects Risk Assessment (CARA), all other GMP aspects and all engineering aspects listed in the User Requirement Specification are integrated into the design.

2.0 Scope

2.1 This document includes the results of the Critical Aspects Risk Assessment and Design Qualification of equipment <…> for project <…> which will be operational in facility <…>

2.2 Limitations: This document does not cover … <activities that are excluded for the scope of the project, or from the Critical Aspect Risk Assessment>

2.3 …

3.0 References/Related documents

3.1 Reference to Specification, Design and Verification SOPs

3.2 Reference to SOP regarding Critical Aspects Risk Assessment (CARA) and Design -Qualification documents

3.3 Project specific documents:

3.3.1 <relevant project documents>

3.3.2 …

Appendix 5: Customer: Design Review and Design Qualification (DQ)

4.0 Definitions and acronyms

The following abbreviations may be used in this document. Generally well-known acronyms are not given, e.g. GMP, SOP, FDA.

BMS: Building Management System
CIP: Clean in Place
DCS: Distributed Control Interface
EHS: Environment, Health and Safety
PID: Piping and Instrumentation Diagram (…)

5.0 Project (and system) Description

< In this section, the author of this document briefly describes the goals and limits of the project. Include elements such as project location, product(s), process(es), and activities involved etc. >

5.1 Product Description

< This section summarizes, in short terms, the product(s) at a high level associated with the project, equipment or system. It should include relation of CQA and CPP
(The word “product” has here a general meaning and can mean a drug product, drug substance, medical device, an ingredient such as water, a utility if this utility is produced in the system, materials, data, etc. …) >

5.2 Equipment/Process Description

< This section summarizes, in short terms, the process associated with the project, equipment or system >

5.2.1 The input (solids, liquids, gases) into the process

5.2.2 Description of the process steps

5.2.3 The output from the process (solids, liquids, gases)

5.2.4 Required equipment: only major equipment that is involved in the process is mentioned here

5.2.5 A flowchart (PFD) which indicates major process steps and associated processes.

6.0 Critical Aspects Risk Assessment (CARA)

< Describe which risk ranking system or local procedure is used during the execution of the Critical Aspect Risk Assessment. Describe how the Critical Aspect Risk Assessment is executed attaching the FMEA results. FMEA results are included in the CARA in the first FMEA steps (QRA 1) >

Appendix 5: Customer: Design Review and Design Qualification (DQ)

A process Failure Modes, Effects Analysis (FMEA) were used to perform the Critical Aspect Risk Assessment for the equipment <…>. The FMEA process met the general intent and requirements of ICH Q9, Quality Risk Management and company SOP <…>

First, the team brainstormed what might go wrong, in terms of hazards and the various pathways by which a given hazard could occur. Each CQA was assigned a Severity rating based on <SOP-xyz – Quality Risk Management>. Based on the Severity rating, the Team considered the impact to the Product if the hazard were to occur, independent of the likelihood of occurrence. For each pathway, the Design, Automation, and Quality System Controls were identified.

Given those controls, the team assigned the probability that the hazard could occur. The team then identified direct or indirect indicators for detection that the hazard might be present via the given pathway. From these estimators, a Risk Priority Number [RPN] was computed that was used to evaluate the need for further Risk Control Strategies, where warranted.

The following information was available and referenced during the FMEA sessions

- Process Flow Diagrams
- User Requirement Specification(s)
- P&ID …
- …

6.1 Critical Aspects Risk Assessment Results

< List all open issues and explain the final result >

FMEA results regarding critical aspects risk assessment are included in the CARA.

List the definition and ranking scale of the risk scoring elements:

- Severity (definitions + numeric ranking scale)
- Probability (definitions + numeric ranking scale)
- Detectability (definitions + numeric ranking scale)
- Define action level for Risk Mitigation/Risk Acceptance for the RPN scale

Compute the Risk Priority Number [RPN] based on Severity x Probability x Detectability.

<It is recommended document only the design elements with the highest risk scores, e.g. that are not acceptable or requires actions (depending on the customer company definitions).
There should be a conclusion on the elements with lower score and that the residual risk of these has been considered acceptable >

…

Appendix 5: Customer: Design Review and Design Qualification (DQ)

7.0 Critical Aspects Design Qualification

< Describe how the Critical Aspects Design Qualification was conducted >

The following documents were used to perform the Design Qualification.

- User Requirement Specification
- P&ID …
- Functional Specification(s)… Critical Aspects Design Qualification Results

< List all open issues and explain the final result >

Design Qualification results regarding critical aspects risk assessment are included in the CARA including agreed actions.

For open issues the following actions were agreed.

- …

8.0 User Requirements Design Qualification

< Describe how the User Requirements Design Qualification was conducted >

The User Requirements Specifications Design Review includes a review of Design Documents for all requirements, including the critical requirements coming from CARA as described above, according to the User Requirements Specification (URS).

A Requirement Traceability Matrix (RTM) was used to trace the link between all User Requirement Specifications (critical and non critical) to the relevant design documents where they are addressed.

The User Requirements Specification Design Review was completed and specific Components, Features, and Functions that relate to the Design and Automation Controls were identified. The User Requirement Specifications will form the basis for Commissioning and a focus of Qualification Inspections and Testing…

8.1 User Requirement Specification Design Qualification Results

< List all open issues and explain the final result >

Design Qualification results are listed in appendix <…>

For open issues the following actions were agreed:

- …

Appendix 5: Customer: Design Review and Design Qualification (DQ)

9.0 Conclusion

< Based on equipment size and complexity, separate Critical Aspect Risk Assessment and Design Review/Qualification reports may be necessary. The author should select the appropriate text listed below based on content of the report >

All hazards for equipment/system <…> are assessed and critical aspects are assigned to control the risks to product to an appropriate level.

All Critical Process Requirements have been incorporated into the design, all risks to Product Quality have been assessed, and a Control Program has been or will be included in the design.

There is no Deviation associated with this Phase.

Following Hazards are identified, which have no control mechanisms to control the risk to an appropriate level and therefore need further mitigation:

- …

All Risk Control Mechanisms, as defined in the Critical Aspect Risk Assessment are provided in the design and acceptance criteria for verification testing and final acceptance and release of these risk control mechanisms are defined.

10.0 Appendices/Attachments

< Attach the Critical Aspects Risk Assessment (CARA) and other relevant documents as appendices>

Annex 1: Critical Aspects Risk Assessment (CARA) document <DocID>

Annex 2: Requirement Traceability Matrix (RTM) <DocID>

Annex 3: Test Matrix

<…>

History of Change

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

Appendix 6: Customer: Requirement Traceability Matrix (RTM)

In order to ensure that all requirements in the User Requirement Specification (URS) have been addressed, it is useful with a table that list a summary of all the review activities in order to check and document that the design drawings and specifications from the supplier does meet the URS requirements

Figure 1 shows an example of a Traceability Matrix from a project where the URS is compared with these design document types: P&I Diagram, Functional Specification and Design Specification. It includes all requirements, including those related to Critical Aspect, which are identified separately

The columns in the example are the following:

- Requirement Traceability Matrix ID (RTM ID)
- User Requirement Specification ID (URS ID)

P&I Diagram section:

- Drawing number
- Revision
- P&ID element ID (e.g. Tag number)

Functional Specification section:

- Document number
- Revision
- FS element ID

Design Specification section:

- Document number
- Revision
- DS element ID

Appendix 6: Customer: Requirement Traceability Matrix (RTM)

The table details can be seen in the example below:

RTM ID	URS ID	Requirement	P&ID Review			Functional Specification Review			Design Specification Review			Comment	OK?
			Doc ID	Rev.	PID Element ID	Doc ID	Rev.	FS Requirement ID	Doc ID	Rev.	DS Element ID		
URS Section 1													
xyz	xyz	The product volume will be xyz-xyz liter	xyz	xyz	Tank XYZ	N/A	N/A	N/A	N/A	N/A	N/A	Checked	OK
…													
URS Section 2													
xyz	xyz	Purified water will be circulated at 72°C	N/A	N/A	N/A	FS XYZ	01	#xyz	N/A	N/A	N/A	Checked	OK
…													
URS Section …													

Appendix 7: Customer: Test Matrix (TM)

The Test Matrix tool is used the planning, tracking and execution of test and qualification activities and related documentation for all URS requirements, including the critical aspects. It includes acceptance criteria in order to ensure that the main activities are properly completed and signed off.

The following template is based on a project example and consists of a number of sections related to the commissioning activities of FAT, Construction Testing, Pre-functional testing and Functional testing. If relevant there may be subsequent test activities for e.g. seasonal performance of HVAC systems.

A more detailed version is illustrated below

Appendix 7: Customer: Test Matrix (TM)

#	Title	Description	Verification Method	Supporting Documentation	Critical Aspect Reference	URS Reference	Acceptance Criteria	Initial & Date	Status
FAT testing									
xyz	Ejection test	Xyz machine must inject defect items	Supplier Test Plan	Certificate from Supplier	Ref xyz	URS ID xyz	Documents are received and complete	Xyz yyyy-mm- dd	complete
…									
Installation testing									
xyz	System Installation Verification – Equipment and Installation Drawings	Verify equipment received matches description on PO and vendor documentation is complete.	Visual inspection, document review						
…									
#	Title	Description	Verification Method	Supporting Documentation	Critical Aspect Reference	URS Reference	Acceptance Criteria	Initial & Date	Status
Operational testing									
xyz	XYZ System Pre-functional Check Punchlist	Punchlist from XYZ System Pre-functional Checklist walkdown is closed out for functional testing	Visual inspection, document review	Punchlist closed out by contractor			Punchlist is closed out for functional testing		
…									

Appendix 7: Customer: Test Matrix (TM)

#	Title	Description	Verification Method	Supporting Documentation	Critical Aspect Reference	URS Reference	Acceptance Criteria	Initial & Date	Status
XYZ System Follow-up Performance Testing (e.g. for HVAC systems)									
xyz	System Seasonal Performance Testing	Follow-up testing (e.g. for HVAC: test at peak heating or cooling Season)	xyz test script	Completed test report			Test report received and is complete		
…									

Appendix 8: Supplier: Change Management and Deviation Management

Change Management

Normally the suppliers have an internal change management process, based on their internal quality system. The linking 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 test, resulting in related changes. Typically, it is managed with a so-called 'punch list' with agreed changes that awaits implementation, re-testing and sign-off.

Changes to design, test, qualification or other activities and documents that are agreed or approved with the customer must be approved by the customer organisation and some of these will require approval by the customer's quality organisation, depending on the customer's procedures and organisation.

Some companies use the term "Engineering Change Management" for changes that requires documentation, track record, approval etc. but not necessarily involvement of the customer's quality organisation. Changes that require approval of the customer's quality organisation (e.g. changes related to Critical Aspects) are typically called "Quality Change Management".

Management of changes all the way through documentation, implementation and approval incl. re-testing when relevant, is an important part of ensuring the quality of the equipment, utility or system and should be encouraged when relevant. Change and deviation management should be addressed in the contract. After completion a joint evaluation of the change should be undertaken to confirm that the change objectives were achieved and that there was no deleterious impact on product quality

For engineering or project changes that cannot be managed immediately but must be documented and followed-up in a formal system, the below template example may be used for change management documentation.

Change management should be linked with risk management and especially quality risk management. The design review activities and risk management activities should include focus on the mitigation, including decreasing or elimination of risk, including of risk to the quality of the product.

Appendix 8: Supplier: Change Management and Deviation Management

Change Registration Form

Title:

Change # (ID)

Project Name:

Activity:

Observation (actual situation)
Should be (planned situation)
Proposed action (proposed change)
Risk (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 8: Supplier: Change Management and Deviation Management

Deviation Management

The management of deviations and non-conformities should not only focus on documenting deviations and non-conformities but on the correction of errors, including mistakes and misunderstandings from specifications and design.

It should also cover agreed procedures and methods (and agreed exceptions) and should be clear on terminology, since companies may use other terms, e.g. ‘observations’, ‘defects’ etc.

Preferably, mistakes and errors should be corrected during the review, inspection and test activities and they should be documented and managed as agreed between customer and supplier as part of deviation management and possibly change management.

The following form may be used for deviation management documentation.

Appendix 8: Supplier: Change Management and Deviation Management

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 8: Supplier: Change Management and Deviation Management

Punch List

Project ID | **Project Name**

Project:

Customer

Open issues							Closed issue	
Punch ID	**Test ID**	**Description**	**Date**	**Corrective action**	**Responsible**	**Critical? (Y/N)**	**Re-test reference**	**Responsible**
Remarks							**Closeout (init, date, sign.)**	

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

A Project Quality Plan between customer and supplier should be the basis for the cooperation and regulate important aspects during the project. All quality relevant verification activities, responsibilities and applicable procedures should be covered as well as condition, e.g. that sufficient resources should be applied, the handling of raw data etc.

The following template example is based on a project where there was no separation between Installation and Operational Testing, similar to what some projects do when they combine qualification into Installation/Operational Qualification (IOQ) as mentioned in EU GMP Annex 15 on Qualification and Validation. The example was used as the joint Project Quality Plan (PQP) between customer and supplier throughout the project.

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

Project Quality Plan for Qualification

Project name

Document number
Revision

Customer	<…>
Project ID	
Project Name	
Site	
Unit/Equipment	

Approval Table				
Signs for	Function	Department	Date	Signature
Prepared by	Author …	<name>	<date>	<signature>
Reviewed by	…	…		
Reviewed by				
Approved by	…	…		

Change log

Revision	Date	Responsible	Change description
<…>			

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

Table of Content

1. Scope and Background

This document describes the general requirements on Documentation and Qualification activities for the Project <…> at the Customer <…> site <…> building <…>.

The present document summarizes the scope of delivery for the supplier in terms of requirements for Documentation, Commissioning and Qualification.

All requirements shall be understood as minimum requirements on the content and required quality for the preparation of documents as well as for the operational performance of qualification actions and activities.

2. Project Description

<The goal of the project shall be described as well as project borders / equipment borders>

The documentation language in the project is <…>

3. Document Management

3.1 Data format
All derived and prepared documents for GMP relevant systems shall be delivered at least as PDF file Microsoft Office is preferred.
All drawings as well as layout plans and schemes shall be delivered in DWG or DXF format and shall be delivered as PDF.

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

3.2 Official correspondence and communication

Decisions and declarations shall be documented in written form.

All changes which may impact contracts and / or deliverables shall be approved by supplier in written form. All different communications (phone calls, E- Mails and oral communication) does not have any binding character. All decisions shall be communicated by agreed method (e.g. letter, email, agreed electronic storage system or in special cases via signed Memo).

3.3 Document specific language

Document	Language
Project documents	English
Specifications (Functional, hardware spec, etc.	English
Technical documents (flow charts, layouts, wiring diagrams etc.)	English
Commissioning and qualification documents	English
Manuals and user manuals	…
As-Built documentation (past qualification)	
Documents for authority use (local)	

3.4 Content of Documents

At least the following information shall be covered in each prepared document (if there are no different agreements or understandings)

Information	Covered in:					
	Header	Footer	On each page	Cover page	Change history	On appendixes
Name of project:		X	X	X		
Project ID: <…>				X		
Document Name / Title				X		X
Document ID:	X		X	X		
Author				X	X	
Revision	X		X	X		
Preparation date				X	X	
Number of pages (X of Y)		X	X	X		X
Number of pages (including appendixes)				X		

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

Appendixes to Master documents will be handled as important part of each document.
The appendixes shall contain clear reference to the master document.

Each document will be approved including all appendixes if any appendix changes the master documents shall be approved accordingly.

3.5 Document Handover to Customer

Electronic documents shall be handed over either via E- Mail or web-based via project specific tools (Extra- net, Share-Point etc.)
The document Handover shall be confirmed by the Sponsor for each document

3.6 Project Responsibilities

The responsibilities related to documents and operative qualification activities are described in the following tables as well as the specified requirements

	Approval		Technical Review		Review Qualification		Execution		Participation		Support

In general the design planner is responsible for the technical review of the documentation. The Qualification coordinator is responsible for the review in accordance to the accurate implementation and fulfilment of general requirements on documentation and accurate signatures. The Qualification coordinator shall also review the documents on fulfilment of GMP-requirements.

The design planner is responsible for tracing Gaps and deviations during the planning and realization phase.

3.7 Review and Approval of Documents

All GMP- relevant documents shall be approved by Sponsor. At least the following documents have been classified as GMP- relevant:

- Specifications (e.g. User Requirement Specification (URS), Functional Specification (FS), Hardware Design Specification (HDS), Software Design Specification (SDS))
- Qualification Protocols and Reports
- Risk Assessments
- Other documents which have been classified with GMP-impact

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

Each document which needs approval of the project sponsor shall contain the following signatures

Name	Function	Department	Date	Signature
Prepared by <…>	Equipment Design	<name>	<date>	<signature>
Reviewed by <…>	Design Planner	…		
Reviewed by <…>	Q Coordinator			
…				
Approved by <…>	QA	…		

Qualification documents shall be approved prior the execution otherwise the tests are not valid and repetition is mandatory

Meetings must be called in with agenda and documented by minutes with clear decisions.
Preferably meeting minutes should be agreed, printed and signed immediately.

3.8 Qualification activities / Preparation of documents

For the purchased package the supplier has to perform qualification in accordance to the present document.

All requirements which have been classified as GMP- relevant in the URS and /or requirements which have been classified in the GMP- risk assessment shall be considered during qualification. All requirements without any GMP- impact shall be checked during commissioning phase (GEP).

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

4. Document Requirements

The following general rules for the document requirements apply to the project:

Nr.	Requirement	Supplier	Customer	Design Planner	Q- Coordinator
1.	All documents which are mandatory for realization / installation and / or qualification shall be approved by Customer Especially qualification protocols and equivalent Test plans shall be reviewed and approved by Customer The Sponsors approval does not discharge the supplier to fulfil all legal requirements				
2.	The supplier shall know all deliverables, documentation, guidelines and if applicable all references to Pharmacopeia or has to study all requirements prior design and realization of any equipment.				
3.	Past project Kick off a summary of documents shall be prepared which shall be considered as scope of supply (system specific document list) this list shall be prepared in accordance to URS.				
4.	Appendixes shall be indicated as appendix and shall always be referenced to the respective document Numbering concept shall be clear and traceable				
5.	The supplier is responsible for the quality and fulfilment of requirements (customer requirements) of sub suppliers as well, especially requirements on the commissioning, documentation and qualification process as described in the following chapters				
6.	Systems for preparation of P&IDs and wiring diagrams shall be identified and communicated				
7.	Documents which are exchanged electronically (E- Mail and data carriers, etc) and shall be approved by Sponsor shall be delivered as hard copy document for approval				
8.	All documents shall be delivered as paper based hard copy and for GMP-systems the documents shall be delivered as electronic working file as well (Word File, etc.)				
9.	DQ- documents in accordance to the respective (system specific) document list serve as release documents for equipment / system realization. These documents shall be approved at the time of release for realization by customer				
10.	*The acceptance of installation shall be performed after release and approval of relevant design documents by customer and respective Construction Manager*				
11.	*Listing of all relevant and applicable minimum requirements by law (ATEX, HSE requirements, CE- conformity, etc.)*				

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

5. Requirements for Commissioning and Qualification

5.1 General Requirements

Nr.	Requirement	Supplier	Customer	Design planner	Q-Coordinator
12.	The customer shall perform a functional GMP- risk assessment which shall identify components and functions which are critical on product quality as well as on patient safety this RA shall identify mandatory and necessary qualification activities - The supplier shall support this risk assessment - Identified actions out of the risk assessment shall be considered in installation and operational test protocols of the supplier.				
13.	The risk analysis also serves or may serve as traceability matrix to ensure the operational transformation into specific test cases during qualification				
14.	The system supplier shall prepare a Functional Specification (FS)				
15.	The description out of FS, all actions out of RA and the requirements out of URS shall serve as a basis for the preparation of Qualification test protocols (IQ/OQ and PQ)				
16.	*The overall qualification planning document shall be prepared by Q- Coordinator and shall at least contain the following facts:* - *Description of responsibilities* - *Description of all executable Q- phases and tests (IQ/ OQ and PQ)* - *Indication of time plan and schedule (best estimation as possible)*				
17.	Each qualification phase shall be considered in independent phase plans and protocols, the protocols and plans shall be prepared by Supplier				
18.	Q-Coordinator hast to check the documents (from supplier) on accuracy and completeness in accordance to basic documents				
19.	All planning documents and protocols shall be approved by customer prior operational execution of the tests				
20.	The protocols shall consider the way of test execution as well as a description of the acceptance criterion for each test case				
21.	The place of operational execution of IQ and OQ shall be clearly fixed. The operational tests for IQ and OQ can be either performed on suppliers' site during FAT or on final installation site at the user. IQ and OQ test can only be considered for qualification purpose if the test results during FAT remain valid after disassembling on supplier`s site and installation on final operation site if there have been any changes the tests shall be executed again to have proven evidence of system suitability				

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

Nr.	Requirement	Supplier	Customer	Design planner	Q-Coordinator
22.	The operator (test executor) witnesses the accuracy of test execution and fulfilment of acceptance criterion with signature and date (time if necessary)				
23.	After test execution the protocols and reports shall be presented to the customer. By customer approval all test results, the test execution and deviations will be released				
24.	The traceability of all test cases shall be documented beginning with the URS stage of the project / system through the entire qualification process as well as through all qualification documents This traceability shall be documented in a separate document (Traceability matrix)				
25.	The confirmation of each qualification phase shall be documented on a release sheet. A following qualification phase shall only be started if the prior phase has already been approved and the system has been released for the following phase Exceptions to this rule may be applied if there are no constraints				
26.	The overall qualification report shall be prepared by Q-Coordinator and shall be approved by customer				
27.	Suppliers shall prepare Org charts, time schedule, list of signatures and list of phone number for all involved project operators including their roles and responsibilities				
29.	The supplier shall clarify if the extent and the formal realization of documents is sufficient. Based on this information further actions can be defined				
30.	The review cycle time for documents shall be fixed (e.g. 5 working days)				
31.	How document will be transferred shall be clearly defined (e.g. only Word Files for transfer and final document as PDF,…)				
32.	If applicable the way of realization of GAMP 5 requirements shall be clearly stated				
33.	Required SOPs and manuals shall be identified and defined which are mandatory for designing and manufacturing of equipment (Welding, Programming,…) including measurable quality indicators				
34	If possible and required a time schedule shall be fixed when the manufacturing steps have to be finished. Also reporting shall be defined to identify critical project paths as early as possible				

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

Nr.	Requirement	Supplier	Customer	Design planner	Q-Coordinator
35	Definition of all documents shall be done that need to be delivered for each project phase including respective definition of responsible and required approvals for each document This can be done either in qualification protocols or in an separate document lists				

5.2 Changes and Deviations

Nr.	Requirement	Supplier	Customer	Design planner	Q-Coordinator
36.	Starting with the approved Design documents (DQ) the supplier shall use a detailed Change Management system				
37.	Technical changes until DQ shall be clarified and discussed with the design planner. The design planner clarifies the changes with the customer. Approval of all changes by customer is mandatory				
38.	Past approval of design documents in DQ all technical changes shall be implemented and handled in the formal change management system. All changes shall be reported at the time of occurrence or in scheduled meetings. Change control and list of all changes shall be overhanded to design planner				
39.	All deviations which occurred during test execution shall be recorded as „acceptance criterion not met“ in the respective test protocols and shall be documented in deviation reports (root cause, actions taken, preventive actions) Acceptance criteria must not be changed except the acceptance criterion has been defined wrong. Change of acceptance criteria must be approved by customer				
40.	*Additional requirements*				

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

5.3 Design Qualification

Nr.	Requirement	Supplier	Supplier	Design planner	Q-Coordinator
42.	All documents which shall be prepared in Design phase shall be documented in an independent document list of the supplier				
43.	In the DQ phase all documents which are listed in document list shall be reviewed by customer and shall be approved with date and signature for realization. Prior approval by customer all documents shall be signed and approved by supplier				
44.	For finalization of DQ all documents which are listed in the document list shall be available in fully approved versions				
45.	*Additional requirements*				

5.4 Factory Acceptance Test (FAT) and Site Acceptance Test (SAT)

Nr.	Requirement	Supplier	Customer	Design planner	Q-Coordinator
46.	Prerequisites for FAT execution: - DQ-Documents prepared and approved - *Pre-FAT testing (if applicable) is fully executed and approved* - *Approved IQ/ OQ documents of supplier*				
47.	Supplier shall prepare FAT- protocols to test installation and functionality of the system. The documents shall be approved by customer prior FAT execution Customer specific adjustments of the test shall be possible / feasible				
48.	The supplier is responsible for the FAT execution. Q- Coordinator, design planner and customer shall at least participate in the FAT				

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

Nr.	Requirement	Supplier	Customer	Design planner	Q-Coordinator
49.	Following tests shall be at least executed in FAT: - Realization in accordance to approved drawings and technical specifications - Compliance of system with the P&ID and BOM (Bill of materials) - Critical to quality attributes based on randomized control *(Measurement, surface, visual control, 3D rule, etc*) - Compliance of system with reference scheme, list of cables, Bill-of- Materials (BOM), disposition, electric cabinet scheme - *Certificates of used lubricants* - Calibration certificates of supplier - *Initial calibration of instruments* - Compliance of Computer Hardware in accordance to Hardware De- sign Specification (HDS) - Functional tests during FAT shall be performed after calibration and execution and documentation of line testing - Functional checks of controls in accordance to approved test documents - Interface functionality (SCADA and / or MES connections) - Completeness and accuracy of specified technical documents *Add more*				
50.	Results of FAT/ SAT shall be used for the qualification protocols in accordance with the Q-coordinator if all requirements (quality, documentation, pre specified,…) have been met				
51.	The following tests shall be executed at the installation site: - Check the accuracy of installation of the complete system including all supply media and energy (based on P&ID) - Full test of the equipment train (based on E/MSRT scheme, BOM, Specifications) - Check accurate installation and labeling of measuring devices Calibration of all quality relevant measuring devices in accordance to valid SOP and/ or Calibration instruction				
52.	SAT test execution shall be performed by supplier Q-coordinator, design planner and customer shall participate SAT				
53.	*Additional requirements*				

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

6 Installation Test (or Installation Qualification (IQ)

Nr.	Requirement	Supplier	Customer	Design planner	Q-Coordinator
54.	The supplier shall prepare Installation Test/IQ test protocols			-	
55.	At least the following tests shall be performed in Installation Test: - Implementation in accordance to approved system drawings, technical specifications and URS - Accordance of system with P&ID, BOM, and installation at the interface positions to other systems - Critical quality attributes based on a randomized control (check of dimensions, surface quality, visual checks, 3d rule,…) - Certificate of used lubricants - Loop-Check for all measuring devices especially if connections have been disassembled for transportation purpose. - Completeness and availability of certificates - Calibration certificates of supplier - *Initial calibration of measuring devices* - Check Computer Hardware in accordance to HDS - Completeness and integrity of technical documents - Check review and approval of IQ protocols and executed tests during IQ phase, if relevant - Check all IQ Tests which have been identified as action in functional Risk assessment, if relevant *A backup of the control and application software shall be handed over to the customer*				
56.	The calibration of the measuring devices shall be performed by supplier, the documentation and the design of the calibration protocols shall be in accordance with customer requirements				
57.	Approved Design documents shall serve as basis for the execution of the Installation Test/IQ If there is a check on a respective design document the approval of the design document is mandatory (approval by customer)				
58.	Installation/IQ test execution shall be performed by supplier Q- coordinator, design planner and customer shall participate IQ				
59.	Recorded deviations from FAT shall be checked again latest in Installation Test/IQ if the deviation has not been resolved so far				
60	The Installation Test/IQ documentation of the supplier shall confirm that the system has been delivered completely and accurately				
61	To finalize Installation Test/IQ all documents referenced in document list shall be available in approved versions				
62	Additional requirements				

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

6.1 Operational Test (or Operational Qualification (OQ)

Nr.	Requirement	Supplier	Customer	Design planner	Q-Coordinator
63.	The supplier shall prepare Functional/OQ test documents and protocols				
64.	Approved Design documents shall serve as basis for the execution of the Installation Test/IQ If there is a check on a respective design document the approval of the design document is mandatory (approval of customer)				
65.	Installation/IQ test execution shall be performed by supplier Q-coordinator, design planner and customer shall participate in the Installation Test/IQ				
66	At least the following tests shall be performed during Functional Test/OQ: - Check of all relevant (for Functional Test/OQ) requirements in accordance with URS - Check of Computer Hardware in accordance to Hardware Design Specification (HDS) as well as Software in accordance to Software Design Specification (SDS), including alarm simulation or complete alarm testing - *If applicable: Data transfer to MES* - *If applicable: interface testing of SCADA connection or connection to Manufacturing Execution System (MES)* - *If applicable: Interface and synchronisation testing between connected systems and software systems* - Functional verification of all functional components (including systems of sub suppliers) - Verification of technical functionality of system in accordance to FDS, including Alarm tests, safety system tests as well as access control and access concepts - Software testing (e.g. *HMI Navigation, Menu structure, plausibility checks, Disaster Recovery, …*) All other Functional/OQ-Tests specified in the URS				
67	To finalize OQ all documents referenced in document list shall be available in approved versions				
68	A performance run of the whole equipment train shall be performed in OQ				
69	Supplier shall support Sponsor for execution of additional qualification tests if necessary				
70	*Additional requirements*				

Appendix 9: Customer and Supplier: Project Quality Plan (PQP)

7 Performance Test (or Performance Qualification (PQ)

Nr.	Requirement	Supplier	Customer	Design planner	Q-Coordinator
71.	PQ shall be executed by Customer	-	A	-	P_Q
72.	PQ test are not executed by supplier but the supplier shall support PQ- execution This support shall be defined at the purchase of the PQ support package	U	A		P_Q
73.	*PQ protocols shall be prepared by Q- coordinator in accordance with customer requirements*	-	*U/G*	*U*	*A*
74	The PQ test execution shall be performed by customer with support of Q- coordinator				
75	*PQ report shall be prepared by Q-coordinator in accordance with customer requirements*				
76	Technical deviations and concerns which will be identified during PQ shall be resolved by supplier of the system				
77	*Additional requirements*				

6. Object Structure

The project scope of this plan consists of the following main equipment parts:

Main Equipment	Sub Equipment	Equipment ID	Description
Filling Line	Syringe unloader	<…>	Unloader for syringe trays
	Syringe transfer unit		
Isolator			

7. Documents

7.1 Document References

The following documents are the basis of this plan:
<…>

7.2 Applicable documents

>
The following documents applies:
<…>

Appendix 10: Supplier: Testing Activity Plan

The Testing Activity Plan is an example of a supplier document that has been proposed by the supplier and agreed with the customer. It gives an overview of all the relevant reference documents to be used during the testing and qualification activities.

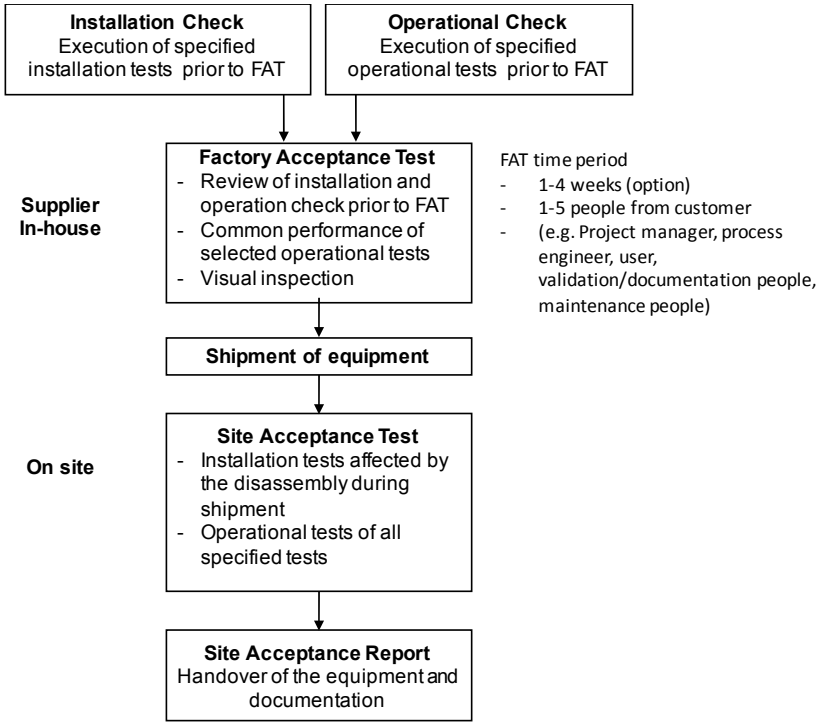
Suppliers typically have their own procedures and documents for their activities, and these may be acceptable for the customer or necessary changes may be agreed. Typically, they consist of a Testing Activity Plan (or similar) and a number of detailed test plans. For the detailed test plans it should be ensured that the testing encompass at least

- Name of the test
- ID of the test (e.g. number)
- Procedure of the test
- Objective (purpose) of the test
- Acceptance criteria
- Test person
- Date and time
- Test result
- Conclusion (pass/fail)
- Comments
- Reference to related documentation

The test documentation should be managed according to good documentation practice and all test results should be recorded immediately during the test by readable and traceable recording of the test person test time, test result etc.

Appendix 10: Supplier: Testing Activity Plan

In this example the suppliers testing activities are organized as follows:



Explanation of the Supplier FAT/SAT and Qualification approach:

- Supplier will perform internal tests listed in this document prior to FAT to verify the correct installation and function of the system
- Supplier may start performance of installation checks at the workshop (tests are marked in table below)
- During FAT commonly selected critical tests will be performed to allow the shipment of the system.
- On site we will repeat all installation tests where disassembly of the system may have an impact to previous test results. It should be ensured that the executed FAT tests are not affected.
- All listed Functional tests will be performed on site. If software FAT takes place it can be commonly agreed not to repeat specific tests if the functionality is related to SCADA system only (e.g. Password Test, Audit Trail Test).

A target of each project should be an 'Integrated Commissioning & Qualification Approach'. This can be discussed in detail during project meetings

Appendix 10: Supplier: Testing Activity Plan

Supplier Documentation Plan for Qualification

Project name

Document number

Revision

Customer	<…>
Project ID	
Project Name	
Site	
Unit/Equipment	

Unit <…> Installation Check:

Installation Check Protocols		
	Installation Check Protocol for FAT	Document ID <…>
	Installation Check Protocol for SAT	Document ID <…>

Appendix 10: Supplier: Testing Activity Plan

Comprise the following tests:

#	Procedure	Title	Subject	Related Documents	Doc. No.	Doc. Type	Attached Or Ref.?	Before/ During FAT	During SAT
1		Observation List		Empty Template	<...>				
2	Ref <...>	Verification of the technical documentation	To verify the documentation defined in doc. <...>	List of unit documentation	<...>	Design as part of quality plan	Attached	x	x
3	Ref <...>	Check of drainability	To check that the equipment and all piping in contact with water, steam or product has a drainable slope towards a drain	P&I Diagram	<...>	Design	Attached	x	(x) For disassembled parts
4	Ref <...>	Check of dead legs	To check that no dead legs exists in piping in contact with clean media	P&I Diagram	<...>	Design	Attached	x	(x) For disassembled parts
4	Ref <...>	Check of correct installation	To check the component installation with the drawing and component list	P&I Diagram Component list	<...>	Design Design	Attached Attached	x	(x) For disassembled parts
5	Ref <...>	Verification of correct reassembling of dismounted connections	To check the piping and system connections which were dismounted for transport in order to ensure correct reinstallation on site and to verify the correct levelling of the equipment	P&I Diagram	<...>	Design	Attached		x
...									

Appendix 10: Supplier: Testing Activity Plan

#	Procedure	Title	Subject	Related Documents	Doc. No.	Doc. Type	Attached Or Ref.?	Before/ During FAT	During SAT
7	Ref <...>	Verification of electrical components	To check the correct installation, wiring, labelling and setting of the electrical components, Fieldbus and Ethernet network	Wiring and terminal diagrams	<...>	Design	Attached	x	(x) For disassembled parts
8	Ref <...>	Verification of the software installation	To check the correct installation, labelling and completeness of SCADA computer	SOP for installation of SCADA computer Configuration of the SCADA computer	<...>	SOP Design	Referenced Attached	x	x
9	Ref <...>	Verification of inputs and outputs, incl. loop test	To check the correct installation and function of the inputs and outputs of the PLC	Wiring and terminal diagram List of AI and AO of PLC List of DI and DO of PLC	<..>	Design Design Design	Referenced Attached Attached	x	(x) For disassembled parts
...									
	Ref <...>	Verification of the surface roughness	To check that the roughness (R_a) of surfaces in contact with product or clean media are conforming to specification	Specification				x	
	Ref <...>	Verification of welded seams	To check that all specified material requirements are fulfilled	Work instruction for welding of process piping Pickling and passivation plan Welding and material documentation	<..>	SOP SOP SOP	Referenced Referenced Referenced	x	(x) For weldings done on- site

Appendix 10: Supplier: Testing Activity Plan

XYZ Unit Operational Check:

Operational Check Protocols		
	Operational Check Protocol for FAT	Document ID <...>
	Operational Check Protocol for SAT	Document ID <...>

Comprise the following tests:

#	Proce-dure	Title	Subject	Related Documents	Doc. No.	Doc. Type	Attached Or Ref.?	Before/ During FAT	During SAT
		Observation List		Empty Template	<...>				
1	Ref <...>	Functional Test of the XYZ equipment startup	To check the correct startup of the XYZ equipment before production	Functional Specification Sequence diagram List of parameters	<..>	Design Design Design	Referenced Attached Attached		x
2	Ref <...>	Functional Test of the XYZ equipment production functions	To check the correct startup of the XYZ equipment for production	Functional Specification Sequence diagram List of parameters		Design Design Design	Referenced Attached Attached		x
3	Ref <...>	Functional Test of the XYZ equipment CIP	To check the correct CIP of the XYZ equipment	Functional Specification Sequence diagram List of parameters		Design Design Design	Referenced Attached Attached		x
4	Ref <...>	Functional Test of the XYZ equipment production functions	To check the correct shutdown of the XYZ equipment after production	Functional Specification Sequence diagram List of parameters		Design Design Design	Referenced Attached Attached		x
5	Ref <...>	Functional Test of the XYZ equipment emergency functions	To check the correct performance of the XYZ equipment emergency functions	Functional Specification Hardwire interlock drawing		Design Design	Referenced Attached		x

Appendix 10: Supplier: Testing Activity Plan

#	Procedure	Title	Subject	Related Documents	Doc. No.	Doc. Type	Attached Or Ref.?	Before/ During FAT	During SAT
6	Ref <...>	Functional Test of process and failure messages	To check the correct display of the process and failure messages on the indicators and acoustic failure signal	Functional Specification Wirering and terminal diagram List of failure messages		Design Design Design	Referenced Attached Attached		x
7	Ref <...>	Functional Test of SCADA password protection	To check the correct password protection of SCADA system	Functional Specification Software design spec. for SCADA		Design Design	Referenced Attached		x
8	Ref <...>	Verification of Audit Trail Functionality	To check the traceability and recording of modifications of audit trail data and the user log function	Check audit trail testing		Test	Attached		x
9	Ref <...>	Verification of screen layouts	Verification of screen layout of SCADA screens	Functional Specification Software design spec. for SCADA		Design Design	Referenced Attached		x
10	Ref <...>	Verification of batch report	To check the correct content of the batch report	Functional Specification Software design spec. for SCADA		Design Design	Referenced Attached		x
...									

Appendix 11: Integrated Qualification and Validation: The “Red Thread”

Introduction

The integration of commissioning and qualification activities between customer and supplier is overall the responsibility of the pharmaceutical customer company. The cooperation and the “red thread” of Critical Aspects of the manufacturing system into commissioning and qualification activities can be a joint effort that enables the use of commissioning activities as part of the qualification documentation without unnecessary retest activities.

This section describes the activities of the customer and the supplier in using Good Engineering Practices and Good Documentation Practices in a project example that involves the customer’s engineering function (or similar), quality function and the supplier’s organisation. The example is a tablet press machine which is part of a larger project with other manufacturing systems (equipment) involved. The example can be applied to small or large projects containing other types of manufacturing systems.

In this project the customer had a high-level Product- and Process User Requirement Specification (PPURS) that describes the manufacturing process including associated quality risk assessments. In other cases the starting point is simply a high-level product and process quality risk assessment based on development data or manufacturing history data. It should be based on the intended use of the manufacturing system, including the critical quality attributes (CQA) of the product and the critical process parameters (CPP) of the process. From this initial Quality Risk Assessment the Critical Aspects of the manufacturing system should be identified.

The Critical Aspects of the manufacturing system are related to risk from an end user perspective (the patient, ultimately). The Quality Function of the pharmaceutical customer is normally involved in key activities on the Critical Aspects, All other specification and qualification activities are in this example managed by the engineering function according to Good Engineering Practices, but this depends on the organisational setup of each pharmaceutical company (customer) organisation.

The customer’s engineering function and the supplier will typically cooperate during the project based on GEP etc. and the relevant Subject Matter Experts (SME) on both sides will typically work together on the specification, test etc. of the relevant requirements and qualification activities, typically as a cross-functional team covering quality, process, utilities, automation etc. The approach and the tools described in this section supports these principles by enabling clear agreements on activities, acceptance criteria and responsibilities for a successful and cost-effective cooperation.

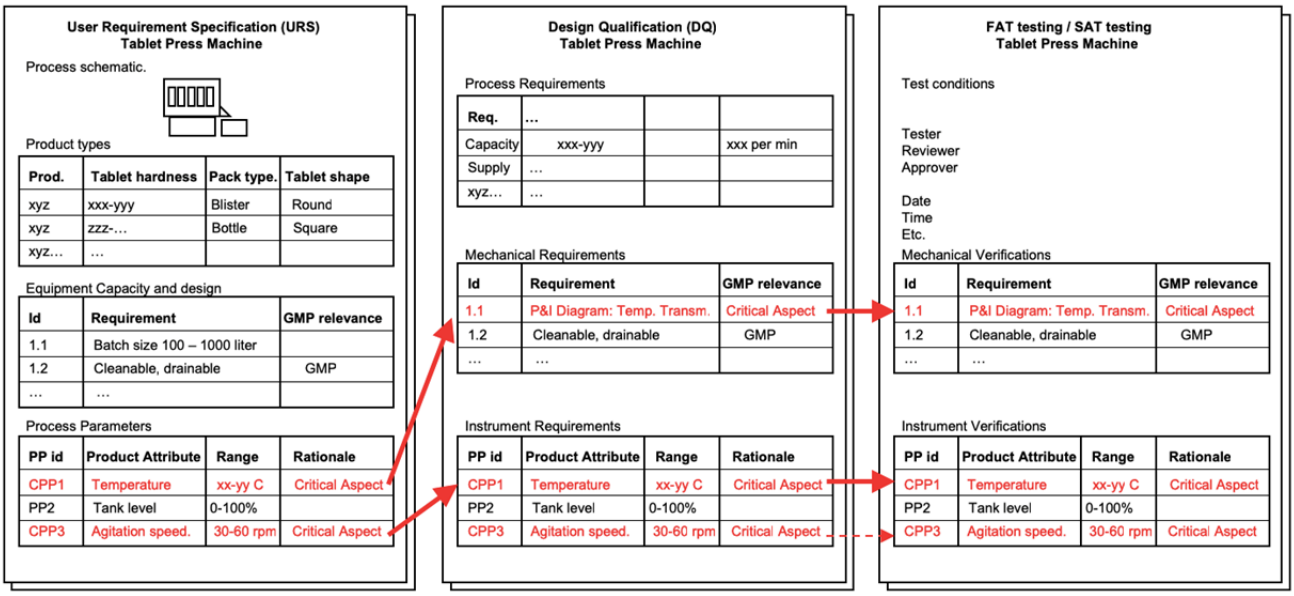
The Quality Function of the pharmaceutical customer reviews that all the Critical Aspects of all manufacturing systems have been assessed, tested and been accepted. This may be documented in an overall Acceptance and Release Report to release the integrated system including all involved equipment, utilities etc. for the subsequent Process Validation activities, which demonstrates the Process Performance capabilities of the manufacturing system and thereby its ability to consistently produce a product meeting its specifications and quality characteristics for commercial distribution.

Appendix 11: Integrated Qualification and Validation: The "Red Thread"

The Process Validation (aka Process Performance Qualification) activities may in some cases involve the supplier, depending on what has been agreed of scope.

The overall project flow of the requirements and qualifications of a tablet press machine and especially its critical aspects are illustrated in the figure below. All activities are based on Good Engineering Practices and Good Documentation Practices
The activities related to Critical Aspects are marked with the color red. They normally require a deeper involvement of the customer's quality function to ensure quality risk management consistency and quality throughout the project execution as illustrated in Figure 1.

Figure 1

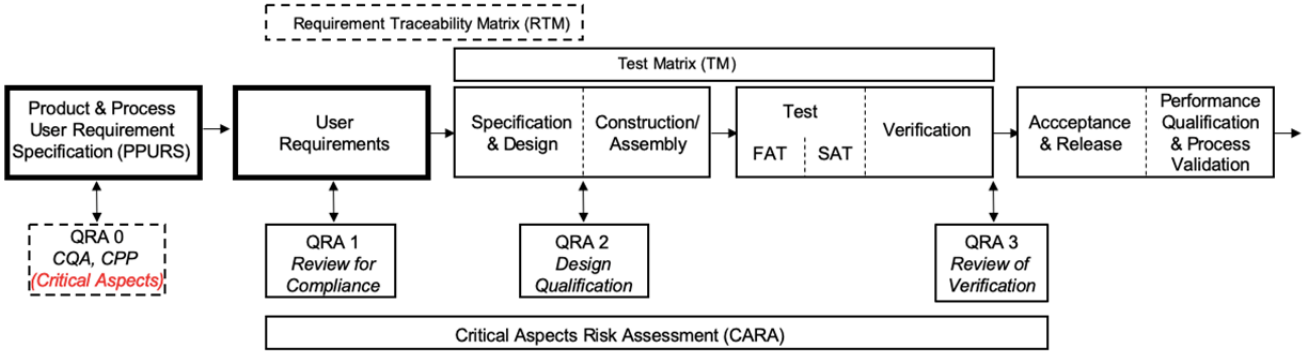


1. Project flow

An initial risk assessment (QRA 0) should be available, ideally based on the product- and process information from the development or tech transfer of the pharmaceutical process so that it can be used for the subsequent risk management activities throughout the project. It should identify at least the Critical Quality Attributes (CQA) of the product, the Critical Process Parameters (CPP) of the process and possibly other quality risk assessment assumptions in order to be able to identify the Critical Aspects (CA) of the manufacturing system.

Appendix 11: Integrated Qualification and Validation: The "Red Thread"

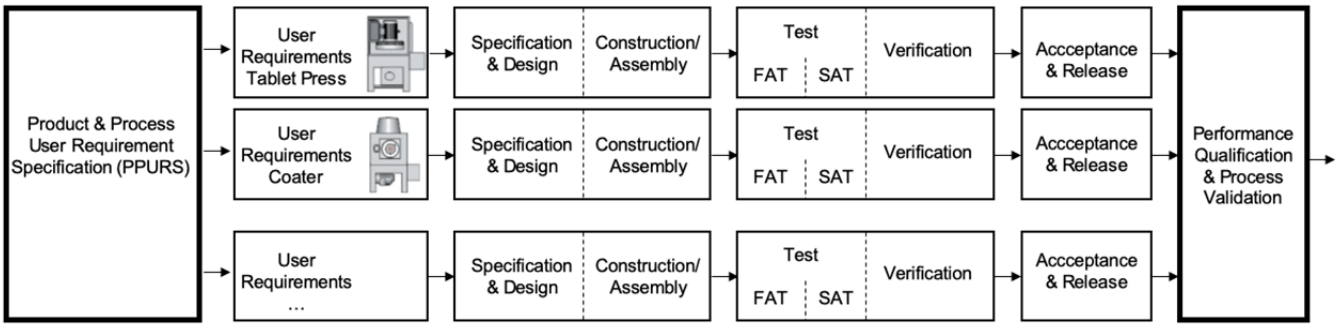
Figure 2



The customer should develop an *initial* User Requirement Specifications (URS) for each manufacturing system of the project, based on the PPURS or other requirements, including company standard requirements for certain equipment (e.g. WFI systems, HVAC or other).

The following is an illustration of the overall project flow and document collection for an equipment for pressing tablets. In the example the Tablet Press Machine is part of a production line with Coater, Blister Machine etc. as illustrated in the end.

Figure 3



After completion of all the qualification activities for all involved manufacturing systems are completed the customer's quality function and the relevant subject matter experts from the qualification team will review the result. The quality function will have special focus on results regarding the Critical Aspects and that all activities have reached satisfactory results to demonstrate that the manufacturing system(s) are fit for intended use.

Subsequent activities for Performance Qualification and Process Validation, Cleaning Validation, and subsequent manufacturing operations for commercial release of the pharmaceutical product(s) are not descried in this section.

Appendix 11: Integrated Qualification and Validation: The "Red Thread"

2. Product and Process User Requirement Specification (PPURS)

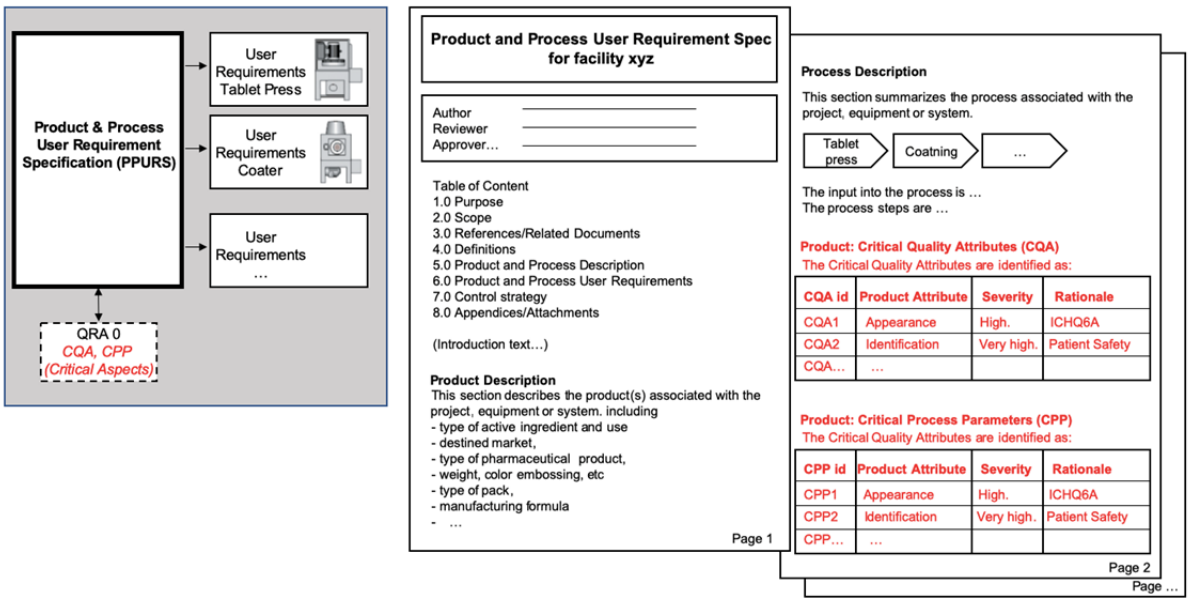
Typical responsibility Customer, involves the Quality Function (QA):

The Product and Process User Requirement Specification (PPURS, see appendix 1) is an overview of the **manufacturing equipment involved, incl. relevant utility systems. It is based on input from the research, tech** transfer etc. before the project starts and contains an initial Quality Risk Assessment, which is a reference for subsequent quality risk assessments, URS documents and other activities.

The PPURS document typically covers the whole facility (or project scope) including several equipment or systems. It includes an overview of the manufacturing equipment involved, incl. relevant utility systems. It includes enough process description and quality risk assessment information, including Critical Quality Attributes (CQA) for the product and Critical Process Parameters (CPP) for the process to enable the identification of Critical Aspects of the equipment and systems involved.

The CQA, CPP are the basis for identifying the Critical Aspects of the manufacturing system are emphasized with red text in figure 4. They are the starting point for the "red thread" throughout this example that is the main focus of the Quality Function (QA), namely the Critical Aspects. Everything is conducted as Good Engineering Practice and documented by Good Documentation Practice.

Figure 4



Appendix 11: Integrated Qualification and Validation: The "Red Thread"

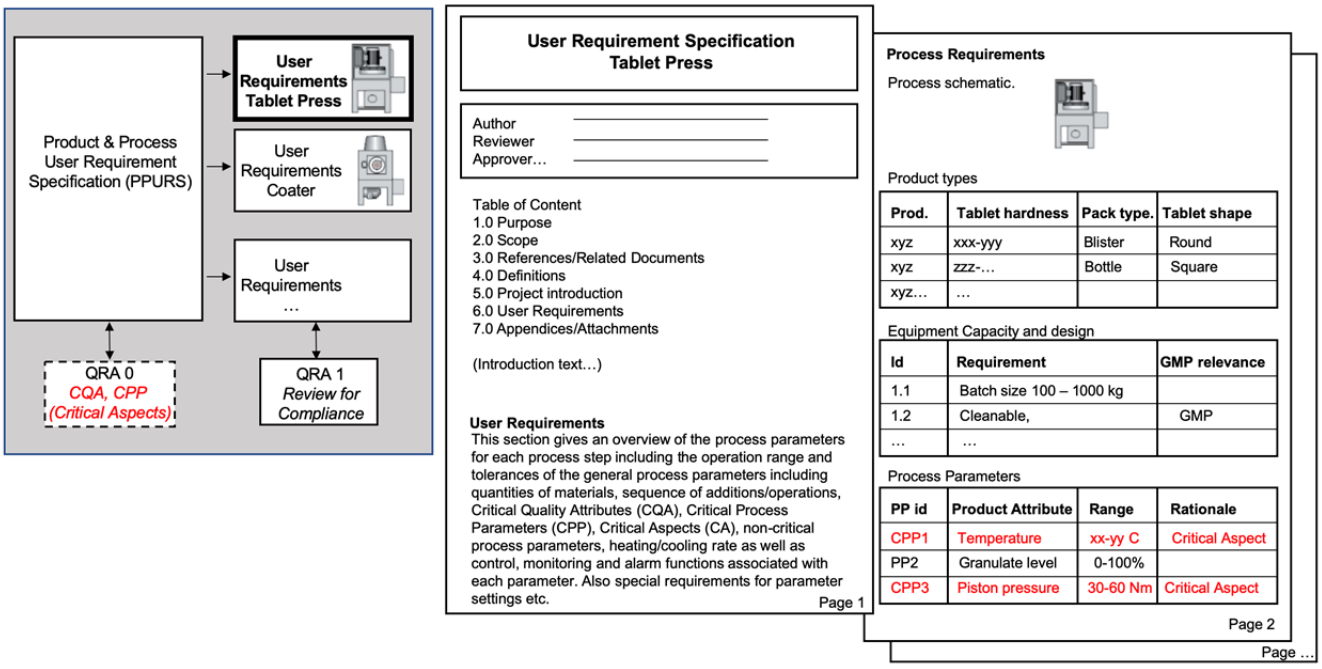
3. User Requirement Specification (URS)

Typical responsibility Customer Engineering (and QA):

A User Requirement Specification (URS, see appendix 2) is developed for each equipment, e.g. the tablet pressing machine.

All requirements require "Good Engineering Practice" design and verification later, but the requirements related to Critical Aspects require involvement by the quality function of the pharmaceutical company. The requirements related to Critical Aspects of the machine are marked as "Critical Aspect" or CA requirements in Red, in figure 5.

Figure 5



Appendix 11: Integrated Qualification and Validation: The "Red Thread"

4. Design activities

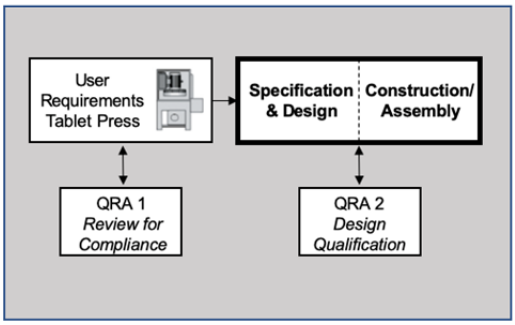
Typical responsibility: Supplier, reviewed by customer engineering, involving QA

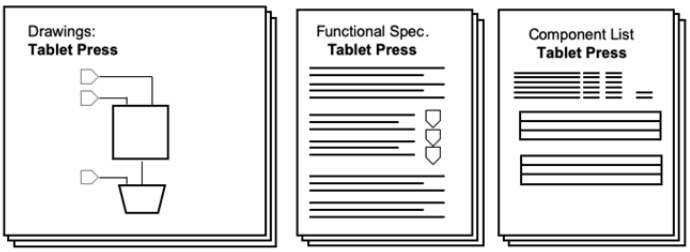
Once a final version of the User Requirement Specification (URS) has been agreed, the suppliers design activities, purchase of components, construction etc. will start.

For standard equipment the documents are already made during the development of the equipment models and they may need customization for the specific customer project. For fully customized equipment the design activities, purchase etc. follows and should be organized in a way where the customer's review and approval of the design specifications are approved.

These design documents including functional specifications etc. are the basis for design reviews and ultimately Design Qualification. These activities are further described in the Supplier section Activities during Engineering.

Figure 6





Appendix 11: Integrated Qualification and Validation: The "Red Thread"

5. Design Review and Design Qualification

Typical responsibility: Customer Engineering and QA:

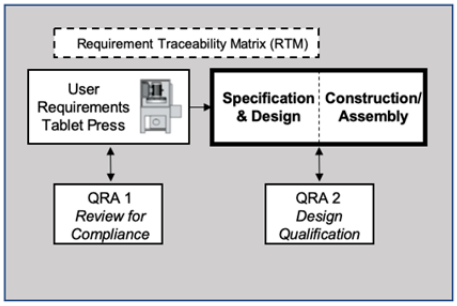
After selection the supplier provides the design documentation and specifications for the equipment. This is reviewed and approved in one or more Design Reviews (DR see appendix 5) and ultimate in a Design Qualification (DQ, see appendix 5) to ensure that all requirements in the final URS document is met in the design of the manufacturing system, including those requirements related to Critical Aspects.

In general the design review is done at cross-functional meetings and the design qualification may be a summary based on the review meetings or it may be a separate meeting. The review is based on Good Engineering Practices and should involve the relevant Subject Matter Experts, both on the Customer and the Supplier side.

For requirements related to Critical Aspects the customer's Quality Function will be involved to ensure that the requirements are met.

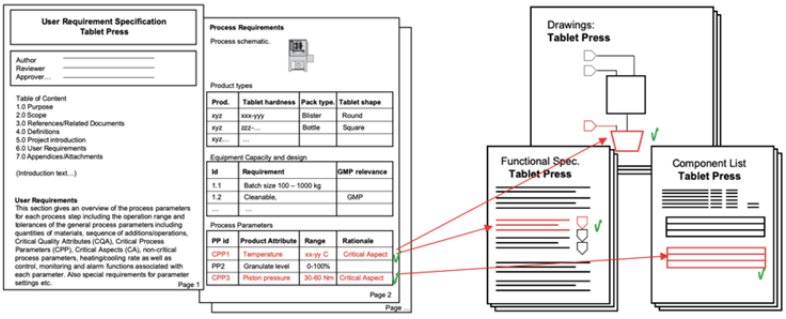
Some companies uses a tool called Requirement Traceability Matrix (RTM, see appendix 6) to give an overview of how the URS requirements are addressed in the design of the equipment etc. See figure 7 below

Figure 7



RTM Requirement Traceability Matrix

Manufacturing System: Tablet Press	Accomplished verification	Doc Identification	Comment
General Requirements #1.1 Will be operated 24/7 #1.2 Temperature between xx and yy C	√ Verified by xyay Follow up by …	Drawing xx.xx.yy Func Spec xy.xx	Add night alarm
Equipment Requirements #2.1 Piston pressure between 30 and 60 Nm #2.2 Tablet bin must be easily movable …	√ Verified by xyay	Func Spec yy.xx Component list z	



Appendix 11: Integrated Qualification and Validation: The "Red Thread"

Test Matrix (TM)

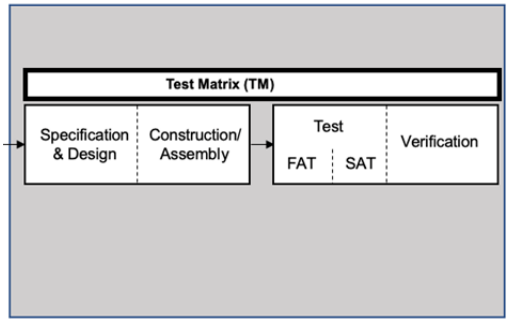
Typical responsibility: Customer, Engineering (in cooperation with supplier)

Once the design is agreed the supplier will work on procurement, receiving, assembly, construction etc. A number of supervisory activities are necessary to ensure the quality of the work, including receiving of components, handling of material certificates, welding documentation, surface treatment, installation inspection, calibration, operational tests etc. These should be documented according to Good Documentation Practice for those that is agreed to be part of the documentation of the qualification activities.

The test activities, including the split of work, responsibilities and acceptance criteria can be planned with a Test Matrix (TM) tool describing what is tested in which test activity, e.g. Factory Acceptance Test (FAT), Site Acceptance Test (SAT) etc. and by whom, e.g. customer or supplier.

The Test Matrix should be agreed as early as possible with the supplier to agree what tests are doing in FAT, SAT etc. respectively.

Figure 8



Test Matrix
(testing of all requirements, incl. Critical Aspects)

Manufacturing System: Tablet Press	ID.	Title	Description.	Testing ref.	Test doc ref.	CA ref	Remarks
Tablet functional test verification	#1.1 #1.2	FS test Part 11	Verify FS req Verify ER/ES	Doc xyz. Doc sss.	Doc zzz. Doc ttt.	- CA #3.4	Both FAT and SAT FAT
Integration test verification	#2.1 #2.2	Utilities Network	Verify supply. Verify ER/ES	Doc fff Dox yyy	Doc abc. Doc defg	-	SAT test
...							

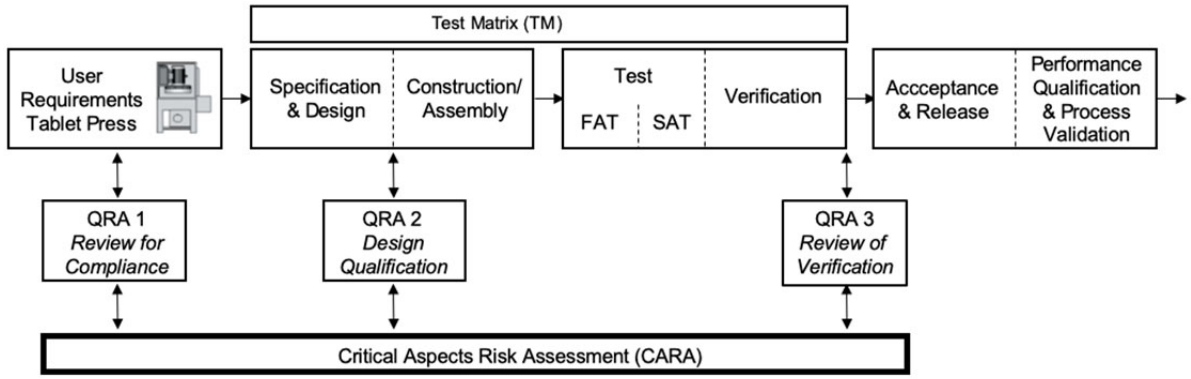
Appendix 11: Integrated Qualification and Validation: The "Red Thread"

CARA Critical Aspects Risk Assessment

Typical responsibility: Customer Engineering and QA:

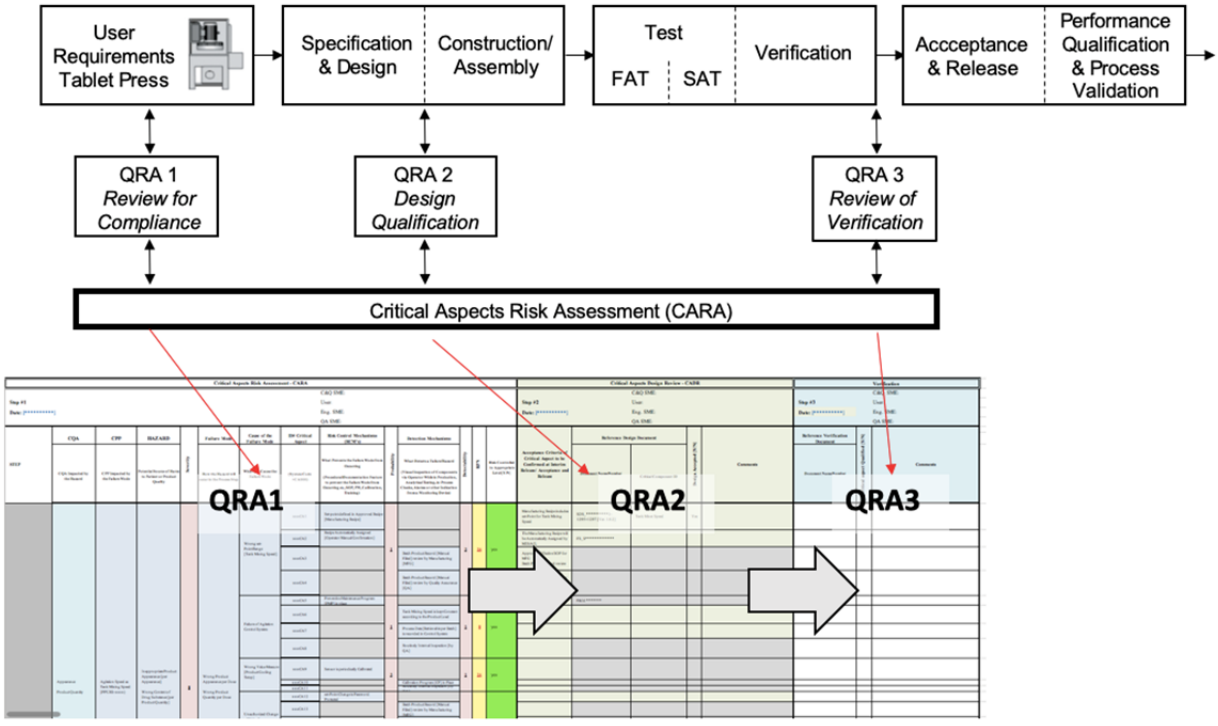
The qualification activities for the Critical Aspects of the manufacturing system are typically controlled by the customer company's Qualify Function. The activities may be managed and documented with a tool for Critical Aspects Risk Assessment (CARA, see appendix 4)

Figure 9



The CARA tool is used through the project activities to document the activities related to the Critical Aspects Design Review , as illustrated in figure 10 below.

Figure 10



Appendix 11: Integrated Qualification and Validation: The "Red Thread"

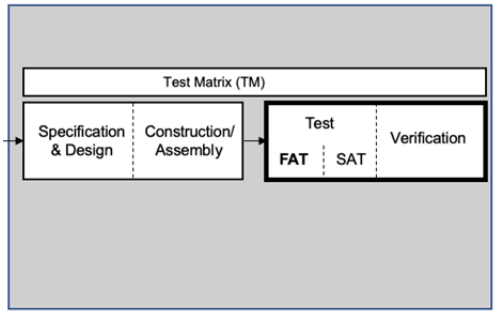
6. Factory Acceptance Test (FAT)

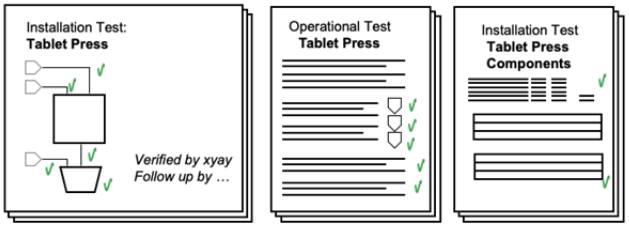
Typical responsibility: Customer Engineering and Supplier:

FAT is executed at the supplier's factory before the equipment is transported to the customer's factory or site. All these tests are traced in the Test Matrix. FAT includes both installation test and operational test.

This evaluation is done on the basis of the test completions according to the Test Matrix overview, now filled out with all the completed verifications from the FAT. Deviations are reported if they are not already solved. Deviations that have an impact on the Operational Tests in FAT and SAT are identified. Deviations that have an impact on Critical Aspects typically requires involvement of the Quality Function of the pharmaceutical customer.

Figure 11





Test Matrix (FAT verifications)

Manufacturing System: Tablet Press	ID.	Title	Description.	Testing ref.	Test doc ref.	CA ref	Remarks.	Verified
Tablet functional test verification	#1.1 #1.2	FS test Part 11	Verify FS req Verify ER/ES	Doc xyz. Doc sss.	Doc zzz. Doc ttt.	- CA #3.4	FAT and SAT FAT	Xyz 1-NOV-2009
Integration test verification	#2.1 #2.2	Utilities Network	Verify supply. Verify ER/ES	Doc fff Dox yyy	Doc abc. Doc defg	-	SAT test	Xyz 1-NOV-2009
…								

Appendix 11: Integrated Qualification and Validation: The "Red Thread"

7. Site Acceptance Test (SAT)

Typical responsibility: Customer Engineering and Supplier:

SAT is executed in the pharma factory after transportation and final installation at the customer's site. The tests are done the same way on both GMP and non-GMP equipment and controlled by the Test Matrix.

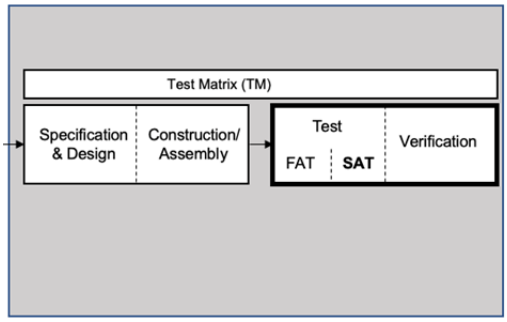
The FAT and SAT tests are typically separated into static testing (some calls it pre-functional testing or installation verification) and dynamic testing (some calls it functional testing or operational testing).

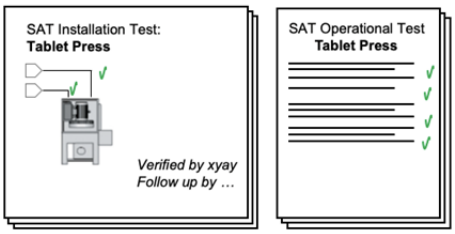
Some companies confirms the completion of all the static testing by a so-called Green Tag report as a pre-requisite to connect the equipment to electrical power and possible utilities. It confirms that the system is ready for functional testing, that all construction and installation activities are completed, all quality activities regarding the installation are completed, the supporting documentation is available and the systems is ready for the functional testing.

Similarly these companies confirms the completion of the functional testing by a Blue Tag report that all functional testing has been completed, documented and approved. Both the Green Tag report and the Blue Tag report are based on Good Engineering Practices and documents the completion of commissioning activities.

All the tests are traced in the Test Matrix and upon the completion the documentation can be reviewed and approved by the Quality Function of the pharmaceutical customer. They should mainly focus on the testing and documentation of Critical Aspects testing and documentation and confirms it by an interim release after which the full process can be started for the process validation (process performance qualification in US FDA terminology).

Figure 12





Test Matrix (SAT verifications)

Manufacturing System: Tablet Press	ID.	Title	Description.	Testing ref.	Test doc ref.	CA ref	Remarks.	Verified
Tablet functional test verification	#1.1 #1.2	FS test Part 11	Verify FS req Verify ER/ES	Doc xyz. Doc sss.	Doc zzz. Doc ttt.	- CA #3.4	FAT and SAT FAT	Xyz 1-NOV-2009
Integration test verification	#2.1 #2.2	Utilities Network	Verify supply. Verify ER/ES	Doc fff Dox yyy	Doc abc. Doc defg	-	SAT test	Xyz 1-NOV-2009
…								

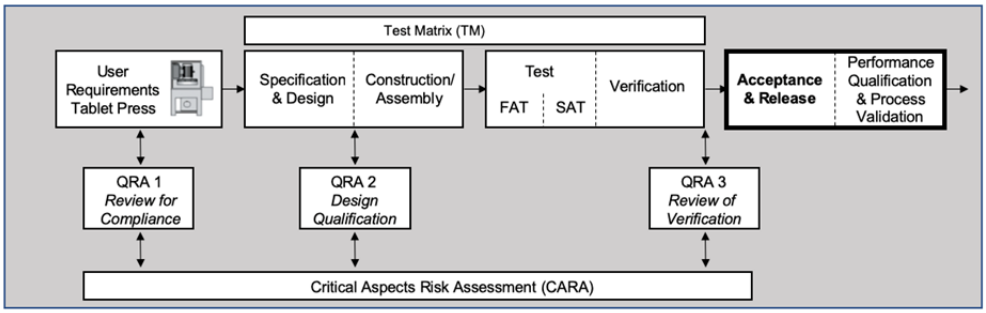
Appendix 11: Integrated Qualification and Validation: The "Red Thread"

8. Review and approval of qualification activities

Typical responsibility: Customer Engineering and QA

When all tests are completed for each of the manufacturing systems, the test completion is reviewed in a Quality Risk Assessment (QRA 3). All Critical aspects are reviewed for the completion of the associated verification activities.

Figure 13

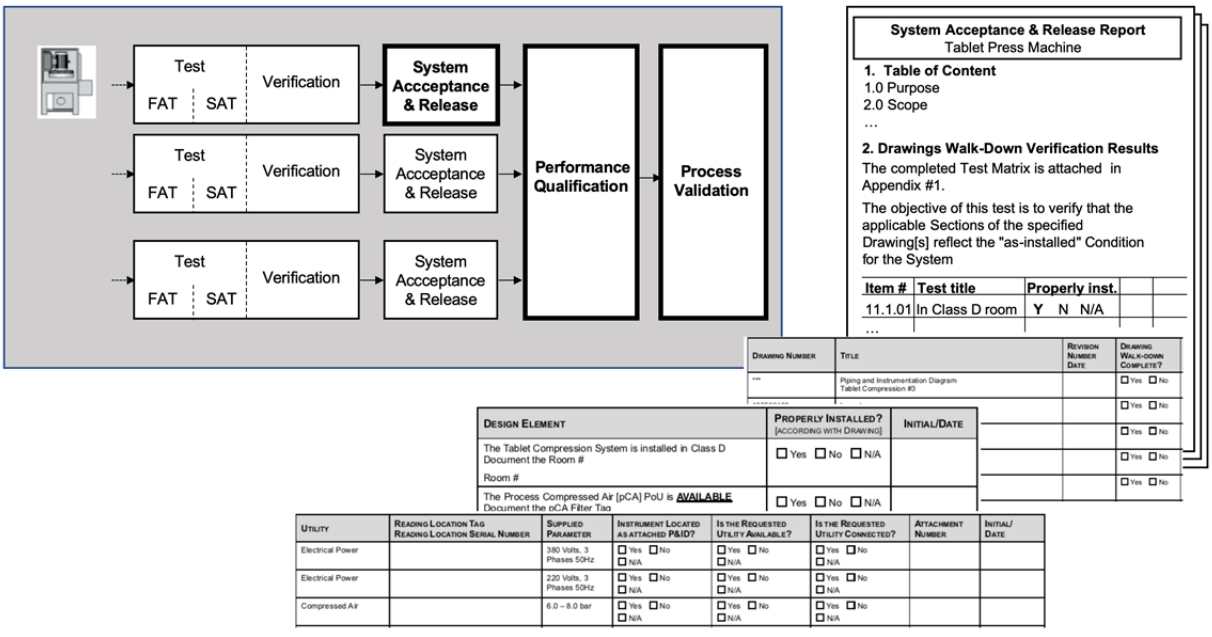


Test Matrix (after completion of all verifications)

Manufacturing System: Tablet Press	ID.	Title	Description.	Testing ref.	Test doc ref.	CA ref	Remarks.	Verified
Tablet functional test verification	#1.1 #1.2	FS test Part 11	Verify FS req Verify ER/ES	Doc xyz. Doc sss.	Doc zzz. Doc ttt.	- CA #3.4	FAT and SAT FAT	Xyz 1-DEC-2009 ✓
Integration test verification	#2.1 #2.2	Utilities Network	Verify supply. Verify ER/ES	Doc fff Dox yyy	Doc abc. Doc defg	-	SAT test	Xyz 1-DEC-2009 ✓
...								

If the QRA 3 is accepted, the system is released with an interim System Acceptance and Release Report (SARR) for each manufacturing system.

Figure 14



Appendix 11: Integrated Qualification and Validation: The "Red Thread"

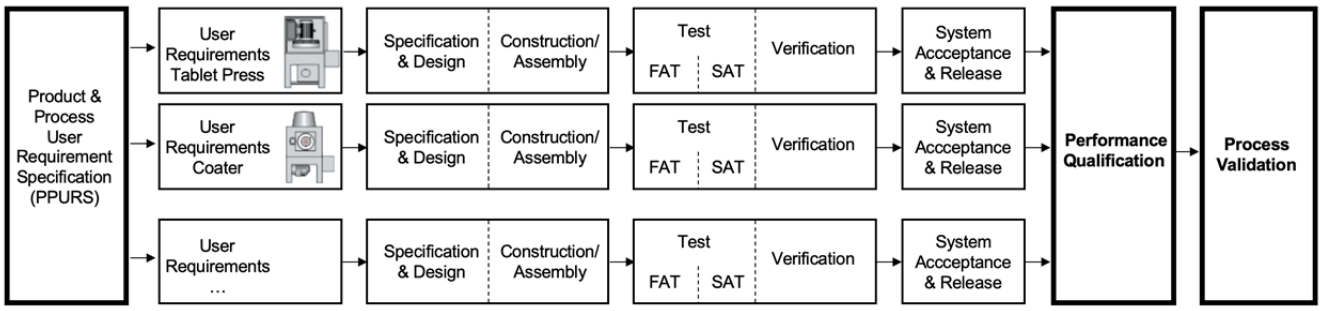
9. Overall Acceptance and Release (of all manufacturing systems)

Typical responsibility: Customer Engineering and QA

When all test on all manufacturing systems are executed and accepted (incl. possible corrections) the equipment are all ready for integrated Performance Qualification (PQ) of the overall manufacturing system with all equipment, utility systems, automation systems etc. in operation to ensure that the overall manufacturing system (including all facility, utility and equipment elements) is fit for its intended use.

After the successful completion of Performance Qualification (PQ) an overall Acceptance and Release report is used in many pharmaceutical companies and normally requires approval by the Quality Function. The System Acceptance and Release Report is issued to document that the system is qualified to be fit for its intended use. After this, the process validation activities (or process performance qualification activities (US)) can be completed

Figure 15



Appendix 11: Integrated Qualification and Validation: The "Red Thread"

10. Process Validation and Ongoing Process Verification

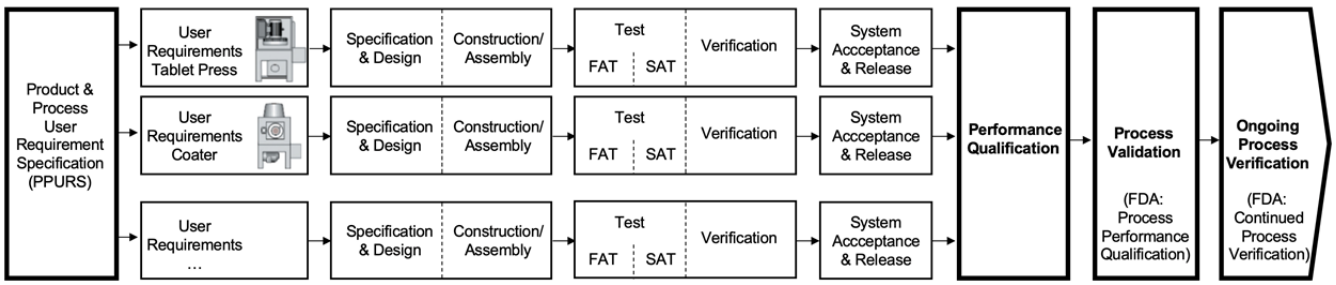
The Process Validation (PV) activities are executed on the same basis as the original Quality Risk Assessment (QRA 0) as described above and the "red thread" of focus on the Critical Quality Attributes (CQA) and Critical Process Parameters (CPP) as well as other key elements of the process validation activities, including packaging validation, cleaning validation, transport validation etc. according to the EU GMP Annex 15 on Qualification and Validation.

(The EU GMP Annex 15 on Qualification and Validation uses the term "Process Validation" whereas FDA uses the term "Process Performance Qualification". Similarly Annex 15 uses "Ongoing Process Verification" and FDA "Continued Process Verification" see section 5.10)

This links back to the Product & Process User Requirement Specification (PPURS) that typically covers the whole facility or project scope including all involved manufacturing systems for a specific product. Thus, the Process Validation may have to be repeated or adjusted to cover all the relevant pharmaceutical products.

The Ongoing Process Validation (OPV) activities continue as long as the product is produced commercially.

Figure 16



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 star-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 E2500-13)
Critical Aspects Design Element (CADE)	The design elements that directly impacts the Critical Aspect and detection controls, and design elements that have the ability to discover or determine the existence/presence or fact of a hazard. These design-based risk controls constitute CADEs (PDA TR54-5)
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 E2500-13)
Factory Acceptance Test (FAT)	An Acceptance Test in the Supplier's factory, usually involving the Customer (IEEE).

Term	Explanation
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)
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)
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 E2500-13)
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 E2500-13)
Supplier	A supplier is a person, company, or organisation that sells or supplies something such as goods or equipment to customers (Collins Dictionary)
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 E2500-13)
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 E2500-13)

Feedback Form for ECA Good Practice Guide for Integrated Qualification and Validation

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#	Page	Line	Comment/Rationale	Proposed change/Suggested text	Class. H/M/L	Originator	Action

Please email comments to Pommeranz@concept-heidelberg.de